MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application Number: NDA 20-463, SE5-002
Sponsor: Pharmacia & Upjohn Company
Category of Drug: Non-corticosteroid anti-inflammatory
Medical Reviewer: Charles E. Lee, M.D.
Application Type: Pediatric supplement to NDA
Proprietary Name: NasalCrom™ nasal spray
USAN Name: Cromolyn sodium nasal solution
Route of Administration: Intranasal spray
Review Date: 4/13/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type and Comments
8/19/99	08/31/99	Pediatric supplement, 4 volumes
8/19/99	8/31/99	N 20-463, SE-002
10/27/99	10/27/99	Amendment 1 to Pediatric supplement, 2 volumes
4/6/00	pending	IR, telecon, drug product in Protocol M\3235\0002

RELATED APPLICATIONS:

NDA #20-463

Approval Date: 01/03/97 **Comments:** NDA for OTC cromolyn nasal spray

REVIEW SUMMARY:

The sponsor has submitted this pediatric supplement in support of the use of NasalCrom (cromolyn sodium) nasal spray in children ≥ 2 to < 6 years of age. The proposed indication is for prevention and relief of nasal symptoms of hay fever and other nasal allergies. The proposed dose is one spray each nostril 3-4 times a day (every 4-6 hours), up to 6 times a day. The sponsor submitted the results of one study in support of this indication. This study was primarily a safety study that secondarily evaluated efficacy in a descriptive fashion. This study, M\3235\0002, supports the safety of the product in this age group. Adverse events (AEs) occurred at a similar frequency in NasalCrom-treated patients (57%) and in placebo-treated patients (55%). AEs were mild and local in character. The sponsor presented efficacy data in a descriptive fashion. There were small differences favoring NasalCrom over placebo in each of the efficacy endpoints. The sponsor also submitted a literature review and a global drug surveillance report which support the safety of this product in children ages ≥ 2 to < 6 years of age. This pediatric efficacy supplement is recommended for approval under the Pediatric Use provision, 21 CFR 201.57(f)(9)(iv). The pathophysiology and course of allergic rhinitis and the beneficial and adverse effects of the drug are similar in children 2 to ≤ 6 years of age and adults. NasalCrom has previously been approved for OTC use in adults and in children ≥ 6 to <12 years of age on the basis of adequate and well controlled studies. This drug is topically active, systemic absorption is low, and pharmacokinetic data would not be useful. The study submitted in this application, M\3235\0002, establishes the proper dose in children ages ≥ 2 to < 6 years of age and provides additional support of the safety and efficacy of this product in this age group. This reviewer recommends approval of this application on the basis of the Pediatric Use provision, 21 CFR 201.57(f)(9)(iv).

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION:

N drive location:

New Clinical Studies: **Clinical Hold:** **Study May Proceed:**

NDA, Efficacy/Label Supplement is: **Approvable: X**

SIGNED:

Medical Reviewer: /S/ **Date:** 4/13/00

Medical Team Leader: /S/ **Date:** 4/14/00

1. TABLE OF CONTENTS

2. Material Reviewed 2
3. Chemistry/Manufacturing and Controls 3
4. Animal Pharmacology/Toxicology 3
5. Clinical Background 3
6. Clinical Studies 4
6.1. M\3235\0002 4
6.2. Participating centers 4
6.3. Objectives 4
6.4. Study population 4
6.4.1. Inclusion criteria 4
6.4.2. Exclusion criteria 4
6.5. Medication restrictions 5
6.6. Study design 6
6.7. Endpoints 6
6.7.1. Primary endpoint 6
6.7.2. Secondary endpoints 6
6.8. Statistical analysis 7
6.8.1. Analysis of data 7
6.8.2. Randomization 8
6.8.3. Power analysis 8
6.8.4. Assessment of rhinitis severity 8
6.8.5. Drug product and placebo 8
6.8.6. Assessment of patient compliance 8
6.9. Results 8
6.9.1. Disposition of patients 8
6.9.2. Patient demographics 9
6.9.3. Protocol deviations 10
6.9.4. Compliance 10
6.9.5. Rescue medication use 11
6.9.6. Efficacy endpoint outcomes 11
6.9.7. Safety endpoint outcomes 13
6.10. Conclusion from study results 18
7. Review of literature survey 18
8. Review of Global Drug Surveillance reports 18
9. Interated summary of safety 19
10. Executive summary and recommendation 19

2. MATERIAL REVIEWED

This document is a review of an application for approval of the use of NasalCrom™ Nasal Spray for the prevention and relief of nasal symptoms of hay fever and other nasal allergies in children ≥ 2 to < 6 years of age. The application includes one clinical study, a literature survey on the use of cromolyn in the pediatric population, and reports from the sponsor's spontaneous medical event reporting system.

3. CHEMISTRY/MANUFACTURING AND CONTROLS

The drug product used in the clinical study in this submission is the currently marketed product (Telecon, 4/6/00).

4. ANIMAL PHARMACOLOGY/TOXICOLOGY

There are no new animal pharmacology/toxicology issues with this application (IND [redacted]

5. CLINICAL BACKGROUND

NasalCrom nasal spray, (cromolyn sodium, 5.2 mg/spray), is marketed by the Pharmacia and Upjohn Company. Cromolyn sodium is an anti-allergic drug considered to have mast cell stabilizing properties. Cromolyn sodium has been shown to prevent both the immediate and late phases of the allergic reaction in clinical allergy challenge models. NasalCrom is currently indicated for the prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis. The currently marketed product is approved for adults and children 6 years of age and older at the dose of one spray each nostril 3-4 times a day, every 4-6 hours. If needed, the product may be used up to 6 times a day.

