CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-463/S-002

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/PLA/PMA # 20-463 Supplement # S-002 Circle one: SE1 SE2 SE3 SE4 (SE5) SE6

HFD-560____ Trade and generic names/dosage form: NasalCrom Nasal Solution (cromolyn sodium nasal solution) Action: (AP) AE NA

Applicant Pharmacia Consumer Healthcare Therapeutic Class Nasal Allergy Symptom Controller

Indication(s) previously approved nasal spray for use in persons 6 years of age and above

Pediatric information in labeling of approved indication(s) is (adequate) ✓ inadequate __

Proposed indication in this application nasal spray for use in children 2 years to less than 6 years

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? _X__ Yes (Continue with questions) ___ No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___Neonates (Birth-1month) ___Infants (1month-2yrs) _X__Children (2-12yrs) ___Adolescents(12-16yrs)

_X__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- __ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __ c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes XX No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Team Leader/Project Manager (e.g., medical review, medical officer, team leader).

/S/ Project Manager 3/13/01
Signature of Preparer and Title Date

cc: Archival NDA/PLA/PMA # 20-463-
HFD-560____/Div File
NDA/PLA Action Package
HFD-104/Peds/T.Crescenzi

(revised 3/6/00)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, TERRIE CRESCENZI, HFD-104 (CRESCENZIT)

EXCLUSIVITY SUMMARY for NDA # 20-463 SUPPL # 002

Trade Name NasalCrom Nasal Solution
Generic Name cromolyn sodium nasal solution
Applicant Name Pharmacia Consumer Healthcare **HFD-** 560
Approval Date to be determined

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /XX_/

   b) Is it an effectiveness supplement? YES /X/ NO

   If yes, what type(SE1, SE2, etc.)? SE5

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /___/ NO /_XX_/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /X/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /X/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /X/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/ _____ _____

Signature of Preparer Date

Title: _____

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA 20-463
HFD-560/Division File
HFD-570/R.Meyer/D.Hilfiker
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

Item 16: Debarment Certification

A Debarment Certificate for NasalCrom®Nasal Solution, NDA 20-463, is submitted on the page that follows.

DEBARMENT CERTIFICATION FOR NASALCROM Nasal Solution
NDA # 20-463

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Ed L. Patt

Ed L. Patt
Associate Director
Global Regulatory Affairs, CMC

10/22/99

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmacia & Upjohn Company	June 5, 2000
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
908-306-8259	908-306-8713
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
100 Route 206 North Peapack, NJ 07977	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-463

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
NasalCrom	Cromolyn Sodium Nasal Solution, USP

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* — CODE NAME *(If any)*

DOSAGE FORM: Solution	STRENGTHS: 4%	ROUTE OF ADMINISTRATION: Nasal Spray

(PROPOSED) INDICATION(S) FOR USE: Allergic Rhinitis

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ■ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ■ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Product information requested by FDA during the May 16, 2000 FDA teleconference

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ■ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ■ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmacia & Upjohn Company	October 27, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
908-306-8259	908-306-8713

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

100 Route 206 North
Peapack, NJ 07977

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State,ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-463

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
NasalCrom™	Cromolyn sodium nasal solution, USP

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	4%	Nasal Spray

(PROPOSED) INDICATION(S) FOR USE: Allergic Rhinitis

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
FDA requested information in support of 8/19/99 NDA Supplement regarding Pediatric Exclusivity Determination

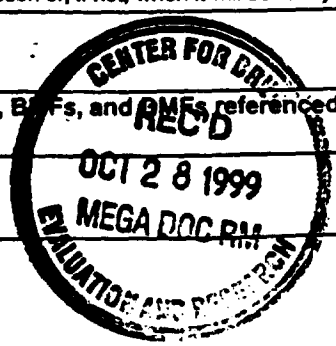
PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 2 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telepone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BLAs, and DMFs referenced in the current application)



EF

This application contains the following items: *(Check all that apply)*

X	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
X	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Toni Ann Dudor	Toni Ann Dudor, Senior Regulatory Manager	October 27, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
100 Route 206 North, Peapack, NJ 07977	(908) 306-8259

1643

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	SEE ATTACHED LIST	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Stefan Appelgren	Sr VP Finance & Bus Administration
FIRM/ORGANIZATION	
Pharmacia & Upjohn, Consumer Healthcare	
SIGNATURE	**DATE**
	August 17, 1999

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

NDA # 20-463/S-002; Amendment No. 8

Submission Date: 2/28/01
Review Date: 3/08/01
Reviewer: Cazemiro R. Martin

Applicant: Pharmacia & Upjohn Company
Consumer Healthcare

Applicant's Representative: Raymond E. Dann, Ph.D.
Director
Regulatory Affairs

Drug: NasalCrom Nasal Nasal Spray
Cromolyn sodium 5.2 mg per spray

Pharmacologic Category: Nasal Allergy Symptom Controller

Submitted:

Revised draft labeling for NasalCrom Nasal Solution:

- 13 mL and 26 mL Bottle (Full Labeling)
- 13 mL and 26 mL Carton (Full Labeling)
- Package Insert Text/Graphics common to both product sizes (13 mL and 26 mL)

Background:

In response to the approvable letter dated June 30, 2000 from the Agency to Pharmacia & Upjohn Company for its OTC NasalCrom Nasal Solution (NDA 20-463), the sponsor submitted revised labeling on November 22, 2000, which they further modified on December 14, 2000 (Amendments Nos. 6 and 7, respectively). On February 9, 2001, the Division of OTC Drug Product (HFD-560) sent a fax to the sponsor which included required and recommended changes to the sponsor's proposed labeling of its 13 mL and 26 mL package size NasalCrom Nasal Solution drug product and accompanying package insert common to both sizes.

Reviewer Comments:

This amended supplement includes revised draft labeling for the 13 mL and 26 mL package size NasalCrom Nasal Solution product and accompanying package insert common to both sizes. The sponsor indicates that the draft labeling incorporates all the labeling revisions required and recommended by the Agency (fax dated 2/9/01), including revised wording within the insert that adds special cautions regarding administration of the product to young children. The labeling is acceptable.

Recommendations:

Based on my review of the labeling submitted and concurrence by the Division of Pulmonary and Allergy Drug Products, I recommend that an approval letter can be sent to the sponsor requesting final printed labeling.

/S/

/S/ Cazemiro R. Martin 3/12/01

Team Leader: Marina Chang 3/12/01

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 20, 2000 JUN 22 2000

FROM: Claudia B. Karwoski, Pharm.D.
Postmarketing Safety Evaluator Team Leader
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director /S/ 6/22/00
Division of Drug Risk Evaluation I, HFD-430

TO: Charles Ganley, M.D., Director
Division of Over-The-Counter Drug Products, HFD-560

SUBJECT: OPDRA Postmarketing Safety Review (PID # D000280)
Drug: Cromolyn (Nasalcrom, NDAs 18-306, 20-463)
Reaction: Review of Selected Adverse Events

EXECUTIVE SUMMARY

This document summarizes an evaluation of selected postmarketing adverse reactions associated with Nasalcrom to determine if there is any serious safety issues of concern. An overview of all adverse event reports for Nasalcrom indicates that 83% were reported by consumers and there was a sharp increase in adverse event reporting after the product became available over-the-counter (OTC). Although there were a large number of reports with a reported serious outcome, only 37 were submitted as 15 day or expedited reports, which probably indicates that many of the events were either not serious or they were labeled events.

