CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-762/S001

APPROVAL LETTER

NOV 18 1998

NDA 20-762/S-001

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attention: Joseph Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your supplemental new drug application dated October 24, 1997, received November 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nasonex (mometasone furoate) Nasal Spray, 50 mcg.

We acknowledge receipt of your submissions dated March 30, July 24, and October 19, 1998.

This supplemental new drug application provides for revised labeling which addresses the onset of action of Nasonex Nasal Spray, 50 mcg.

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter with the revisions listed below.

1. The second paragraph of the CLINICAL PHARMACOLOGY, Clinical Studies subsection, should be revised to "In patients with seasonal allergic rhinitis, NASONEX Nasal Spray, 50 mcg demonstrated improvement in nasal symptoms (vs. placebo) within 11 hours after the first dose based on one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study, and within 2 days in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing."
2. The fifth and sixth sentences of the PRECAUTIONS, Information for Patients subsection should be revised to "Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing."

3. A new paragraph should be added at the end of the ADVERSE REACTIONS section. It should read as follows: "In postmarketing surveillance of this product, cases of nasal burning and irritation, and rare cases of nasal septal perforation have been reported."

4. The third paragraph of the DOSAGE AND ADMINISTRATION section should be revised to "Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks. Patients should use NASONEX Nasal Spray, 50 mcg only once daily at a regular interval."

5. The sentences "Based on single day studies done in a park during pollen season or in a controlled pollen exposure room, improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose. In other studies that lasted up to 2 weeks, improvement in nasal symptoms of seasonal allergic rhinitis was shown to occur within 2 days after the first dose. The full benefit of NASONEX Nasal Spray, 50 mcg is usually achieved within 1 to 2 weeks." should replace the last sentence in the Caution section of the Patient's Instructions for Use.

These revisions are terms of the supplemental NDA approval. The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted October 19, 1998) with the revisions noted above.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-762/S-001." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Dr. Denise Toyer, Project Manager, at (301) 827-5584.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-762/S001

MEDICAL REVIEW(S)

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MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

Application #:	20-762	**Application Type:**	NDA
Sponsor:	Schering Corporation	**Product/Proprietary Name:**	Nasonex
Principal Investigator:	Several listed	**USAN/Established Name:**	Mometasone furoate
Category of Drug:	Corticosteroid	**Route of Administration:**	Topical intranasal
Reviewer:	Alexandra S. Worobec, M.D.	**Review Date:**	08/31/98

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
October 24, 1997	October 27, 1997	NDA	Labeling supplement: Park Study for onset of action of mometasone furoate aqueous nasal spray (P97-019).
July 24, 1998	July 27, 1998	NDA	Labeling supplement: Park Study for onset of action of mometasone furoate aqueous nasal spray (P97-020) and Environmental Exposure Unit (EEU) Study of onset of action (I97-341).

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
October 1, 1996	NDA 20-762	Original NDA for NASONEX Nasal Spray for the treatment and prophylaxis of SAR and treatment of PAR in adults and children ≥ 12 years of age.

Overview of Application/Review:.

This is a labeling supplement to NDA 20-762 to evaluate onset of action of mometasone furoate nasal spray (MFNS) in decreasing the nasal symptoms of SAR (rhinorrhea, nasal congestion, nasal itching, and sneezing). A total of 3 studies were submitted: 2 'park' studies and 1 environmental exposure unit (EEU) study. Of these 3 studies, 2 studies (park study P97-019 and the environmental exposure unit study I97-341) showed onset of action of MFNS in decreasing TNSS compared to placebo within 12 hours. It is possible that the 3rd study failed because of low pollen counts on the day of the park study. Nonetheless, based on these data, the recommendation of the medical reviewer is to appropriately change the labeling section in the NASONEX to reflect onset of action within 12 hours.

Outstanding Issues:

None

Recommended Regulatory Action: NA

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

NDAs:

Efficacy/Label Supp.: __X__ **Approvable** _____ **Not Approvable**

Signed: **Medical Reviewer:** /S/ **Date:** 09/14/98

Medical Team Leader: /S/ **Date:** 9/15/98

ONSET OF ACTION:

Onset of action of Mometasone Furoate Aqueous Nasal Spray was evaluated during review of the original NDA for Mometasone Nasal Spray (NDA 20-762) and was based on 2 randomized, double-blind, placebo-controlled, parallel group SAR studies (C93-184 and C93-013); one of which (C93-184) was specifically designed to assess onset of action as an a priori primary efficacy endpoint. Based on data from these 2 studies, statistically significant and consistent efficacy of mometasone 200 µg qd in decreasing total nasal symptoms of SAR (i.e. onset of action), as compared with placebo, appeared to be between 2.0-2.5 days after initiation of treatment, although some subjects experienced SAR symptom relief earlier than this time point [NDA 20-762, 175:47, 122, 125-126, SAS Datafiles, C93-013, Dr. James Gebert, and Medical Officer Review, NDA 20-762, p. 327-330].