NasalCrom (cromolyn sodium nasal spray),NDA 18-306, was originally sponsored by Fisons. It was approved in 1983 for the treatment and prevention of the symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children ≥ 12 years of age. The product was sold to McNeil, Inc. McNeil, Inc. submitted an application in 1996 seeking approval for OTC use of NasalCrom for the SAR indication while seeking to retain Rx use for the PAR indication. The product was approved for OTC use on 1/3/97 for the treatment and prevention of seasonal and perennial allergic rhinitis. The approval was based on studies from NDA 18-306, one pivotal clinical study, Study 94-433, and other supporting studies. Study 94-433 was carried out to demonstrate the efficacy of NasalCrom in the OTC population. The efficacy of the product in this pivotal clinical study was marginal, with a difference from placebo of approximately 0.3 points on a 5-point symptom scale. Safety issues were mainly local and were related to nasal soreness, burning, stinging, and epistaxis. Headache was the most common generalized adverse event (AE). A favorable risk:benefit ratio for use in the OTC population was demonstrated. A Pulmonary and Allergy Drug Advisory Committee meeting on 10/10/96 reached a consensus that the product was safe and effective in the OTC setting for the treatment of allergic rhinitis. The Division of Pulmonary Drug Products (HFD-570) reached an agreement with the sponsor that the both the prophylaxis and treatment indications were acceptable because efficacy was demonstrated in Study 94-433. (NDA 20-463, Medical Officer Review, 1/20/96, pages i-v)

This application, NDA 20-463, SE5-002, was submitted in response to an amended Written Request for pediatric exclusivity, dated 1/25/99. Pediatric Exclusivity was granted by the Agency on 11/2/99. This application is for the use of this product in

children ≥ 2 to < 6 years of age. The proposed indication is for prevention and relief of nasal symptoms of hay fever and other nasal allergies. The proposed dose is one spray each nostril 3-4 times a day (every 4-6 hours), up to 6 times a day.

6. CLINICAL STUDIES

This application includes one clinical study. This study is described below.

6.1. M\3235\0002: An Evaluation of Safety and Tolerance of Cromolyn Sodium Following the Administration of a Nasal Solution to Pediatric Patients

6.2. Participating centers

There were 20 U.S. centers participating in this multi-dose study (Volume 1.2, pages 600-602).

6.3. Objectives

The objective of this study was to compare the safety of NasalCrom nasal spray to placebo in the treatment of allergic rhinitis in pediatric patients ≥ 2 to < 6 years of age.

6.4. Study population

Patients meeting the following criteria were selected for participation in this study:

6.4.1. Inclusion criteria (Volume 1.1, page 382)

- The patient and/or patient's guardian must have signed an informed consent form prior to entry in the study
- Patients were to be ≥ 2 and < 6 years of age at the time of entry into the study
- Patients ≥ 3 years of age must have had a documented history of seasonal allergic rhinitis (SAR) and/or perennial allergic rhinitis (PAR) and were to be symptomatic of SAR and/or PAR at entry
- Patients ≥ 3 years of age must have had a positive epicutaneous skin test response (wheal ≥ 3 mm in diameter greater than diluent within 15 minutes of skin prick) to at least one allergen indigenous to the study site area at the screening visit or must have had documentation of a positive skin test to a regional allergen within the previous 12 month period
- Patients were to be symptomatic with at least, "mild" symptoms of allergic rhinitis (AR) on the global assessment
- The patient or patient's guardian was to be required to demonstrate the ability to use a nasal spray

6.4.2. Exclusion criteria (Volume 1.1, page 383-384)

- Known prior history of sensitivity to cromolyn sodium
- Use of any prescription medication that might affect the use of study medication within 72 hours prior to randomization and/or use of a proscribed medication within the designated number of hours prior to randomization

- Use of any new prescription medication, or any OTC product delivered intranasally and/or ocularly during the study period
- Patients on immunotherapy were required to be at a constant dose for at least one week
- Evidence of an upper or lower respiratory tract infection within 14 days prior to randomization
- Evidence of otitis media within 14 days prior to randomization
- Use of any investigational product within 30 days prior to randomization
- Patients with vasomotor rhinitis
- Any medical condition which in the judgement of the principal investigator would compromise the patient's participation in this study
- Evidence of acute or chronic sinusitis within 14 days prior to randomization
- Patients with clinically significant nasal polyps, nasal septal deviation or nasal septum perforation
- Patients or guardians with limited mental capacity to the extent that information regarding efficacy, side effects, and tolerance of study drug cannot be assessed
- Patients who are directly involved in the conduct or administration of this study

6.5. Medication restrictions (Volume 1.1, page 421)

The following medications were not permitted from the time listed prior to randomization until the end of the study:

Table 1. Medication restrictions (Volume 1.1, page 421)

Drug	Excluded from Time Prior to Randomization
Antacids	≤ 8 hours
Anticholingergic agents	≤ 72 hours
Astemizole	≤90 days
Cetirizine	≤ 5 days
Diphenhydramine	≤ 5 days
Fexofenadine	≤ 5 days
Hydroxyzine	≤ 5 days
Loratadine	≤ 5 days
Other antihistamines (oral, intranasal, or ocular)	≤ 72 hours
Beta agonist inhalers	≤ 72 hours
Cromolyn sodium	≤ 14 days
Decongestants (oral, intranasal, ocular)	≤ 72 hours
Initiation or change in immunotherapy	≤ 7 days
Leukotriene receptor antagonists	≤ 14 days
5-lipoxygenase inhibitors	≤ 14 days
Monamine oxidase inhibitors	≤ 14 days
Nedocromil	≤ 14 days
Other ocular medications	≤ 72 hours
Saline eye drops	≤ 4 hours
Salmeterol	≤ 14 days
Sleep aids	≤ 36 hours
Tricyclic antidepressants	≤ 14 days

Asthmatic patients could be enrolled if they were on stable regimens of daily inhaled corticosteroids, daily beta-agonists, or other stable daily asthma therapy with no known effect on rhinitis or combination therapies that met the preceding requirements. Patients must have been on this asthma treatment regimen for at least 7 days and were required to

continue on the treatment regimen for the duration of the study. Topical corticosteroids for dermatologic disease were allowed. The use of oral or intranasal steroids for any reason was prohibited during the treatment period (Volume 1.1, page 421).

Each patient was supplied with Children's Sudafed® Nasal Decongestant Liquid for use as a rescue medication for symptoms of allergic rhinitis. No other rescue medications were permitted during the study period. The patient could use the rescue medication on an as needed basis (Volume 1.1, page 385). Lot numbers were not provided for Children's Sudafed® Nasal Decongestant Liquid used in this study.