We evaluated 19 expedited (15-day) reports that were considered possibly related to the use of Nasalcrom. The outcomes include hospitalization (11), required intervention with medication (1), emergency room treatment (1), recovered with no intervention (1), and disability (1). The outcomes of four reports are unknown. There were four seizure cases. Three were new onset, one occurred in an individual with a history of epilepsy. Two involved pediatric patients. Because of the diversity of the events and the small number of reports for each of these events, they do not appear to represent a clear safety signal.

We evaluated 91 cases of hypersensitivity or allergic reactions that were possibly related to Nasalcrom. The events ranged in severity from mild urticaria to laryngeal edema and anaphylaxis. The outcomes include 12 hospitalizations, four requiring emergency room treatment, one reported as life-threatening, and 18 that required treatment with a medication.

We evaluated 67 cases of difficulty breathing in association with Nasalcrom use. The types of reactions reported include asthma, bronchospasm, chest tightness, dyspnea, nasal congestion, rhinitis, shortness of breath, and wheezing. Approximately 25% of these cases were possibly associated with nasal congestion or rhinitis symptoms. Some of these cases appeared to be hypersensitivity type reactions. The outcomes include five patients that required hospitalization, five requiring emergency room treatment, and four that required treatment with medications.

We evaluated 54 cardiac cases including tachycardia (18), palpitations (30), and miscellaneous rhythm disorders (6). Although, most of the cases did not appear to result in a serious outcome, there were two patients who required emergency room treatment and three that required hospitalization. Most of these reports were consumer- reported and did not provide sufficient detail or medical substantiation of the event.

We evaluated 89 cases involving eye disorders temporally related to the use of Nasalcrom. Most disorders were minor. There were three reports that appeared to be serious events including corneal erosion, extraocular muscle paralysis, and glaucoma however none of these reports provided sufficient follow up information.

In conclusion, we evaluated 319 adverse event reports that were possibly related to the use of Nasalcrom. Many of the reports involved possible hypersensitivity or allergic reactions to Nasalcrom. The expedited reports, cardiac adverse events, and disorders involving the eye did not provide compelling evidence or were not sufficient in number to warrant labeling of these events. We agree with the division in strengthening the hypersensitivity or allergic section of the product labeling.

INTRODUCTION

The Division of Over-the-Counter Drug Products requested a review of the postmarketing Adverse Event Reporting System (AERS) to determine if there are any serious safety issues of concern and to determine if that product is adequately labeled. An efficacy supplement proposes to extend the indication in children ages 2 to 6 years of age. In agreement with Dr. Linda Hu, M.D. (DOTCDP) and Dr. Charles Lee, M.D. (DPADP) we concentrated our efforts on events that either appeared to be serious or those that occurred at a high frequency. These events include terms related to dyspnea or difficulty breathing, nausea, dizziness, headache, insomnia, asthma, cardiac events, and hypersensitivity, allergic or anaphylactic reactions.

Cromolyn sodium is a mast cell stabilizing antiallergic agent that inhibits degranulation of mast cells.[1] Cromolyn has no direct antiinflammatory or antihistaminic effects, and minimal bronchodilator effects.[2-6] The drug has purely prophylactic actions and has no role in the treatment of an acute attack of asthma. Cromolyn has been demonstrated to produce mast-cell protective effects against antigen-antibody reactions (IgE-type) and block liberation of mediators of anaphylaxis, such as histamine. It is available as the following nine marketed products:

- Nasalcrom Nasal Spray and Childrens Nasalcrom
- Nasalcrom A prevention pack – Nasalcrom Nasal Spray and oral chlorpheniramine.
- Nasalcrom CA prevention pack – Nasalcrom Nasal Spray and oral pseudoephedrine and acetaminophen.
- Intal oral inhaler and nebulizer solution
- Gastrocrom – oral formulation for mastocytosis
- Crolom and Opticrom – both ophthalmic formulations

For the purpose of this review, we limited our search to only the intranasal products. Nasalcrom Nasal Spray is manufactured by Pharmacia Upjohn and was approved by the FDA on March 18, 1983 as a prescription product (NDA 18306). Nasalcrom Nasal Spray and Children's Nasalcrom were approved for over-the-counter use on June 3, 1997 (NDA 20-463). They are indicated for the prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis in adults and children six years of age and older.

REVIEW CONTENTS

NASALCROM LABELING

The current labeling addresses the following warnings:

Ask a doctor before use if you have:

- Fever
- Discolored nasal discharge
- Sinus pain
- Wheezing

- When using this product:
- It may take several days of use to notice an effect. The best effect may not be seen for 1 to 2 weeks.
- Brief stinging or sneezing may occur right after use.
- Do not use this product to treat sinus infection, asthma, or cold symptoms.
- Do not share this bottle with anyone else as this may spread germs.

- Stop using this product if:
- Symptoms worsen.
- New symptoms occur.
- Symptoms do not begin to improve within two weeks.

The proposed labeling includes the following additional warnings:

Do not use – If you are allergic to any of the ingredients

Stop use and ask a doctor if:

- Shortness of breath, wheezing, or chest tightness occurs.
- Hives or swelling of the mouth or throat occurs.
- You need to use for more than 12 weeks.

OVERVIEW OF ADVERSE EVENT REPORTING SYSTEM

As of June 12, 2000, there were 1581 adverse event reports reported with Nasalcrom in the AERS database. Of these, 941 reported a serious outcome. There was one report with death as an outcome. The 20 most commonly reported events are as follows (a report may contain an unlimited number of terms):

Rhinitis	184	Dermatitis	42
Headache	145	Sore throat	40
Dizziness	108	Pruritus	39
Epistaxis	93	Pharyngitis	36
Nasal congestion	74	Palpitations	35
Drug ineffective	69	Pain	34
Insomnia	59	Urticaria	34

Nausea	55	Chest pain	30
Dyspnea	52	Nasal passage irritation	29
Condition aggravated	47	Face edema	28

Individual safety report characteristics

Distribution by age:	1 mon-< 2yrs (5), 2-5yrs (35), 6-11yrs (76), 12-16yrs (27), 17-20yrs (22), 21-30yrs (86), 31-40yrs (195), 41-50yrs (251), 51-60yrs (193), 61-70yrs (193), 71-80yrs (136), 81-90yrs (32), >91yrs (2), null age values (328)
Gender distribution:	Female-971, Male-550, Unknown-60
Distribution by year:	1984-4, 1985-17, 1986-4, 1987-58, 1988-3, 1989-54, 1990-48, 1991-45, 1992-32, 1993-34, 1994-56, 1995-43, 1996-50, 1997-390, 1998-318, 1999-421, 2000-4
Report type:	Direct-25, 15 day-37, Periodic-1519
Report source:	Consumer-1314, HCP-234, and other -33

Most of these reports can be classified as consumer reports submitted to the FDA as periodic reports. Pediatric (less than 17 years old) reports make up less than 10% of all adverse event reports. Report distribution by year indicates that there was an increase of adverse event reporting after Nasalcrom went OTC. Although there were a large number of reports with a reported serious outcome, distribution by report type indicates that many of the events were either not serious or they were labeled events given the fact that only 35 were submitted as 15 day or expedited reports. Consumers reported approximately 83% of the adverse event reports.

SELECTION AND SUMMARY OF CASES

In accordance with Dr. Linda Hu, M.D. (DOTCDP) and Dr. Charles Lee, M.D. (DPADP) we concentrated our efforts on events that either appeared to be serious or those that occurred at a high frequency. These events include terms related to dyspnea or difficulty breathing, nausea, dizziness, headache, insomnia, asthma, cardiac events, and hypersensitivity, allergic or anaphylactic reactions. We also reviewed all 15-day or expedited reports as well as a death report.