Since approval of NDA 20-762, 3 additional studies were performed by the sponsor which evaluated onset of action of mometasone nasal spray in SAR (P97-019, P97-020, and I97-341). Two of these studies (P97-019 and P97-020) were replicate park studies performed that specifically evaluated onset of action of nasal symptom relief on a hourly basis for the first 12 hours of the study post-treatment with the 1st dose of study medication, and one study was an environmental exposure unit (EEU) study which evaluated onset of action of nasal symptom relief after exposure to ragweed pollen on an hourly basis over a 12 hour time period, after initial priming of study patients.

Hence, the medical officer review of onset of action for Mometasone Aqueous Nasal Spray for this Labeling Supplement will focus on these 2 park studies and the EEU study performed subsequent to approval of the NASONEX NDA.

1.1. Protocol P97-019: Onset of Action of Mometasone Furoate Nasal Spray vs. Placebo in SAR During and Acute Outdoor Exposure.

Principal Investigator: Robert B. Berkowitz, M.D.

Participating Center: Atlanta Allergy and Immunology Research Foundation, Atlanta, GA
Atlanta Jewish Community Center, Dunwoody, GA (outdoor exposure site)

1.1.a. Objectives

The primary objective of this study was to define the onset of action after one dose of mometasone furoate nasal spray (MFNS) vs. one dose of placebo nasal spray in treating the nasal symptoms of seasonal allergic rhinitis (SAR).

1.1.b. Study Design

The study was a single-center, randomized, double-blind, placebo-controlled, parallel group onset of action park study of mometasone furoate nasal spray (MFNS) 200 µg qd, vs. placebo nasal spray qd conducted during the spring allergy season (April, 1997) in 240 patients with SAR. After a screening period (Visit 1) in which patients were required to have fulfilled certain pre-defined criteria (e.g. be ≥ 12 years of age and have a history of SAR for at least 2 seasons with a documented a positive skin test within the prior 12 months to at least 1 relevant seasonal allergen prevalent in the local area, along with a total nasal symptom score ≥ 6 and a congestion score ≥ 2, on 6 of the 14 diary time points recorded during the 7 days prior to Visit 2) [specifics of skin testing described in: Labeling Supplement to NDA 20-762, 10/24/97, 18.1:27-28, 60, 62-63], patients were randomly assigned to 1 of the 2 treatment groups delineated above for a 12 hour treatment period (Day 1) [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:18, 60, 67]. Hence, this study consisted of 2 visits, in which Visit 1 of the study was conducted in a clinic, whereas Visit 2 was conducted in a park [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:27, 61]. The protocol and case report form are provided in Appendix 1 and 2, respectively, of volume 35.2 [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:51-133].

Pollen counts were recorded at the investigational site as counts/m^3. Pollen counts were measured on at least 5 days during the week prior to Visit 2 and during Visit 2 [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:25, 62].

During Visit 1 (the screening visit), patients underwent the usual screening procedures [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:26, 73-75]. For the 7 days prior to Visit 2, patients recorded on their diary cards nasal and non-nasal signs and symptoms of SAR every a.m. and p.m., along with adverse events, and concomitant medications.

Nasal symptoms of SAR were the same as those assessed during the original review of NDA 20-762 and included rhinorrhea, nasal congestion, itchy nose, and sneezing. Non-nasal symptoms of SAR were likewise the same as those assessed during original review of NDA 20-762 and included itchy eyes, watering eyes, red eyes, and itchy eyes/palate. Importantly, the non-nasal symptoms of SAR were not used to assess onset of action in the original NDA for mometasone furoate nasal spray, as onset of action specifically focused on nasal symptoms of SAR and hence, will not be assessed here for onset of action. Each symptom was evaluated on a 0-3 (0=no symptoms, 1=mild, 2=moderate, and 3=severe symptoms) scale [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:23, 79].

The total nasal symptom score (TNSS=composite score comprised of the sum of the individual symptom scores of: rhinorrhea, nasal congestion, itchy nose, and sneezing) was utilized in determining the primary efficacy endpoint or the time of onset of symptom relief. These 4 symptoms combined yielded a TNSS scale which could range from score of 0 to 12 (the maximum possible score). If the scores for one of the nasal or non-nasal symptoms was missing, then the total (i.e. total nasal, total non-nasal or total SAR symptom: the sum of nasal and non-nasal symptoms) was missing [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:31].