6.6. Study design

This study was a multi-center, multiple dose, randomized, double-blind, parallel group study. At baseline, eligible patients were randomized to either the NasalCrom or placebo treatment groups. Patients took their first dose of study medication on the day of randomization while at the site. Patients enrolled into the study were treated with either NasalCrom or placebo for 4 weeks. The study timetable is displayed in Table 2.

Table 2. Study timetable (Volume 1.1, page 400)

Procedure	Baseline	Week 1	Week 2	Week 4
Written informed consent	X			
History of positive skin test[1]	X			
Medical history	X			
Physical examination	X			X
Nasal examination	X	X	X	X
Inclusion/exclusion criteria	X			
Concomitant medication	X	X	X	X
Rhinitis medication history	X			
Randomization	X			
Dispense study medication[2]	X		X	
Collect study medication			X	X
Assessment of symptoms[3]	X	X	X	X
Query for adverse events		X	X	X
Review diary cards		X	X	X
Study completion				x

[1]Not required for patients ≥ 2 to < 3 years of age
[2]Study medication was weighed prior to dispensing and at time of collection. One bottle of medication was dispensed every 2 weeks
[3]Global assessments by clinic staff and patient/ patient's guardian

6.7. Endpoints

The primary endpoint was a safety assessment, as described below. Secondary endpoints included both safety and efficacy evaluations.

6.7.1. Primary endpoint (Volume 1.1, page 380)

The primary endpoint was patient incidence of nasal mucosa adverse events (AEs) based on nasal examination performed by the physician. Changes normally associated with allergic rhinitis (AR) such as rhinorrhea, itchy nose, sneezing not associated with drug administration, or nasal congestion) were excluded.

6.7.2. Secondary endpoints (Volume 1.1, page 381)

Secondary endpoints were as follows:

6.7.2.1. Other safety endpoints

- Patient incidence of AEs
- Serious AEs (SAEs)
- Changes in physical exam from baseline to end of study
- Changes in vital signs (VS) from baseline to end of study

ECGs or laboratory studies were not performed. Patients and patients' guardians were prompted to report AEs at each clinic visit. Clinic staff prompted the report of AEs by asking the question "Since your last clinic visit have you had any health problems?"

6.7.2.2. Efficacy endpoints

Efficacy endpoints included:

- Changes in patient global assessment of rhinitis
- Changes in investigator global assessment of rhinitis

6.8. Statistical analysis

This study was primarily a safety study. Statistical analysis was performed for safety endpoints. Efficacy endpoints were described in a descriptive fashion.

6.8.1. Analysis of data (Volume 1.1, page 395-397)

Patient accountability and baseline conditions including demographics, medical histories, and signs and symptoms of AR were tabulated.

The primary population of interest for safety included all patients who took at least one dose of study medication. Adverse events (AEs) were coded using COSTART terminology. AEs were summarized by severity and relationship to study medication. AEs were summarized by race, gender, and age class. AEs and SAEs causing study withdrawal were tabulated.

The proportions of patients with clinically relevant changes in VS were presented at the initial visit and at each subsequent visit. Abnormal was defined as a 20% change from baseline.

Subgroup analyses of safety endpoints were conducted based on study drug usage and age categories. Study drug usage was categorized as less than adequate (< 2 doses/day), adequate (2-6 doses/day), and greater than adequate (> 6 doses/day). Drug usage was calculated as average doses per day based on changes in bottle weight. Patient ages were categorized as ≥ 2 to ≤ 3 years and > 3 to < 6 years.

Investigator and patients global assessment of AR was recorded and tabulated. In addition, patients' overall impressions of nasal allergy symptom relief and overall impression of the study medication were recorded and tabulated.

6.8.2. Randomization

Patients were randomized to receive either NasalCrom or placebo in the ratio of 1:1. Randomization was performed at the baseline visit.

6.8.3. Power analysis

No formal power analysis was performed since this study was primarily a safety and tolerance study. The sponsor, the Division of Pulmonary and Allergy Drug Products, and the Division of Over-The-Counter Drug Products agreed that recruitment of a minimum of 200 patients, 100 per treatment group, would be required to meet the primary objective of the study (Volume 1.1, page 397).

6.8.4. Assessment of rhinitis severity

The clinic staff and patients (or patients' guardians) globally assessed the severity of rhinitis. The 5-point scale used for assessment of intensity is displayed in Table 3. Clinic staff and patients (or patient's guardians) used the same severity scale.

Table 3. Scale for assessment of rhinitis severity by clinic staff and patients.(Volume 1.1, page 392)

Severity of rhinitis	Severity score
None	0
Mild	1
Moderate	2
Moderately severe	3
Severe	4

6.8.5. Drug product and placebo

Pharmacia & Upjohn supplied cromolyn sodium (NasalCrom) and placebo (cromolyn sodium vehicle) to all sites. Active drug and placebo were packaged in identical 26 ml bottles. Batch numbers used were (Volume 1.1, page 30):

- NasalCrom PB9702
- Placebo 38379, 38380

Patients were instructed to use their study medication at the dose of one spray in each nostril 3-4 times a day (every 4-6 hours), up to 6 times a day (Volume 1.1, page 389).

6.8.6. Assessment of patient compliance (Volume 1.1, page 391)

The patient or patients' guardian was asked at each visit if the study medication had been administered as directed. Compliance with medication use was determined by the difference between the weight of medication dispensed and the weight of medication returned. Weights were measured to the nearest [redacted]

6.9. Results

6.9.1. Disposition of patients

Enrollment in the study is displayed in Table 4. A minimum of 200 patients (100 per treatment group) were to be recruited to allow for 100 completing patients (50 in each group). Twenty of the completing patients (10 in each group) were to be ≥ 2 to < 3 years of age. Enrollment was kept open after recruitment of 200 patients because there was an insufficient

number of patients ≥ 2 to < 3 years of age. This resulted in a larger sample size than the sponsor originally had planned.