Review of Death Report

There was one report with death as an outcome [redacted]
A 43-year-old male was prescribed Nasalcrom for allergic rhinoconjunctivitis. After eight months, he presented to his physician with a chief complaint of personality change and flat affect. He stated that these symptoms occurred while using the product in the spring as well as the fall. He continued use of the product however because it worked well on his symptoms. He was also receiving triazolam for intermittent insomnia, the duration of which was not reported. Sometime within a month of the initial report, the patient committed suicide. It is not clear if he was taking Nasalcrom at the time of his death or whether there were contributing factors.

Review of 15 Day or Expedited Reports

We searched AERS for all 15-day reports for Nasalcrom. After duplicates were matched, a total of 34 unique cases were reviewed. One report was a periodic report identified as a 15-day report in AERS. Of the remaining 33 cases, the reported adverse events include cardiovascular disorders such as abnormal heartbeat (1), pericarditis (1), increased blood pressure (1), atrial fibrillation (2), chest pain (2), and stroke (1); gastrointestinal events include esophageal fungal infection (1), stomach pain (1), and gastroenteritis (1); urinary and renal system events including renal failure (1) and kidney stones (2); and miscellaneous events to include transverse myelitis (1), myalgia (1), hemoptysis and worsening asthma and asthma attack (2), high blood sugar (1), vertigo (1), paranoia (1), convulsions or seizure (4), impetigo (1), facial pain (1), depression (1), skin lesion (1), polymyositis (1) dry skin (1), severe epistaxis (1), and swelling of the tongue (1).

Fourteen cases may have had other contributing factors or there was insufficient documentation of the event to assess the causality or the severity of the event.

- Negative dechallenge or rechallenge/not temporally related (5)
- Insufficient information to determine/possibly related to underlying disease (8)
- More temporally related to another medication/surgery (1)

The remaining 19 cases were temporally related to the use of Nasalcrom. The reported outcome of all of these cases includes hospitalization (11), required intervention with medication (1), emergency room treatment (1), recovered with no intervention (1), disability (1), and not reported (4). Two of the reports (dry skin and facial pain) did not require any intervention and did not seem serious. It is unclear why they were submitted as 15-day reports. Because of the diversity of the events reported and the small number of reports for each of these events, they do not appear to represent a safety signal. Brief summaries of all cases are provided in attachment 1.

Seizures

We searched the AERS database utilizing the higher level group term (HLGT) "seizures" associated with the use of Nasalcrom. Our search identified a total of four unique cases. The demographic information of these four cases is provided below.

Age in years:	5.5, 8, 29, and 55
Gender:	Female-3, Male-1
Time to onset:	1 to 5 days (unknown-1)
Outcome:	Hospitalized-1, Permanent disability-1, Not reported-2
Report type:	15 day-4
Reporter:	HCP-1, consumer-3
Report Year:	1990-1, 1995-1, 1998-2
Country:	US-4

One case of seizure did not appear to be directly related to the use of Nasalcrom. This involves a patient with a history of epilepsy who reported other events or symptoms (developing a chest cold and coughing up blood) possibly associated with Nasalcrom use.

This led to her seeking intervention by her physician and gynecologist. She reported all of these pressures caused her to have epileptic seizures. The other three cases were new onset seizures. Two of the cases were consumer reports and were not well documented. There was also no followup information provided. The best case is described below.

[redacted]

An 8-year-old female experienced a seizure and respiratory failure after her seventh dose of Nasalcrom. Her respiratory rate dropped to 10 breaths per minute requiring intubation. Seizures persisted despite addition of lorazepam, diazepam and discontinuation of Nasalcrom. She was admitted to the hospital in a comatose state with a diagnosis of status epilepticus/seizure disorder and sinusitis. She was treated with phenytoin and was discharged after six days on oral anticonvulsant therapy.

This case however is not clear because at the time of the report, the patient was being treated with anticonvulsants so it is unclear if the child had an underlying previously undiagnosed seizure disorder.

Allergic or Hypersensitivity Reactions

We searched the AERS database utilizing the system organ class term (SOC) "immune disorders" to identify all allergic and hypersensitivity reactions associated with the use of Nasalcrom. Our search identified a total of 108 unduplicated reports. Seventeen reports were not further evaluated for the following reasons:

- Not temporally related or more temporally related to another medication (4). All were minor reactions except one, which was a report of renal failure, hemolytic uremic syndrome and thrombocytopenic purpura in a 54-year-old while using Nasalcrom. The patient had been on the product for 2.5 years. It was temporarily discontinued but reintroduced with no recurrence of symptoms.
- Reported worsening of allergies or symptoms (possible lack of effect) with use of Nasalcrom (5).
- Did not appear to be an allergic reaction (3) – In three reports sleepiness, drowiness, and dysuria and increased urinary frequency were reported.
- Insufficient information (2) – two consumers report an unspecified allergic reaction. None of the reports provided any details of the event or dates of administration.
- Unevaluable report (1) – consumer reported numerous events to include somnolence, nausea, pharyngitis, lack of effect, headache, pruritus, rhinitis, tremor, weight gain while receiving numerous Zyrtec, Nasalcrom, terfenadine, Allegra, pseudoephedrine, and unspecified over-the-counter medications.
- Did not appear to be nasally inhaled disodium cromoglycate (2) – of possible interest is a literature report of near death allergic or asthmatic reactions occurring in two patients from Japan after receiving disodium cromoglycate. It is not clear exactly which formulation the patients were taking however, they appeared to be oral inhalers and in both cases they were receiving it for asthma. The coded reactions also included allergic reaction and hypergammaglobinemia. The article included a table, which listed at least seven more patients that experienced dyspnea (see difficulty breathing

section below). The article has been attached to this document for your review. (attachment 1)

The remaining 91 cases were temporally related to the use of Nasalcrom. Demographics of these cases are provided below.

Age in years:	3 to 89, (mean-44, median-45, 11 were ≤ 14), unknown-15
Gender:	Female-57, Male-29, Unknown-5
Time to onset:	1 dose to 11months of use
Outcome:	Life-threatening-1, Hospitalized-2, Emergency room visit-4, Treated with medication-18, Other or not reported -66
Report type:	15 day-3, direct-6, periodic-82
Reporter:	HCP-20, consumer-70, not reported-1
Country:	US-88, Austria-1, Finland-1, France-1

We reviewed 91 cases that ranged in severity from mild urticaria to laryngeal edema and anaphylaxis. These are characterized and summarized below in the following manner: anaphylaxis cases, edema cases, urticaria or rash, and miscellaneous hypersensitivity reactions.

Anaphylaxis

There are two reports in AERS of anaphylactoid reaction (1), or anaphylactic shock associated with Nasalcrom and Rynacrom (foreign product). Both of these were not very well documented. Both are described below for your review.

[redacted]

A 65-year-old male who experienced severe bronchospasm, tachycardia, enuresis, nausea, and unconsciousness five minutes after application of Ryncrom nasal cartridges. The patient was admitted to the hospital, however no further details were provided.

[redacted]

This is a consumer report submitted as a periodic report of a 49-year-old female who experienced heart palpitations, sweaty palms, and lightheadness about one hour after her first dose of Nasalcrom. Symptoms resolved after four hours and she took another dose. She then reported that she developed anaphylactic shock. She was treated in the emergency room and never lost consciousness. Symptoms (not specified) resolved after four hours.

