CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20762

ADMINISTRATIVE DOCUMENTS

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, (HFD-530)
Corporate Building, Room N461

FROM: Division of Pulmonary Drug Products HFD-570
Attention: Craig M. Bertha, Ph.D. Phone: 827-1095

DATE: November 12, 1996

SUBJECT: Request for assessment of the proposed name

Proposed Trademark: NASONEX Nasal Spray **NDA/ANDA #** N 20-762

Established name, including dosage form: mometasone furoate monohydrate nasal spray

Other trademarks by the same firm for comparison products:
VANCENASE AQ Nasal Spray

Indications for use (may be a summary if proposed statement is lengthy):
Prophylaxis and treatment of seasonal allergic rhinitis (SAR), and treatment of perrennial rhinitis (PR)

Initial comments from the submitter: (concerns, observations, etc.) The strength of the product is 50 µg (anhydrous basis)/actuation and the route of administration is intranasal. Each container provides 120 actuations and the daily dose is two actuations in each nostril once daily for adults and adolescents 12 years and older.

NOTE: **Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.**

Rev Dec. 1990

U.S. patents pertaining to the drug mometasone furoate monohydrate: None; however, mometasone furoate monohydrate is being manufactured from an intermediate compound, mometasone furoate, which is claimed in U.S. Patent 4,472,393, having an expiration date of September 18, 2001 and being owned by Schering Corporation.

U.S. patents pertaining to the composition and formulation of NASONEX brand of mometasone furoate monohydrate nasal spray: None.

U.S. patents pertaining to methods of use of NASONEX brand of mometasone furoate monohydrate nasal spray: None.

The person signing this application on behalf of the applicant declares: (1) that U.S. Patent 4,472,393 of Schering Corporation claims mometasone furoate; and (2) that mometasone furoate is used to manufacture mometasone furoate monohydrate, the active ingredient in NASONEX brand of mometasone furoate monohydrate nasal spray; and (3) that with respect to U.S. Patent 4,472,393 a claim of patent infringement could reasonable be asserted against a person, not licensed thereunder by Schering Corporation, who engages in the use of mometasone furoate to manufacture the active ingredient in NASONEX brand of mometasone furoate monohydrate nasal spray.

EXCLUSIVITY SUMMARY for NDA # 20-762 SUPPL #_____

Trade Name NASONEX Nasal Spray Generic Name mometasone furoate

Applicant Name Schering-Corporation HFD-570

Approval Date, if known _____

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 question about the submission.

   a) Is it an original NDA?

   YES /_x_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_x_/

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

   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 /_x_/ NO /___/

   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 /_x__/ NO /___/

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

__Three_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 .

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__/ OTC Switch /___/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8 (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 /_x__/ NO /___/

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

NDA# 19-625 Mometasone furoate topical cream

NDA# 19-796 Mometasone furoate topical lotion

NDA# 19-543 Mometasone furoate topical ointment

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 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /_X_/ NO /___/

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 8:

_____

_____

YES /___/ NO /___/

(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 /_X_/

(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 /_X_/

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 /_X_/

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:

C93-013 C93-215 C92-280

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

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

_____ _____

_____ _____

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

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

_____ _____

_____ _____

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"):

_C93-013_____ _C92-280_____

_C93-215_____ _____

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 /_X_/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # __ YES /_X_/	NO /___/ Explain: _____
Investigation #3	
IND , YES /_X_/	_____

(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 /_X_/

If yes, explain: _____

_____

Denise P. Toyer
Signature
Title: Project Manager

26 September 1997
Date

Signature of Division Director

10/1/97
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Claim for Exclusivity

1. Pursuant to the provisions of Sections 505 (c) (3) (D) (iv) and 505 (j) (4) (D) (iv) of the Food, Drug and Cosmetic Act (FDCA) and 21 CFR 314.108 (b) (5), the applicant claims three (3) years of exclusivity for its NASONEX™ (mometasone furoate monohydrate) NASAL SPRAY, for use in the prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis, in adults and adolescents 12 years of age and older.

2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108 (a).

3. A list of all published studies or publicly available reports of clinical investigations known to the applicant through a computer-assisted literature search that are relevant to the conditions for which the applicant is seeking approval is provided as **Attachment 1.**

4. The applicant certifies that it has thoroughly searched the scientific literature through a computer-assisted search of the Scholar database, and Dialog database encompassing the subfiles MEDLINE, BIOSIS Previews, EMBASE and SciSearch, for English and non-English literature relating to mometasone furoate nasal spray in humans, covering the period from 1985 to 8/28/96.

5. To the best of the applicant's knowledge, the list of scientific literature pertaining to mometasone furoate nasal spray is complete and accurate, and in the opinion of the applicant, such published studies or publicly available information do not provide a sufficient basis for the approval of the use of mometasone furoate monohydrate nasal spray for the prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis, without reference to the new information contained in the clinical trials in the application. The applicant's opinion that the studies or reports are insufficient is based on the following:

   - The literature does not contain adequate characterization of the efficacy and safety profile of mometasone furoate in the management of prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis, which is established by the data from the new

clinical studies conducted by the applicant under IND . and included in this application.