Table 4. Patient enrollment. (Volume 1, page 40)

Enrollment	NasalCrom		Placebo	
Proposed Enrollment				
2 to < 3 years of age	10		10	
Total Proposed Enrollment (Completed)	100	(50)	100	(50)
Actual Enrollment				
2 to < 3 years of age (Completed)	37	(30)	35	(21)
Total Enrolled (Completed)	152	(131)	156	(123)

A total of 21 (14%) of patients in the NasalCrom group and 33 (21%) of patients in the placebo group discontinued the study prematurely. Withdrawals are displayed in Table 5.

Table 5. Withdrawals (Volume 1.1, page 41)

	Treatment			
	NasalCrom		Placebo	
	N	%	N	%
Number of patients enrolled	152	100	156	100
Withdrawals				
Lack of efficacy	0	0	3	1.9
Serious AE	1	0.7	0	0
Non-serious AE	1	0.7	2	1.3
Ineligible	2	1.3	2	1.3
Noncompliance	15	9.9	20	12.8
Personal request	1	0.7	4	2.6
Lost to follow-up	1	0.7	1	0.6
Other	0	0	1	0.6
Total withdrawals	21	13.8	33	21.2
≥ 2 to< 3 years of age	7	33.3	14	42.4
3 to 6 years of age	14	66.7	19	57.6
Total completed	131	86.2	123	78.8
≥ 2 - < 3 years of age	30	22.9	21	17.1
3 - 6 years of age	101	77.1	102	82.9

A similar percentage of patients completed the study in both treatment groups, with 86.2% (131/152) completing the study in the NasalCrom group and 78.8% (123/156) completing the study in the placebo group. Withdrawals were more common in patients ≥ 2 to < 3 years of age than in patients 3 to 6 years of age in both NasalCrom-treated and the placebo-treated groups. There were fewer withdrawals in NasalCrom-treated patients (13.8%, 21/152) than in placebo-treated patients (21.2%, 33/156). In addition, there were fewer withdrawals in NasalCrom-treated patients than in placebo treated patients for the following reasons: lack of efficacy (0%, 0/152 vs. 1.9%, 3/156), noncompliance (9.9%, 15/152 vs. 12.8%, 20/156), and personal request (0.7%, 1/152 vs. 2.6%, 4/156). These withdrawal data provide support of efficacy in the NasalCrom treatment group. Withdrawals due to adverse events are discussed in section **6.9.7.5.** of this review.

6.9.2. Patient demographics

There were approximately 20% more male patients than female patients. Treatment groups were otherwise similar. There were no statistically different differences between treatment groups. The population studied was predominantly white. The age distribution

of patients was similar for both treatment groups and met that which was specified in the protocol. These data are presented in Table 6.

Table 6. Demographics (Volume 1.1, page 43)

Treatment				
	NasalCrom		Placebo	
	N	%	N	%
Number of patients	152	100	156	100
Gender				
Female	73	48.0	61	39.1
Male	79	52.0	95	60.9
Race				
White	94	61.8	110	70.5
Hispanic	34	22.4	28	17.9
Black	20	13.2	15	9.6
Asian	1	0.7	2	1.3
Other	3	2.0	1	0.6
Age in years				
≥2 to < 3	37	24.3	35	22.4
≥ 3 to < 6	115	75.7	121	77.6

6.9.3. Protocol deviations

Protocol deviations were frequent, and occurred at similar rates in both cromolyn-treated and placebo-treated groups. There were 49 protocol deviations in the cromolyn-treated group and there were 57 protocol deviations in the placebo-treated group. Protocol deviations due to use of excluded medications were similar in both treatment groups with 21 in the cromolyn-treated group and 26 in the placebo-treated group. Remaining protocol deviations were largely due to early or late study assessments. Protocol deviations were not likely to affect study results, as they occurred in both groups at similar frequencies (Volume 1.1, page 41).

6.9.4. Compliance

Ninety-six percent (96%) of both NasalCrom-treated patients and placebo-treated patients took > 2 doses per day. Only 38.8% of NasalCrom-treated patients took the study medication > 3 doses per day, and 42.3% of placebo-treated patients took the study medication > 3 doses per day. Compliance was similar in different dosage groups in NasalCrom-treated patients and in placebo-treated patients. These data are displayed in Table 7. The sponsor found compliance to be adequate, as 99.3% of patients had ≥ 2 doses per day (Volume 1.1, page 396). This reviewer concurs with the sponsor's opinion.

Table 7. Patient compliance with therapy (Volume 1, page 100)

	Treatment									
	NasalCrom					Placebo				
	N	%	n[1]	Mean[2]		N	%	n[1]	Mean[2]	SD
Number of patients	152	100				156	100			
Doses taken/day										
0 to <2 doses/day	1	0.7	1	1.01	0	1	0.6	0	0	0
2 - 3 doses/day	91	59.9	83	0.77	0.27	86	55.1	72	0.76	0.21
>3 - 4 doses/day	55	36.2	49	0.90	0.23	64	41.0	61	0.91	0.32
> 4 - 5 doses/day	4	2.6	3	1.33	0.37	2	1.3	2	1.17	0.45
> 5 - 6 doses/day	0	0	0	0	0	0	0	0	0	0
Unknown[3]	1	0.7	1	0.78	0	3	1.9	0	0	0

[1]n represents bottles returned and weighed
[2]Mean change (g) in study medication, calculated by the formula (dispensed weight - returned weight)/days used
[3]Duration of treatment unavailable for calculation of average dose

6.9.5. Rescue medication use

One third of all patients used rescue medication during the study. The use of rescue medication was similar between treatment groups at Weeks 1 and 2, but increased somewhat in placebo patients at Weeks 3 and 4. This is displayed in Table 8. An increase in rescue medication use in placebo-treated patients may indicate that these patients had more severe disease than the NasalCrom-treated patients. Alternatively, the increase in rescue medication use in placebo-treated patients may be an indication of efficacy in the NasalCrom-treated patients.

Table 8. Rescue medication use (Volume 1, page 102)

	Treatment					
Study Week	NasalCrom		Placebo		Total	
	N	%	N	%	N	%
Week 1	46	31.9	51	34.2	97	33.1
Week 2	43	31.4	42	30.0	85	30.7
Week 3	39	27.5	53	37.6	92	32.5
Week 4	38	28.1	45	33.8	83	31.0

6.9.6. Efficacy endpoint outcomes

This study was intended to be a primarily safety study. The sponsor tabulated and presented efficacy data in a descriptive form and did not patient this data to inferential statistical analysis.