Edema

There were 44 reports of edema associated with the use of Nasalcrom. Facial edema to include the eyes or eyelid (18), mouth, lips, or gums (9), general face edema and cheeks (9), and nose (1) accounted for most of these reports. Also included was edema of the tongue (3), nose and throat (1), jaw (1), and larynx edema (2). Difficulty breathing, wheezing, asthma, coughing, rash, or tightness in chest or chest pain and throat was reported in ten cases. A total of eight cases required treatment with medication (benadryl-2, Vancenase-1, Seldane-1, subcutaneous epinephrine-2, and/or corticosteroids-4). One of

these was reported as a life-threatening event. In the remaining cases, the events appeared to resolve with discontinuation of the product. The three most serious cases are described below.

[redacted]

A 47-year-old female experienced nausea, facial angioedema and laryngeal edema with difficulty breathing immediately after using 4% sodium cromoglycate nasal solution. She was found to have a blood pressure of 95/50 mmHg and a pulse of 150 bpm. She was immediately treated with two doses of adrenaline and later with oral prednisolone. The symptoms resolved within 30 minutes. Two years prior, she had discontinued the use of ophthalmic sodium cromoglycate solution due to eye irritation. She had used the product a few months prior and developed burning of the nasal mucosa. Her only concomitant medication was Tetryzoline nasal preparation (dates unknown). Skin prick test two months after the event showed a 3 x3 wheal reaciton to a 1:1000 dilution of 2% sodium cromoglycate.

[redacted]

A 67-year-old male developed tongue swelling one day after starting Nasalcrom. The swelling progressed and he eventually sought emergency room treatment. He was treated with intravenous ranitidine, diphenhydramine, dexamethasone, and zithromycin. He was then instructed to avoid products containing cromolyn sodium. He was discharged from the emergency room the same day.

[redacted]

A 68-year-old female who was a long time user of Nasalcrom, experienced gagging and coughing after a particular unit dispensed was thought to contain too much medication. The patient had immediate onset of angioedema, numbness of the tongue, trouble breathing, and swelling of the tongue and throat. She went to the emergency room where she was treated with parenteral Benadryl and Medrol. The patient had a complicated medical history to include multiple drug allergies. She was receiving a number of concomitant medications two of which (guaifenesin and Beconase) were prescribed six days prior to the reaction. These were not reported as co-suspect medication.

Urticaria

There were 31 reports of urticaria, hives, or rash. Pruritus (7), edema or swelling (6), and chest tightness or pain (2) were accompanying reactions in some of these cases. The anatomical location of the these reactions were the face (4), all over (4), groin and abdomen (1), back (1), trunk (1), wrists (1), hands and feet (3), ears (1), or not reported (13). In most of the cases, the reaction seemed to be self-limiting and did not require any specific intervention besides discontinuation of Nasalcrom. Nine patients were treated with medications to include a Medrol Dose Pak (2), Benadryl (4), prednisone (1), oral and topical corticosteroids and Benadryl (2), and a beta agonist inhaler and epinephrine (1).

Miscellaneous

There were 11 reports with miscellaneous reactions characterized under the SOC "immune disorders". The reactions include purpura or vasculitis (3), serum sickness (described as flu-like aches) (1), nasal congestion or stuffiness (2), bloody nose and sneezing (1), cough (2), hypotension and dyspnea (1), and difficulty breathing (1).

In eight of the cases, no specific treatment appeared to be required. Of the remaining three cases, one required hospitalization (described below), one emergency room visit, and one self treated with loratadine. The patient that required an emergency room visit developed what she described as a "severe allergic reaction". She reported that she first developed coughing spasms, then her throat "closed up", her heart raced, and she had a rise in her blood pressure. She reports spending 2-3 hours in the emergency room, however no specific details regarding treatment were provided. One patient, who developed serum sickness, stated that she took Claritin two hours prior to Nasalcrom, which alleviates her symptoms. All three of the purpura and vasculitis cases are summarized below for your review.

[redacted]

An 89-year-old female was treated with cromoglycate sodium, flunarizine, lisinopril, and naftidrofuryl and was hospitalized with purpura of her lower legs and face edema. Thrombocytes were normal. A cutaneous biopsy showed a leukocytoclastic angeitis. All products were discontinued and she reportedly improved.

[redacted]

A 21/2-year-old female who developed purple bruises on her lower legs three weeks after initiating Nasalcrom. Her pediatrician stated that it looked like "vasculitis" She was receiving no other medication and past medical history was significant only for allergic rhinitis. The Nasalcrom was discontinued and she had improvement in her symptoms.

[redacted]

A 45-year-old male developed vasculitis of the scrotum with some necrosis of the smaller veins one week after initiating Nasalcrom therapy. The patient was also taking Entex LA and it was also considered suspect. The symptoms cleared within two weeks of discontinuing Nasalcrom. It is not clear if the Entex LA was also discontinued.

Breathing Difficulty

We searched the AERS database utilizing the higher level terms (HLT) "breathing difficulties" and "bronchospasm and obstruction" to identify all reports of dyspnea and bronchospasm associated with the use of Nasalcrom. Our search identified a total of 77 unique cases. Ten reports were excluded for the following reasons:

- Difficulty breathing with one canister, resolved when a different canister was used (1)
- Symptoms continued after discontinuation of Nasalcrom (2)
- Insufficient information of asthma event resulting in hospitalization (1)
- Respiratory failure (apnea) related to seizure (1)

- More temporally related to another medication/surgery (1) A 60-year-old physician who has been using Nasalcrom for two years (seasonal basis) developed shortness of breath and pericarditis after an uncomplicated surgical repair of a hernia and after receiving post-operative Toradol pain medication.
- Did not appear to be nasally inhaled disodium cromoglycate (5) – of possible interest is a literature report of near death asthmatic reactions occurring in five patients from Japan after receiving disodium cromoglycate. It is not clear exactly which formulation the patients were taking however, they appeared to be oral inhalers and in all five cases they were receiving it for asthma. The article included a table, which listed at least seven more patients that experienced dyspnea. The article has been attached to this document for your review. (attachment 1)

The remaining 67 cases were temporally related to the use of Nasalcrom. Demographic information is provided below.

Age in years:	1 to 88 (mean-49, median-52), unknown-12
Gender:	Female-37, Male-28, Unknown-3
Time to onset:	1 dose to 2 years
Outcome:	Hospitalized-3, Emergency room-5, Required intervention-4, Other-41, Not reported-13
Report type:	15 day-1, direct-3, periodic-61, not specified-1
Reporter:	HCP-9, consumer-54, not reported-2
Country:	US-64, Austria-1, New Zealand-1

Most of these reports can be classified as consumer reports submitted to the FDA as periodic reports. The ages ranged from 1 to 88 years of age with four occurring in individuals 15 years old and younger. The time to onset ranged from one dose to approximately two years of use. About 38% of all reactions occurred following the first dose or first day of use, and 75% occurred within the first two weeks of Nasalcrom use.

The types of reactions reported include one or more of the following: asthma, bronchospasm, chest tightness, dyspnea, nasal congestion, rhinitis, shortness of breath, and wheezing. There was one case coded as respiratory arrest, however the reported reaction by the consumer was actually described as "lost her breath". Approximately 25% of these cases were possibly associated with nasal congestion, nasal dryness, salivary hypersection, or rhinitis possibly due to Nasalcrom administration. Some of these cases appeared to hypersensitivity type reactions, as a result there may be duplication of these cases in the hypersensitivity section of this document.