- The overall clinical program requirements of this application, and the design of the studies were discussed with the Food and Drug Administration's Pilot Drug Evaluation Staff (Dr. Patricia Love) prior to study initiation. These studies were also review by the Division of Pulmonary/Oncology Drug Products in a July 31, 1995 pre–NDA meeting. Such studies are not available in the published literature without reference to the sponsor's new clinical investigations.

6. The applicant was the sponsor named in the Form FDA-1571 for IND under which the new clinical investigations were conducted

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-762 Trade (generic) names Nasonex Nasal Spray (mometasone furoate)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&MC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. 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 do not need to be encouraged because the drug product has little potential for use in children.

X 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Nasonex Nasal Spray (mometasone furoate) is indicated for the treatment of seasonal allergic rhinitis and perennial allergic rhinitis nasal symptoms and prophylaxis of nasal symptoms of seasonal allergic rhinitis in adults and in pediatric patients between the ages of 12 and 17.

Schering is currently conducting clinical studies in the pediatric population (ages 3 and above). They anticipate submitting the data during the 3rd quarter of 1998.

Denise P. Toyer
Signature of Preparer

26 September 1997
Date

cc: Orig NDA
HFD-570/Div File
NDA Action Package

Memorandum

To: NDA 20-762, Nasonex Nasal Spray
From: Hilary V. Sheevers - Pharm./Tox. Team Leader 9/26/97
Re: Team Leader NDA Summary, HFD 570
Date: September 26, 1997

Nasonex Nasal Spray is an intranasal formulation of the glucocorticosteroid mometasone furoate monohydrate. Nasonex is a potent corticosteroid with anti-inflammatory properties, and in animal models inhibited allergen-induced eosinophil infiltration and Th cell accumulation. The proposed indication for Nasonex Nasal Spray is the prophylaxis and treatment of seasonal and perennial allergic rhinitis. Patients are expected to be greater than 12 years old, and the maximum dose is 200 μg/day. The active ingredient has previously been approved and marketed as a topical dermal product.

Outstanding Issues:

- There are no outstanding pharmacology/toxicology issues to delay approval or this drug product.

- A future concern will be dose comparisons in carcinogenicity studies for nasal products. Recent nasal drug product labels (e.g. Vancenase, Flonase) include dose comparisons between humans and animals based on surface area. The sponsor was asked to do label Nasonex in a similar manner as well, because the human AUC was not quantifiable. However, when (if) the inhalation mometasone products come in as NDAs, the dose comparisons will appear more favorable for the inhalation products than the intranasal products. That is, the carcinogenicity studies will appear to have been performed at a higher dose multiple in animals compared to humans for the inhalation products than for the intranasal product. Thus, although we remain consistent among steroid nasal products, this issue eventually will need to be revisited to decide just what is the best factor for comparison for intranasal products.

Summary of Significant Preclinical Studies:

In general, mometasone furoate **chronic toxicity studies** revealed a pattern of classic glucocorticosteroid toxicity effects. Mometasone was evaluated fully in acute, subchronic, and chronic studies in rats and dogs for 6 months by inhalation. Common changes in rats (the more sensitive species) included HPA axis suppression; adrenal, spleen, thymus and lymph node atrophy; and opportunistic infections probably related to the immunosuppressive properties of the drug. In the 6-month inhalation dog study, changes were noted primarily in the adrenals. In a 12-month intranasal dog study, effects related to steroid treatment decreased, and consisted of absence of nasal lymphoid aggregates, and changes in the adrenals, thymus, and skin were noted. Although no NOAEL doses were identified, the changes were as expected for this drug class and as is generally the case, should be clinically monitorable by following ACTH levels.

Reproduction studies were performed in rats, mice, and rabbits. In rodents (SC), which are quite sensitive to corticosteroid effects, malformations and reduced survival were noted in doses overlapping the clinical dose (based on body surface area comparisons). In rabbits (oral), malformations and effects on fetal growth were noted at doses well above the clinical dose. As with other glucorticosteroids, Nasonex is recommended as pregnancy category C. In general, and particularly for nasal products, results seen in the SC and oral animal studies are far more serious than that experienced in the human population. No changes in fertility were noted in an oral rat multigenerational study, although changes of importance included prolonged gestation and labor and, reduced body weight gain at doses slightly below the clinical dose (on a body surface area basis).

Two inhalation **carcinogenicity studies** were performed. No statistically significant increases in tumors were noted in Sprague Dawley rats in doses up to 3 times the clinical dose and in Swiss CD-1 mice up to 4 times the clinical dose on a surface area basis. Mometosone furoate was a weak positive in a single chromosome aberration in vitro study. However, the drug tested negative in a mouse lymphoma assay, a bacterial reverse mutation assay, a Chinese hamster lung cell assay, an in vivo mouse bone-marrow assay, and rat bone-marrow clastogenicity assay, a mouse male germ-cell clastogenicity assay, and it did not induce unscheduled NA synthesis in vivo in rat hepatocytes. Thus, mometasone is not considered to a genotoxic compound.

Labeling changes were discussed with the sponsor and are accurately represented in the final proposed label. Based on preclinical data, the submission is recommended to be approvable.