There were small differences favoring NasalCrom over placebo in each of the efficacy endpoints.

6.9.6.1. Investigator's global assessment rhinitis (Volume 1.1, pages 45-46)

Patients were combined into two groups for comparison of the investigator's global assessment of rhinitis—those with no or mild symptoms, and those with moderate, moderately severe, or severe symptoms. The proportions of patients in NasalCrom and placebo treatment groups with no or mild symptoms and those with moderate, moderately severe, or severe symptoms were similar at baseline. There were 13% fewer patients in

the NasalCrom treatment group with moderate, moderately severe, or severe symptoms at Week 4 than in the placebo group. These data are presented in Table 9.

Table 9. Investigator's global assessment of rhinitis severity

Global assessment	Baseline				Week 4			
	NasalCrom, N = 152		Placebo, N = 156		NasalCrom, N = 137		Placebo, N = 136	
	N	%	N	%	N	%	N	%
None/Mild	35	23.0	35	22.4	87	63.5	73	53.7
Moderate/ Moderately severe/ Severe	117	77.0	121	77.6	50	36.5	63	46.3

Mean intensity scores in NasalCrom and placebo treatment groups were comparable at baseline. There was a slightly greater decrease in mean intensity score at Week 4 in NasalCrom-treated patients than in placebo-treated patients. The difference favoring NasalCrom-treated patients was 0.14 points on a 5-point scale. These data are displayed in Table 10.

Table 10. Investigator global assessment of rhinitis, mean intensity score

Mean intensity score						
	NasalCrom			Placebo		
	Mean	SD	N	Mean	SD	N
Baseline	2.05	0.74	152	20.4	0.72	156
Week 4	1.28	0.84	137	1.46	0.80	136
Difference	-0.76	0.96		-0.62	0.95	

6.9.6.2. Patient assessment of nasal symptoms (Volume 1, pages 46-48)

Patients were combined into two groups for comparison of patient global assessment of nasal symptoms—those with none or mild symptoms, and those with moderate, moderately severe or severe symptoms. The proportions of patients in NasalCrom and placebo treatment groups with none or mild symptoms and moderate, moderately severe, or severe symptoms were similar at baseline. There were 11.3% fewer patients in the NasalCrom treatment group with moderate, moderately severe, or severe symptoms at Week 4 than in the placebo group. These data are presented in Table 11.

Table 11. Patients' global assessment of allergy symptom severity

Global assessment	Baseline				Week 4			
	NasalCrom, N = 152		Placebo, N = 156		NasalCrom, N = 137		Placebo, N = 136	
	N	%	N	%	N	%	N	%
None/Mild	23	15.1	23	14.7	92	67.1	76	55.9
Moderate/ Moderately severe/ Severe	129	84.8	133	85.3	45	32.9	60	44.2

Mean intensity scores in NasalCrom and placebo treatment groups for the patients' global assessment of symptoms were comparable at baseline. There was a slightly greater decrease in mean intensity score at Week 4 in NasalCrom-treated patients than in placebo-treated patients. The difference favoring NasalCrom-treated patients was 0.11 points on a 5-point scale. These data are displayed in Table 12.

Table 12. Patients' global assessment of symptoms, mean intensity score (Volume 1.1, pages 95-96)

Mean intensity score						
	NasalCrom			Placebo		
	Mean	SD	N	Mean	SD	N
Baseline	2.18	.73	152	2.26	0.78	156
Week 4	1.25	0.86	137	1.47	0.89	136
Difference	-0.93	0.97		-0.82	1.06	

A greater proportion of patients reported complete or marked relief of nasal allergy symptoms in the NasalCrom treatment group than in the placebo treatment group at Week 4 (47.0% vs. 36.8% respectively, Volume 1.1, page 48).

A higher proportion of NasalCrom-treated patients reported their overall impression of the study medication to be excellent or very good than did placebo-treated patients at Week 4 (44.8% vs. 34.6% respectively, Volume 1.1, page 48).

6.9.7. Safety endpoint outcomes

6.9.7.1. Extent of drug exposure

The duration of treatment was calculated as last dose day minus first dose day. The majority of patients in both treatment groups received 22-36 days of treatment. Eighty-nine percent (89%, 136/152) of the NasalCrom treatment group and 87% (136/156) of the placebo treatment group received >3 weeks of treatment. There was a slightly higher proportion of placebo-treated patients that had >15 days of treatment with 7.7% (12/156) of patients in the placebo-treated group compared with 5.2% (8/152) in the NasalCrom treated-group (Volume 1.1, pages 50, 99).

6.9.7.2. Nasal Examination

The primary endpoint for this study was patient incidence of nasal mucosa AEs based on nasal examination performed by the physician. Abnormalities in the following nasal examination findings were tabulated in both treatment groups and were compared for each visit:

- Septal deviation
- Septal hemorrhage
- Septal erosion
- Nasal polyps
- Mucosal color
- Mucosal secretions
- Mucosal edema
- Turbinate size
- Turbinate color

There appeared to be slightly lower rates of abnormal mucosa color and abnormal turbinate color in the NasalCrom treatment group compared with the placebo treatment group. The lower rates of abnormal mucosa color and abnormal turbinate color tended to be more pronounced at the later visits. These data provide support of efficacy in the NasalCrom treatment group. These data are displayed in Table 13. There were no

differences in any of the other abnormalities between NasalCrom and placebo treatment groups at any of the visits.

Table 13. Nasal mucosa abnormalities on examination by physician (Volume 1.1, pages 103-121)

		Treatment					
		NasalCrom			Placebo		
Abnormal finding present	Visit	n	N	%	n	N	%
Mucosa color	Baseline	124	152	81.6	125	156	80.1
	Week 1	108	148	73.0	118	152	77.6
	Week 2	101	142	71.6	111	144	77.1
	Week 4	99	137	72.3	106	137	77.9
Turbinate color	Baseline	127	152	83.6	136	156	87.2
	Week 1	110	148	74.3	124	152	82.1
	Week 2	102	142	71.8	118	144	81.9
	Week 4	102	137	74.5	104	137	75.9

6.9.7.3. Adverse events

AEs were examined for all patients. Subgroup analysis was performed for gender, for children ≥ 2 to < 3 years of age and children 3 to < 6 years of age, and for race.