The outcomes include five patients that required hospitalization, five requiring emergency room treatment, and four that required treatment with medications. Those cases with an outcome reported as "other" primarily specified that the reaction abated once Nasalcrom was discontinued. Of all cases, 48 reported a positive dechallenge on discontinuation of Nasalcrom. Twenty cases did not provide dechallenge information, five of which reported continuation of the product despite the reaction. Thirteen did not

report an outcome. Representative cases involving a serious outcome are described below for your review.

[redacted]

A one-year-old female was hospitalized after she experienced coughing, wheezing and exacerbation of asthma following two doses of Lomusol Nasal Spray. This product was reported to be similar to NDA 18-306. She received asthma therapy and recovered on the following day. She had a similar reaction requiring hospitalization 1.5 years later with Intal inhaler.

[redacted]

A 54 year old female was given two sample units of Nasalcrom one of which was expired. She administered one spray intranasally and immediately experienced dyspnea, chest tightness, cold extremities, dizziness, and palpitations. She took one Chlor-Trimeton without relief and paramedics were called. She was found to be tachycardic and hypotensive (BP not reported) however she did not require treatment. Events resolved after 90 minutes.

Cardiac Disorders

We searched the AERS database utilizing the higher level group term (HLGT) "cardiac arrhythmias" and the preferred term (PT) "palpitations" to identify any serious cardiac events associated with the use of Nasalcrom. Our search identified a total of 61 reports. Individual preferred terms of interest and the number of mentions are as follows (a report may have multiple terms):

Arrhythmia NOS	4
Atrial fibrillation	2
Extrasystoles NOS	1
Palpitations	35
Tachycardia	18
Ventricular extrasystoles	1

Seven reports were not further evaluated for the following reasons:

- Symptom resolved without discontinuation of Nasalcrom (3) – 1) A consumer reported that she developed an arrhythmia in association with the use of Nasalcrom. She continued to use the product with resolution of the arrhythmia.2) Two consumers reported that they developed a racing heart and irregular heartbeat. In both cases the symptoms resolved with continued use of Nasalcrom.
- Related to another medication (2) – 1) A 44-year-old consumer reported that she experienced heart palpitations. She discontinued her Nasalcrom and St.Johns Wort and had resolution of symptoms. She restarted the Nasalcrom with no recurrence. 2) A 41-year-old receiving Nasalcrom and Seldane D experienced palpitations. She discontinued both products, then restarted Nasalcrom without recurrence of symptom.

- Not temporally related (1) – A 72-year-old male reported that he developed atrial fibrillation and low heartbeat one year after initiating therapy with Nasalcrom.
- Negative rechallenge (1) – A 41-year-old male developed premature ventricular contractions a few weeks and two years after starting Nasalcrom and Intal, respectively. He discontinued both products with resolution of symptoms, but restarted without recurrence.

Tachycardia

There were 18 cases of tachycardia reported with the use of Nasalcrom. The ages ranged from 11 to 71 years of age (unknown-3). The time to onset ranged from 1 to 38 days of product use. Past cardiac histories were noted in five of the cases and include tachycardia (2), mitral valve prolapse (2), and hypertension (1). None of the cases provided the heart rate.

Nine cases reported a variety of additional symptoms or events to include one or more of the following: hyperexcitability, insomnia, chest tightness, dry mouth, shaking, difficulty swallowing, jitterness, pain, dizziness, emotional lability and hostility, increased blood pressure, appetite and weight increase, hypotension, syncope, chest pain, dyspnea, cold extremities, and epistaxis.

None of the consumers had a reported serious outcome. In one case, the consumer developed dyspnea, chest pain, syncope, and tachycardia immediately after using an expired Nasalcrom container. The paramedics were summoned, but she did not require any medical treatment.

Palpitations

We reviewed 30 cases of palpitations reported with the use of Nasalcrom Nasal Solution. There was one report that listed Nasalcrom CA as a co-suspect agent. This medication contains pseudoephedrine and acetaminophen. Consumers submitted all but one report; 29 were reported after the product went OTC.

The ages ranged from 27 to 71 years of age (unknown-2). The time to onset ranged from 1 to 10 days of product use. Nineteen cases reported a variety of additional symptoms or events to include one or more of the following: weakness, shakiness, dizziness, lightheadness, dyspnea, spasms, myalgia, insomnia, restlessness, fatigue, asthenia, nausea, increased blood pressure, headache, lethargy, nervousness, chest pain, laryngismus, and shortness of breath.

In 24 cases, the consumers did not seek medical attention and symptoms reportedly resolved with discontinuation (13) of Nasalcrom or the outcome was unknown (11). There were four consumers that sought the advice of a health care provider (HCP). In two of the cases the HCP did not feel as though the symptoms were related to Nasalcrom, the other two did not specify the advice rendered by the HCP.

There were two consumers that presented to the emergency room (ER). One was described in a previous section. A 49-year-old self reported that she developed heart

palpitations, sweaty palms, lightheadness, and anaphylactic shock following the use of Nasalcrom. She was treated in the ER and discharged after four hours. The other case is described below.

FDA 3207549-8, MFR 1110/20463, USA, 1998
A 53-year-old male reported that he experienced a dull headache, lethargy, disorientation, and heart "fluttering". He reported to the ER. On arrival, his blood pressure was 200/80. Patient did not have a history of hypertension. His work up included a CAT scan and ECG. Results were not provided and he was discharged after three hours.

Miscellaneous Rhythm Disturbances
We reviewed six cases of cardiac rhythm disturbances during use of Nasalcrom. The reported cardiac events include atrial fibrillation (1), abnormal heartbeat (1), unspecified arrhythmia (2), heart skipping (1), and heart rhythm abnormalities (1).

Five of the cases did not provide sufficient information to determine the type of arrhthymia. Four of these were consumer reports. One was reported by a physician, however he did not remember the patient, therefore he did not recall specific information such as time to onset, arrhythmia type, or past medical history. Four did not report a serious outcome. One case had a serious outcome. It involved a 61-year-old female who experienced an abnormal heartbeat after three days of Nasalcrom and was admitted to an intensive care unit. Medical history and medical confirmation of diagnosis not provided.

The remaining case involves a 70-year-old female who reported that she was hospitalized five days after initiating Nasalcrom for atrial fibrillation. Her past medical history was not provided. At the time of the event she was taking Nasalcrom QID. She reduced her dose of Nasalcrom to BID. There was also a mention that she was started on diltiazem some time during the same month.

<u>Eye Disorders</u>

We searched the AERS database on May 2, 2000 utilizing the system organ class term (SOC) "eye disorders" to identify reports associated with the use of Nasalcrom. Our search identified a total of 94 unique cases. Five reports were excluded for the following reasons:

- More temporally related to another medication (2) – 1) A male physician started using Vancenase and Nasalcrom at the same time. After four months he developed increased intraocular pressure which resolved after discontinuation of Vancenase. He continued Nasalcrom use with no problems. 2)A male patient who was taking Nasalcrom experienced vertigo and blurred vision that resolved when Rogaine was discontinued.
- Not related (1)- Patient with glaucoma initially noted an increase in visual acuity after Nasalcrom was discontinued. On followup, her intraocular pressures had increased and visual acuity decreased while off Nasalcrom.
- Continued to use products with resolution of symptoms (2)

The remaining 89 cases were temporally related to the use of Nasalcrom. Demographic information is provided below.

Age in years:	1 to 83, unknown-19
Gender:	Female-64, Male-24, Unknown-1
Outcome:	Required intervention-8, Disability-1, Other-59, Not reported-21
Report type:	Direct-3, periodic-86
Reporter:	HCP-8, consumer-89, not reported-1
Country:	US-89

The ages ranged from 1 to 88 years of age with six occurring in individuals less than 15 years old (three less than 6 years old). The types of eye disorders reported include one or more of the following: red eye, eye irritation, conjunctivitis, eye pain, eyelid edema, diplopia, amblyopia, blurred vision, keratitis, mydriasis, eye discharge, blood shot eye, burning sensation, dry eye, increase or decrease lacrimation, and vision abnormality. There were four disorders that appeared to be serious corneal erosion, eye hemorrhage, extraocular muscle paralysis, and glaucoma.

The outcomes include eight patients that required some type of intervention, one that reported a disability. Those cases with an outcome reported as "other" primarily specified that the reaction abated once Nasalcrom was discontinued. Twenty-one did not report an outcome.

Of possible interest, six reports stated that the eye event occurred after Nasalcrom was accidentally introduced into the eye. In three additional reports, Nasalcrom was prescribed for ophthalmic use due to non-availability of Opticrom. This resulted in eye burning in all cases.

The cases that are potentially concerning include the following:

- Those that required emergency intervention or resulted in disability (3) – One 5 year old reportedly suffered diplopia and extraocular muscle paralysis which was reported as disabling, however no further information was provided. Two consumers required emergency services. One involved a 24-year-old with a complicated history who was prescribed Nasalcrom for ophthalmic use. She was treated in an emergency room and released. The last case involves a 40-year-old male who developed violent vomiting, mydriasis and other symptoms immediately after his first dose of Nasalcrom. Emergency medical technicians were called, however no treatment was necessary and symptoms resolved.
- Reported severe reactions (corneal abrasion, glaucoma, and eye hemorrhage)- one female consumer used Nasalcrom and her physician noted that it entered the vaso-lacrimal duct, affected the tear film, and re-activated her recurrent corneal erosion. No further information was provided. There was one case involving a patient who took Nasalcrom for years and developed glaucoma. No further information was provided. The case of eye hemorrhage was actually reported as a bruise on the

consumer's eyelid and "blood" in the eye. Both of these latter cases were not well described.

- Those involving children – There were six cases involving children less than 15 years old (3, 4, 5, 9-2, and 13 years old). In five cases the reactions were similar to what was noted in adults. The remaining case involves the 5-year-old who suffered extraocular paralysis (described above).

CONCLUSION

An overview of 1581 adverse event reports for Nasalcrom indicates that consumers submitted most reports, many reported after Nasalcrom became available as an over-the-counter (OTC) product. Although there were a large number of reports with a reported serious outcome, only 37 were submitted as 15 day or expedited reports, which probably indicates that many of the events were either not serious or they were labeled events.

We evaluated 19 expedited (15-day) reports that were considered possibly related to the use of Nasalcrom. Because of the diversity of the events and the small number of reports for each of these events, they do not appear to represent a clear safety signal.

We evaluated 91 cases of hypersensitivity or allergic reactions that were possibly related to Nasalcrom. The events ranged in severity from mild urticaria to laryngeal edema and anaphylaxis. We evaluated 67 cases of difficulty breathing in association with Nasalcrom use. The types of reactions reported include asthma, bronchospasm, chest tightness, dyspnea, nasal congestion, rhinitis, shortness of breath, and wheezing. Approximately 25% of these cases were possibly associated with nasal congestion or rhinitis symptoms. Some of these cases appeared to be hypersensitivity type reactions, therefore, there may be some overlap in the hypersensitivity/allergic cases.

We evaluated 54 cardiac cases and 89 cases involving eye disorders temporally related to the use of Nasalcrom. Most disorders appeared to be minor and most were consumer-reported and did not provide sufficient detail or medical substantiation of the event. Because of the small number of reports for each of these events, they do not appear to represent a clear safety signal.

We evaluated 319 adverse event reports that were possibly related to the use of Nasalcrom. Many of the reports involved possible hypersensitivity or allergic reactions to Nasalcrom. The expedited reports, cardiac adverse events, and disorders involving the eye did not provide compelling evidence or were not sufficient in number to warrant labeling of these events. We agree with the division in strengthening the hypersensitivity or allergic section of the product labeling.

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/S/ 6/20/00

Claudia B. Karwoski, Pharm. D.

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 1: SUMMARY OF 15 DAY REPORTS

Negative dechallenge or rechallenge/not temporally related (5)

- A report of renal failure, hemolytic uremic syndrome and thrombocytopenic purpura in a 54-year-old while using Nasalcrom. The patient had been on the product for 2.5 years. It was temporarily discontinued but reintroduced with no recurrence of symptoms.
- A 65-year-old woman with history of hypertension developed chest pain while on Nasalcrom, which persisted after discontinuation.
- A 73-year-old female was hospitalized for a kidney stone after approximately one year of use of Nasalcrom. She was hospitalized for the event.
- A 64-year-old male experienced vertigo with the use of Nasalcrom, which persisted with discontinuation.
- A 72-year-old male reported that he developed atrial fibrillation and low heartbeat one year after initiating therapy with Nasalcrom.

Insufficient information to determine/possibly related to underlying disease (8)

- A 6-year-old female developed transverse myelitis requiring hospitalization three months after initiating therapy with Nasalcrom. She was treated with methylprednisolone. Unsure if this is generally associated with medication. Patient had history of chronic sinusitis and had been using nasal steroid spray and unspecified antibiotics.
- Another case involved an 8-year-old male who was hospitalized for myalgia, leg cramps, and joint pain 13 months after starting Nasalcrom. The report stated that he has his hips and knees realigned.
- A female (age unknown) was hospitalized for an asthma attack during Nasalcrom therapy. Dates of administration and past medical history not provided.
- A 61-year-old female reported that she experienced an abnormal heartbeat after three days of Nasalcrom and was admitted to an intensive care unit. Medical history and medical confirmation of diagnosis not provided.
- An 82-year-old with diabetes reported an increase in blood sugar while receiving Nasalcrom.
- An 81-year-old female reported her blood pressure was 200/108 after restarting Nasalcrom. She had a history of hypertension and was taking a number of antihypertensive medications.
- A 74-year-old female was hospitalized with stomach pain while receiving Nasalcrom. Had a history of stomach problems.
- A 43-year-old male with a history of paranoid tendencies was hospitalized for paranoia. The time to onset was not reported.

More temporally related to another medication/surgery (1)

- A 60-year-old physician who has been using Nasalcrom for two years (seasonal basis) developed shortness of breath and pericarditis after an uncomplicated surgical repair of a hernia and after receiving post-operative Toradol pain medication.

The remaining 19 cases were temporally related to the use of Nasalcrom.