6.9.7.3.1. Adverse events, all patients

AEs were fairly common, but occurred at similar rates in NasalCrom-treated patients and placebo-treated patients. There were 308 patients included in the safety population of which 152 were in the NasalCrom-treated group and 156 were in the placebo-treated group. A total of 86 patients (57%) in the NasalCrom treatment group developed adverse events. A total of 86 patients (55%) developed AEs in the placebo treatment group (Volume 1.1, page 55).

Table 14. Adverse events occurring more frequently in NasalCrom-treated patients than placebo patients at a rate ≥ 2.0% (Volume 1.1, page 131-134)

COSTART Term	Treatment				
	NasalCrom		Placebo		
	N	%	N	%	P-Value[1]
Epistaxis	12	7.9	10	6.4	0.773
Headache	9	5.9	4	2.6	0.143
Otitis media	9	5.9	8	5.1	0.761
Sneezing[2]	8	5.3	19	12.2	0.009
Pharyngitis	7	4.6	5	3.2	0.376
Infection viral NOS	6	3.9	3	1.9	0.292
Diarrhea	4	2.6	1	0.6	0.167
Sinusitis	4	2.6	2	1.3	0.392
Asthma	3	2.0	0	0.0	0.023
Gastroenteritis	3	2.0	1	0.6	0.302
Hyperkinesia	3	2.0	1	0.6	0.302
Rhinitis	3	2.0	2	1.3	0.396
Rash	3	2.0	2	1.3	0.244
Wheezing[3]	1	0.7	2	1.3	0.577

[1]P-value based on chi-square test.
[2]Occurring less frequently in NasalCrom-treated patients, but included in table because of a large difference in rates.
[3]Rate < 2.0% in NasalCrom-treated patients, but included in table for analysis with asthma adverse events.

AEs occurring more frequently in NasalCrom-treated patients than in placebo-treated patients and at a rate ≥2.0% are displayed in Table 14. Absolute numbers of AEs were

low. As a result, a change of one or two patients in each category could change the results substantially. Relative frequencies of AEs should be interpreted cautiously in this study because of this limitation.

Headache, viral infection, diarrhea, sinusitis, gastroenteritis, and hyperkinesia were more common in NasalCrom-treated patients than in placebo treated patients. Asthma was more common in NasalCrom-treated patients compared with placebo-treated patients, but wheezing was more common in placebo-treated patients than in NasalCrom-treated patients. If the asthma category is combined with the wheezing category, rates remain higher in the NasalCrom treatment group (4/152, or 2.6%) compared with the placebo-treatment group (2/156 or 1.3%). Epistaxis, otitis media, pharyngitis, rhinitis, and rash occurred at slightly higher rates in NasalCrom-treated patients compared with placebo-treated patients. Sneezing was substantially less common in NasalCrom-treated patients than in placebo-treated patients. This may represent a treatment effect of NasalCrom.

Most AEs in NasalCrom-treated patients were mild (46.5%, 40/152) or moderate (46.5%, 40/152). There were 6 severe AEs in NasalCrom-treated patients. These included one patient with fever, one patient with cough, one patient with sneezing, one patient with asthma, one patient with rhinitis, one patient with dehydration, and one patient with leg cramps (Volume 1.1, pages 135-137). Patient 349 was a 2 year old white male with moderately severe allergy symptoms who developed a paroxysm of sneezing immediately after using NasalCrom spray. The sponsor considered this severe AE to be a result of the medication. This patient also had a URI and required an antibiotic, and the study medication was discontinued (Volume 1.3, page 1029, Volume 1.4, page 1614).

6.9.7.3.2. Adverse events, subgroup analyses

Subgroup analysis of AEs was performed by gender, by patients < 3 years of age vs. 3 to < 6 years of age, and by race. Subgroup analysis was hampered by the low absolute numbers of AEs.

A similar incidence of AEs was noted in NasalCrom-treated patients in the subgroup analysis of AEs by gender. The incidence of AEs in male NasalCrom-treated patients was 58% (46/79) and the incidence of AEs in female NasalCrom-treated patients was 55% (40/73) (Volume 1.1, page 57).

Subgroup analysis of AEs was performed in patients 2 to < 3 years of age and in patients 3 to < 6 years of age. Patients with headache were represented at a higher rate in NasalCrom-treated patients in the 3 to < 6 year age group (7.0%, 8/115) than in the 2 to < 3 year age group (2.7%, 1/37) (Volume 1.1, pages 276, 279). There were no other conclusions about differences between these groups that could not be attributed to the low number of AEs.

Subgroup analysis of AEs was performed in patients by race. Overall incidence of AEs in NasalCrom treated patients were slightly higher in White patients (62.8%, 59/94) than in Hispanic patients (50.0%, 17/34) or Black patients (40.0%, 8/20). The only NasalCrom-

treated Asian/Pacific Islander had an AE, and 1 NasalCrom-treated patient of 3 American Indian or Mixed race had an AE. No conclusions could be drawn about differences between these groups that could not be attributed to the low number of AEs (Volume 1.1, pages 283-293).

6.9.7.4. SAEs and deaths

There were 2 SAEs in NasalCrom-treated patients. There were no SAEs in placebo-treated patients.

Patient 127 was 5 year-old White male treated with NasalCrom who developed a fever of 105° F, pharyngitis, and dehydration that required hospitalization, iv fluid therapy, and cefuroxime axetil. This SAE occurred 7 days after starting study drug. The patient was hospitalized for one day. NasalCrom was discontinued. The patient recovered. This reviewer considers the SAE not to be related to study medication (Volume 1.1, page 58, Volume 1.3, page 1023, Volume 1.4, page 1620-1624).

Patient 148 was a 4 year-old Hispanic male treated with NasalCrom who developed a severe asthma exacerbation that required hospitalization 2 days after starting study drug. The patient had stable asthma at admission to the study. NasalCrom was discontinued on the day of admission to the hospital. The asthma exacerbation resolved with treatment with inhaled albuterol and oral prednisolone. The patient recovered. The investigator attributed this SAE a change in the weather. This reviewer considers the SAE not to be related to study medication (Volume 1.1, page 58-59, Volume 3, page 1024, Volume 1.4, pages 1625-1628).

There were no deaths in the study (Volume 1.1, page 58).

6.9.7.5. Withdrawals due to adverse events

(Volume 1.1, pages 59 and 150, Volume 1.3, page 1024)

There were 12 patients in the NasalCrom treated group that developed AEs and subsequently withdrew from the study. One of these twelve patients withdrew from the study due to an AE that was considered to be related to NasalCrom.

Patient 137 was a 5 year-old white male who developed stinging in the nostrils and left eye pain considered to be related to use of NasalCrom. The patient also had a URI. NasalCrom was discontinued. The patient recovered with no residual effects.

Withdrawals due to AEs are displayed in Table 15.

Table 15. Withdrawals due to AEs in NasalCrom-treated patients (Volume 1.1, page 149-152, Volume 1.3, pages 1025-1031).

Patient Number	AE	Age	Gender	Race	Outcome	Related
107	Otitis media URI	3	Female	Hispanic	Recovered Recovered	No No
108	Otitis media	2	Female	Hispanic	Recovered	No
113	Cough Sinusitis	5	Male	Hispanic	Continues Continues	No No
127	Headache Nausea Pharyngitis Dehydration Fever	5	Male	White	Recovered Recovered Recovered Recovered Recovered	No No No No No
137	Localized pain (stinging in nostrils) Eye pain URI	5	Male	White	Recovered Recovered Recovered	Yes Yes No
148	Asthma (exacerbation)	4	Male	Hispanic	Recovered	No
187	Otitis media Sinusitis	3	Male	White	Recovered Recovered	No No
324	Wheezing	2	Male	White	Recovered	No
348	Otitis media	2	Female	White	Recovered	No
362	URI	4	Female	White	Continues	No
416	Pharyngitis	4	Male	Black	Recovered	No
461	Pharyngitis	3	Male	White	Continues	No

6.9.7.6. Vital Signs

Differences in VS were calculated from measurements taken at baseline and measurements taken at the end of the study. Clinically meaningful changes in VS were defined as differences ≥ 20% from baseline. There were no differences in clinically meaningful changes in VS between treatment groups (Volume 1.1, pages 60, 155). There was a ≥ 20% increase in respiratory rate in both NasalCrom (22.0%, 33/150) and placebo-treated patients (21.6%, 33/153). The significance of this change in both NasalCrom and placebo treatment groups is unclear, particularly in children in the age groups who may have changes in VS from crying or anxiety about a doctor visit.

6.9.7.7. Physical Examination

Changes in physical examination in NasalCrom and placebo-treated patients were compared. A slightly higher proportion of NasalCrom-treated patients showed a change from abnormal to normal in the ears/eyes/nose/throat/mouth exam (14.6%, 22/151) than placebo-treated patients (10.4%, 16/154). A slightly higher proportion of NasalCrom-treated patients showed a change from normal to abnormal in ears/eyes/nose/throat/mouth exam (12.6%, 19/151) than placebo-treated patients (8.4%, 13/154). A higher proportion of NasalCrom-treated patients showed change from abnormal to normal in skin (5.3%, 8/151) than placebo-treated patients (1.3%, 2/154).

6.9.7.8. ECGs and Laboratory Studies

ECGs were not performed in this study. There were no laboratory evaluations performed in this study.

6.10. Conclusion from study results

This study primarily evaluates the safety of NasalCrom one spray each nostril 3-4 times a day in children ≥ 2 to < 6 years of age. The study secondarily evaluated the efficacy of the drug product. The results show that the overall frequency of AEs was fairly high, but the AEs were mild and local in nature. There were no deaths in this study. There were 2 SAEs in the study in NasalCrom-treated patients, and both were not likely to be drug-related. The study described small differences favoring NasalCrom over placebo in rescue medication use, investigator-assessed rhinitis severity, and patient-assessed rhinitis severity. Differences favoring NasalCrom over placebo in investigator-assesssed and patient-assessed rhinitis severity were 0.14 and 0.11 points on a 5-point scale, respectively. Placebo was not favored in any efficacy endpoint. This study supports the safety and the efficacy of NasalCrom in children ≥ 2 to < 6 years of age.

7. REVIEW OF LITERATURE SURVEY

The sponsor submitted a survey of the use of cromolyn in the pediatric population. The survey covered 25 articles and abstracts from the medical literature covering the period from 1972 to 1998. The literature survey did not specify the database or search strategy that provided the list of references. The sponsor's survey focused more on efficacy than on safety in the pediatric population. The survey focused mainly on the use of cromolyn for treatment of allergic rhinitis, although a few references referred to use of cromolyn for treatment of asthma.

Overall, AEs reported in the literature surveyed were generally mild and local, but rare serious AEs, such as severe bronchospasm and anaphylaxis, were occasionally reported (Volume 2.1, pages 4-9).

8. REVIEW OF GLOBAL DRUG SURVEILLANCE REPORTS

The sponsor submitted reports from Pharmacia and Upjohn's spontaneous medical event reporting system for NasalCrom nasal solution. The time period covered by these reports was 1/1/97 to 10/3/99. A report was provided listing events occurring in children < 12 years of age. A second report listed events occurring in patients of all ages. The vast majority of these reports are from the U.S.

There were 4326 events reported in 2797 patients in the listing covering all age groups. Most AEs were local in character. Two more serious cases of interest are described below.

One patient, Case 002378, had anaphylactic shock. The line listing indicated the patient had a positive dechallenge and a positive rechallenge. The patient was a 49 year-old woman with multiple sclerosis who developed heart palpitations, sweaty palms, lightheadedness, and anaphylactic shock. The duration of treatment with NasalCrom was not reported. The patient was reported as having full recovery. No hospitalization was required (Volume 2.2, pages 254, 426).