- A 33-year-old female suffered a stroke after one dose of Nasalcrom. This was a consumer-reported event, however she did provide objective MRI results, which indicated that she had three lesions in the cerebellum. No specific etiology for her stroke was provided.
- Convulsions or seizures (4). These were summarized in the document.
- A 17-year-old female was hospitalized after she developed a high fever, heartburn, and dysphagia 10 months after starting Nasalcrom. She was diagnosed with an esophageal fungal infection. She was receiving no other medication. She was treated and improved after three days.
- A pharmacist mistakenly dispensed Nasalcrom instead of Intal inhaler, which resulted in a female (age unknown) orally inhaling the Nasalcrom. Three days later, she experienced severe throat irritation and hemoptysis. The drug was discontinued and one month later she was hospitalized with worsening asthma thought to have been provoked by Nasalcrom.
- A 9-year-old female developed impetigo around her nose while using Nasalcrom. She discontinued use, was treated with antibiotics, and was dispensed a new canister with recurrence of the event.
- A 27-year-old female developed multiple symptoms including nausea, vomiting, dizziness, headache, leg cramps, and depression one month after starting Vancenase and Nasalcrom. She was hospitalized for depression and symptoms resolved after discontinuation of both products and treatment with Prozac. Causality is somewhat questionable because she had other stresses to include college and a history of back injuries.
- A 61-year-old male developed a 1.5 cm skin lesion on his face over a 48 hour period. He reportedly used Nasalcrom during the summer months. The physician felt that the patient developed the "reactive lesion secondary to an insect bite, possibly due to abnormal activation of lymphocytes due to cromolyn".
- A 53-year-old registered nurse reported polymyositis after 6 weeks of therapy with Nasalcrom. She reported some improvement with discontinuation of Nasalcrom and treatment with prednisone.
- Two study patients experienced reactions while on Nasalcrom or placebo 1) A 39-year-old male received Nasalcrom as part of a double-blind study and presented to the emergency room and was hospitalized for two days for a kidney stone. Kidney stone was not recovered. 2) Gastroenteritis in a 30-year-old male 6 days after starting study medication. Presented to ER and was successfully treated.
- A 77-year-old male developed severe epistaxis requiring hospitalization and eight units of blood possibly associated with Nasacort or Nasalcrom. Not on

anticoagulants and no history of bleeding disorders. Had a deviated septum secondary to nose fracture during college.

- A 42-year-old male experienced chest pain when using Nasalcrom. He was hospitalized and cardiac workup was negative. Reportedly did fine after Nasalcrom was discontinued.
- A 67-year-old male developed swelling of his tongue after he used Nasalcrom. The swelling was increased and he was taken to the emergency room. He was treated with treated with ranitidine, Dramamine, and methylprednisolone and instructed to avoid any product containing cromolyn.
- A 70-year-old female who reported that she was hospitalized five days after initiating Nasalcrom for atrial fibrillation. Her past medical history was not provided. At the time of the event she was taking Nasalcrom QID. She reduced her dose of Nasalcrom to BID. There was also a mention that she was started on diltiazem some time during the same month.

The following two cases did not appear to have a serious outcome.

- A male teenager (age unknown) experienced severe facial pain which radiated to the head immediately administration of Nasalcrom from a particular bottle. He had used Nasalcrom for a year with no problems. Event abated within one hour.
- A 14-month-old male experienced patches of dry skin associated with the use of Nasalcrom.

CASE REPORT

2011637

Near-Death Asthmatic Reaction Induced by Disodium Cromoglycate

Hitoshi KATAYAMA, Akihito YOKOYAMA, Shun FUJINO, Kei-ichi KONDO, Masahiro ABE, Wataru NISHIDA, Katsuhiko KOHARA, Nobuoki KOHNO and Kunio HIWADA

A near-death asthmatic reaction was induced by disodium cromoglycate (DSCG) as evidenced by positive skin and inhalation provocation tests. The patient's history revealed an episode of exacerbation by inhalation of DSCG. In spite of such an experience, he inhaled DSCG for relief of asthmatic attack, resulting in near-death exacerbation. This patient emphasizes the need to re-recognize that DSCG is not a reliever and that DSCG could cause fatal asthma.
(Internal Medicine 35: 976–978, 1996)

Key words: drug-induced, bronchial asthma, adverse effect

Introduction

Disodium cromoglycate (DSCG) is an effective anti-allergy agent, and is widely used for allergic diseases including bronchial asthma (1). This compound was discovered in the 1960's, and was used for more than 20 years. Other than local irritation and cough in the use of dry powder, DSCG is considered to have rather few adverse reactions even in long-term treatment. However, there have been some reports concerning skin eruptions, pulmonary infiltrate with eosinophilia (PIE), anaphylaxis and asthmatic reaction (2–10). These reactions seem to be allergic reactions, with the type I allergic reaction mostly involved (11–13), even though DSCG is a potent mast cell stabilizer (14).

Here, we describe a patient with bronchial asthma, who experienced a near-death attack induced by DSCG.

For editorial comment, see p 923.

Case Report

A 39 year-old male was urgently admitted to our hospital with a near-death asthmatic attack in June 20, 1995. Three months before admission, he was admitted to another hospital because of wheeze and dyspnea, which he experienced for the first time. His illness was diagnosed as bronchial asthma (severe persistent). The level of total IgE was 106 IU/ml, and an examination for specific IgE (IgE MAST) to common inhaled allergens disclosed that he had been allergic to the pollen of timothy grass and Japanese cedar. He had no episodes to indicate aspirin intolerance. Two months before the admission to our hospital, treatment with DSCG inhalation was started in addition to sustained-release theophylline, long-acting oral β_2-agonist, inhaled anticholinergic, and inhaled steroid (beclomethasone, 400 μg/day). Since he sometimes experienced chest discomfort followed by wheeze, cough and dyspnea for 10 to 20 minutes following the inhalation of DSCG of either fluid, powder or aerosol, he quit the inhalation one month before the admission. However, his illness was not very improved. Five days before the admission, his asthma was exacerbated and he inhaled β_2-agonist (salbutamol) frequently using a nebulizer. On the day of admission, he inhaled DSCG right after salbutamol inhalation, because DSCG was effective for his daughter's asthma (he used the DSCG fluid prescribed for his daughter using a nebulizer). Then his dyspnea progressively worsened. He lost consciousness 20 to 30 minutes later.

On admission, he was still unconscious (Japan Coma Scale: III-300). Respiration rate was less than 10/min, auscultation of the chest revealed weak piping rales. Blood pressure was 150/90 mmHg. Radial pulse was regular and the rate was 140/min. Arterial blood gas analysis revealed a marked respiratory acidosis, pH 6.99, P_{O_2} 76.2 mmHg, and P_{CO_2} 93.1 mmHg (oxygen was administered in the ambulance). Intubation was performed and respirator management was started. Methylprednisolone 750 mg and aminophylline were administered. He was alert and blood gas was markedly improved the following day. The respirator was taken off. Treatment was continued

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Mfg. Control No. 157/20463

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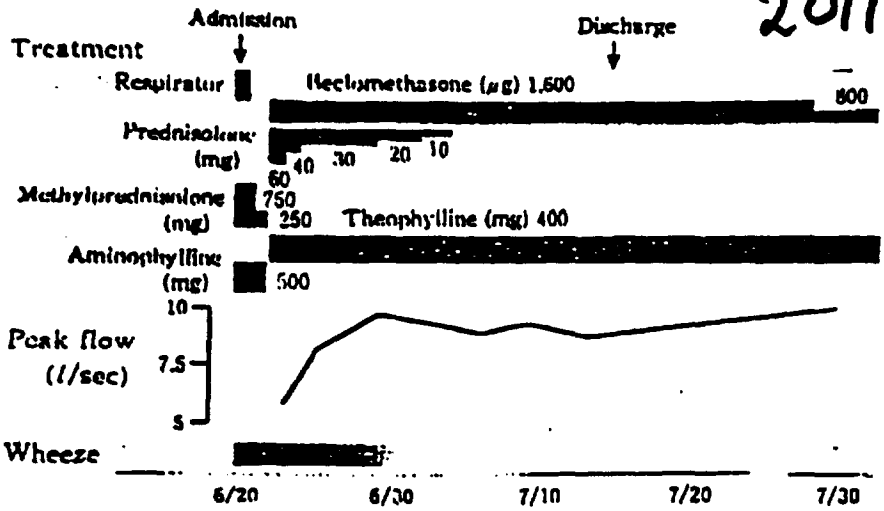

Figure 1. Clinical course.