Case 000154 had the induction of a life-threatening asthmatic reaction. The line listing indicated the patient had a positive dechallenge and a positive rechallenge. He was a 30 year-old male who is reported as having taken NasalCrom for an unknown duration. The patient had been diagnosed with severe persistent asthma, and was allergic to timothy grass and Japanese cedar. He was also taking sustained-release theophylline, a salbutamol inhaler, an inhaled anticholinergic medication, and inhaled beclomethasone. Hospitalization was required, and the patient made a full recovery. There are 5 other patients, Cases 00156, 00157, 00158, 00159, 00160, who also were reported as having induction of life-threatening asthmatic reactions. All were adults ranging from 39 years to 70 years of age. Four of these patients were females and one of these patients was a male. The duration of treatment ranged from 3 days to 72 months. All were cases described in the medical literature (Volume 2.2, pages 235, 438).

Events reported in the summary for children < 12 years of age were similar to those in all ages. AEs in this age group were also mild and local in nature (Volume 2.1, pages 196-215).

9. INTERATED SUMMARY OF SAFETY

AEs were fairly common in the clinical study submitted with this supplement. Mild and local events such epistaxis, otitis media, pharyngitis, rhinitis occurred in both cromolyn and placebo treatment groups. The literature survey noted similar mild and local AEs, as well as rare SAEs such as bronchospasm and anaphylaxis. The drug surveillance reports also describe one case of induction of near-death asthmatic reaction and one case of anaphylaxis. Both of these cases had a positive dechallenge and rechallenge. This reviewer believes that no change in the OTC indication or labeling is warranted. Exposure to the drug has been extensive, and both current and proposed labeling include a warning that the product be discontinued if new symptoms appear. In addition, the label advises that the patient seek medical attention if new symptoms appear or if wheezing is present.

10. EXECUTIVE SUMMARY AND RECOMMENDATION

The sponsor has submitted this pediatric supplement in support of the use of NasalCrom nasal spray in children ≥ 2 to < 6 years of age. The proposed indication is for prevention and relief of nasal symptoms of hay fever and other nasal allergies. The proposed dose is one spray each nostril 3-4 times a day (every 4-6 hours), up to 6 times a day. The sponsor submitted the results of one study, M\3235\0002, in support of this indication. This study was primarily a safety study that secondarily evaluated efficacy in a descriptive fashion.

M\3235\0002 supports the safety of the product in this age group. AEs occurred at a similar frequency in NasalCrom-treated patients (57%) and in placebo-treated patients (55%). AEs were mild and local in character. There were no deaths in this study. There were 2 SAEs in the study in NasalCrom-treated patients, and both were not likely to be drug-related.

M\3235\0002 supports the efficacy of the product in this age group. The sponsor tabulated and presented efficacy data in a descriptive fashion. There were small differences favoring NasalCrom over placebo in each of the efficacy endpoints. These efficacy endpoints were rescue medication use, investigator-assessed rhinitis severity, and patient-assessed rhinitis severity. Differences favoring NasalCrom over placebo in investigator-assesssed and patient-assessed rhinitis severity were 0.14 and 0.11 points on a 5-point scale, respectively. Placebo was not favored in any efficacy endpoint.

The sponsor also submitted a literature review and a global drug surveillance report which support the safety of this product.

It is helpful to compare the magnitude of the effect sizes seen in M\3235\0002 with the two pivotal studies submitted with the application for the original approval for OTC use of NasalCrom. These studies were Study 94-433 and Study 1120-2116. Each of these studies used a similar 5-point scale for assessment of rhinitis severity. It should be noted that efficacy endpoints were measured after one week in Studies 94-433 and 1120-2116 and after four weeks in the study submitted with this application. Even so, a general comparison of the magnitude of change in these studies is helpful. An effect size comparable with that in M\3235\0002 were found in pivotal Study 94-433 and Study 1120-2116. These data are displayed in Table 16. This general comparison further supports the efficacy of the drug in this application.

Table 16. Comparison of effect sizes of the original NasalCrom NDA[1] and this pediatric efficacy supplement, mean changes in nasal symptom scores between baseline and endpoint.

Study	Endpoint	Time of endpoint assessment	Effect size favoring NasalCrom, points	Scale size, points
M\3235\0002	Patient global assessment of rhinitis	Week 4	0.11	5
94-433[2]	Patient assessment of rhinitis	Day 7	0.14	5
M\3235\0002	Investigator global assessment of rhinitis	Week 4	0.14	5
1120-2116[3]	Physician assessment of rhinitis	Day 7	0.13	5

[1]Source: (Dr. Otulana's Medical Officer review of NDA 20-463, 9/5/96, pages 25, 34)
[2]Study duration was 2 weeks. Dose was 1 spray each nostril every 4 to 6 hours, not to exceed 6 times daily.
[3]Study duration was 4 weeks. Dose was 1 spray each nostril 4 times daily.

This pediatric efficacy supplement is recommended for approval under the Pediatric Use provision, 21 CFR 201.57(f)(9)(iv). The pathophysiology and course of allergic rhinitis and the beneficial and adverse effects of the drug are similar in children 2 to ≤ 6 years of age and adults. This drug is topically active, systemic absorption is low, and pharmacokinetic data would not be useful. NasalCrom has previously been approved for OTC use in adults and in children ≥ 6 to <12 years of age on the basis of adequate and well controlled studies. The study submitted in application, M\3235\0002, establishes the proper dose in children ages ≥ 2 to < 6 years of age, and provides additional support of the safety and efficacy of this product in this age group. Extrapolation of efficacy from

the data in patients ≥ 6 years of age is possible. This reviewer recommends approval of this application on the basis of the Pediatric Use provision, 21 CFR 201.57(f)(9)(iv).

Reviewed by:

/S/ 4/13/00

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Badrul A. Chowdhury, M.D., Ph.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: HFD-560/Division File
HFD-570/Division File
HFD-560/Hu/Medical Officer
HFD-570/Lee/Medical Officer
HFD-570/Chowdhury/Team Leader
HFD-560/Katz/Deputy Division Director
HFD-570/Meyer/Division Director
HFD-570/Jafari/Project Manager
HFD-560/Merritt/Project Manager