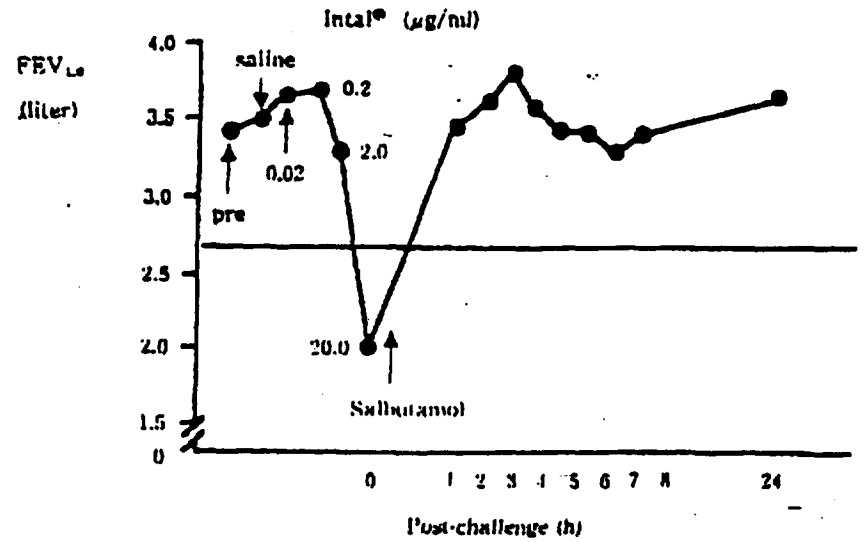

Figure 2. Bronchial provocation test by DSCG.

with theophylline, inhaled steroid, β_2-agonist inhalation and prednisolone. His wheeze had totally disappeared two weeks later. His clinical course is shown in Fig. 1.

Since his illness was suspected to be drug allergy induced by DSCG, skin test and bronchial provocation test using DSCG were performed following informed consent was obtained. Intradermal skin test was performed in the forearm using 0.02 ml of serial 10-fold diluted DSCG (0.2–2,000 μg/ml). A positive result (≥9×9 mm wheal or ≥20×20 mm flare) was obtained at the concentration of 20 μg/ml or more. The flares were no longer visible at the examination 6 or 48 hours later. No reaction was observed in the same skin test performed on a normal volunteer (25-year-old male). Bronchial provocation test was then performed by the standard methods described by the Japanese Society for Allergology (Fig. 2). The beginning concentration for inhalation of DSCG was 0.02 μg/ml. Ten-fold dose escalation resulted the decrease of $FEV_{1.0}$ at the dose of 20 μg/ml down to 58.1% of pre-$FEV_{1.0}$ value.

Discussion

The past history and skin reaction and provocation challenge of DSCG indicated that the near-death attack of this middle-aged man was induced by inhalation of DSCG. These results

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Table 1. Asthmatic Response Induced by DSCG in Japan

	Age/Sex	Medicated periods	Chief complaints	IgE	Skin test	Provocation test
1	9/M	7 Mo	Cough, Wheeze, Dyspnea	703	Positive	Positive
2	53/F	30 Mo	Dyspnea	960	Positive	Positive
3	54/F	12 Mo	Dyspnea	583	Positive	NR
4	42/M	3 Mo	Chest oppression, Wheeze	56	Positive	Positive (only LAR)
5	4/M	38 Mo	Wheeze, Dyspnea	NR	NR	NR
6	38/F	<12 Mo	Dyspnea	NR	NR	Positive (only LAR)
7	48/F	1 Day	Sneeze, Vomiting	NR	NR	NR
8	54/F	18 Mo	Cough, Fever, Dyspnea	63.7	Negative	Positive (only LAR)
9	49/F	1 Mo	(near death)	NR	NR	NR
10	20/F	3 Days	(near death)	NR	NR	NR
11	51/F	19 Days	(near death)	NR	Positive	NR
12	57/F	72 Mo	(near death)	680	Positive	Positive
13	39/M	2 Mo	(near death)	106	Positive	Positive

NR: not reported, Mo: months, LAR: late asthmatic response.
References for this table; patient 1: ref. 13, patients 2, 3: ref. 10, patient 4: Furuya et al. Kyoubu Shikkan Gakkai Zasshi 27: 1245, 1989 (abstract), patients 5, 6, 11: report from Fujisawa Pharm. Co., 1995, patient 7: Akizawa et al. Chiryo 70: 186, 1988 (abstract), patient 8: ref. 8, patient 9: Kinoshita et al. Arerugi 43: 369, 1994 (abstract), patient 10: Ozawa et al. Gunma Igaku 54: 54, 1991 (abstract), patient 12: Sato et al. Shiritu Sapporo Byouin-Shi 46: 71, 1986, patient 13: present case.

Genut Report
156-160/20463

also suggest that DSCG-induced near-death asthmatic attack would be mediated by type I allergic reaction. To our knowledge, twelve patients who have experienced possible DSCG-induced asthmatic attack have been reported in Japan (including literature, abstracts at local meetings, and reports to the manufacturer) (Table 1). The age and the medication period ranged from 4 to 70 years old and from 1 day to 72 months, respectively. Among these patients, 4 patients experienced a near-death attack. There seems to be no specific clinical characteristics of these patients.

We believe that the near-death attack of the present patient could be avoided in view of following two points. First, his past-history should not have been ignored; the fact that he experienced exacerbation of his symptoms following induction of DSCG. He could have been given advice to avoid the drug. Secondly, he used DSCG with the expectation that DSCG is a symptom-reliever, although DSCG is not a reliever. At that time, he had an asthmatic attack which had been a severe enough attack that was not relieved by inhalation of β_2-agonist. DSCG was considered to have induced the near-death asthma. This notion should be emphasized, since sometimes DSCG inhalation is recommended for the treatment of exacerbation as a mixture with β_2-agonist, especially in the pediatric clinic. We believe that inhalation of such a mixture should be avoided in patients who have experienced any possible adverse effect of DSCG because this drug may induce an allergic reaction which may be very rare, but it could be near fatal as observed in the present patient.

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Mfg. Control No. 157/20463

MERRITT

MEMORANDUM

Date: April 13, 2000

To: Charles Ganley, M.D.
Director, Division of OTC Drug Products

/S/

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

/S/

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

/S/

Through: Robert J. Meyer, M.D.
Director, Division of Pulmonary and Allergy Drug Products

Subject: Medical Officer Consultation regarding pediatric efficacy supplement for NDA 20-463, SE5-002, NasalCrom™ nasal spray (cromolyn sodium solution, 5.2 mg/spray)

General Information
NDA#: 20-463, SE5-002
Sponsor: Pharmacia & Upjohn Company
Drug Product: cromolyn sodium solution, 5.2 mg/spray, (NasalCrom™ nasal spray)
Request from: HFD-560
Materials: Request for Consultation, date 10/6/99
NDA 20-463, SE5-002

This application has been reviewed. We recommend approval of this application. Please see attached review document.