After recording nasal and non-nasal symptoms on a diary card at 7:30 a.m. on Day 2--the park portion of the study, patients were assembled in a park setting for a 12 hour period post-dosing with study medication for 1 day only. For patients admitted to the study, the 7:30 a.m. symptom scores on Day 2 of the study were used as the baseline. The dose of study medication was administered at 9:45 a.m. and patients were asked to refrain from blowing their noses for 30 minutes following administration of study medication but were allowed to wipe their noses as necessary [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:28, 77]. Patients were also instructed to remain outdoors at the park for 12 hours after dosing, eat only food provided by the investigator, consume no alcoholic beverages, and limit physical activity to mild, nonstrenous activities. Starting 1 hour post-dosing with study medication and continuing until 12 hours after dosing, patients completed diaries every hour in which they recorded nasal and non-nasal symptoms that were based on the patient's status over the previous hour (i.e. reflective scoring), along with recording of adverse events and concomitant medications [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:28, 77-78]. These hourly recordings were used to determine the onset of action. At the final hourly assessment (t=12 hours post-dosing or the time of early termination), patients recorded their evaluation of the response of their SAR to therapy. Patients who withdrew from the study were not replaced [Labeling Supplement to NDA 20-762, 10/24/97 18.1:20].

The primary efficacy endpoint for this study, as defined by the sponsor was the onset of symptom relief, defined as the first occurrence of a total nasal symptom score at least 35% lower than the baseline value (again, baseline score defined as the 7:30 a.m. score on Visit 2) [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:20, 90]. No mention is provided in the study protocol regarding whether the onset of action needed to be a sustained (i.e. more than one time point) difference between a given time point and baseline of 35% in the TNSS.

Reviewer's Note: The medical reviewer did not deem this efficacy endpoint to be a primary efficacy endpoint, because this endpoint did state a priori that a comparison would be made of patients treated with active drug vs. those treated with placebo. Furthermore, the sponsor's analysis does not address maintaining the effect over balance of the dosing interval. This onset of action endpoint was treated as a secondary efficacy endpoint by the medical reviewer.

The medical reviewer, for consistency sake, based on previous SAR onset of action studies reviewed for mometasone furoate and what the Pulmonary Division deems the best choice as a primary efficacy endpoint for onset of action in SAR, chose to use **the change from baseline in TNSS for the MFNS group vs. placebo as the primary efficacy variable** for this study [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:211]. A number of secondary efficacy variables were likewise determined, none of which were used to determine onset of action and will not be further discussed in this review.

For the medical reviewer's chosen primary efficacy variable for the onset of action, the mean, the standard deviation, the median, and the change from baseline, were

presented by treatment group and time for the TNSS, the total non-nasal symptom score, and total SAR symptom score. The difference between treatment groups at each time point was evaluated with the t-test [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:31, 90].

The sponsor's pre-defined onset of action was analyzed using the method of evaluating the distribution of onset times for relief of total nasal symptoms. In this analysis, the exact time of relief for each patient was analyzed, and the cumulative distribution of times was summarized at hourly intervals. Patients who had at least 1 diary assessment after dosing but did not experience symptom relief within 12 hours were considered to be censored at the last time of assessment at Visit 2. The between-group difference in onset time was evaluated for statistical significance with the Wilcoxon test [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:30, 90].

The study was powered such that 96 patients/treatment arm would provide at least 90% power to detect a 20% difference in relief rate (where relief is defined as a 35% decreased from baseline in total nasal symptom scores) with a significance level of α=0.05 (one-sided), assuming a relief rate of 25% in the placebo group *(Desu and Raghavarao, Sample size methodology. Academic Press. 1990)*. Hence, approximately 335 patients were to be screened to provide a total of 192 evaluable patients [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:18, 91].

1.1.c. Results

A total of 240 patients were randomized into the study, 120 patients to the MFNS group and 120 patients to the placebo group. One placebo patient withdrew consent before receiving study medication, leaving 119 placebo patients who received double-blind medication [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:32]. Hence, the safety and ITT populations for this study comprised 120 MFNS patients and 119 placebo patients.

A total of 5 (0.4%) of patients were withdrawn from the study: 4 (3%) for the placebo group and 1 (0.8%) from the MFNS group [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:33].

With regard to protocol violations, because of inclement weather, the last 3 hourly patient evaluations were recorded earlier than called for in the protocol. The hour 10 and hour 11 observations were recorded at hour 9:45 and 10:45, respectively, and the hour 12 observation was recorded at 11:30 [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:33]. Additionally, 4 patients in the MFNS group and 3 in the placebo group failed to observe the required washout period for prohibited medications. These violations were reviewed by the sponsor before the blind was broken and were not considered likely to affect patients' eligibility for evaluation of treatment efficacy [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:33]. Only minimal use of specifically excluded medications (e.g. antihistamines, corticosteroids) occurred during the trial, with 11 patients in the placebo group and 15 patients in the MFNS group for the ITT population taking medications specifically prohibited by the study protocol [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:184]. The number of patients who used concomitant medications, though not necessarily those specifically prohibited by the study protocol for the ITT

population consisted of 21 MFNS patients and 21 placebo patients [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:238].

Patient demographics and patient baseline rhinitis symptoms (including the TNSS) were similar at baseline and were comparable for the 2 treatment groups. More female than male patients were enrolled in the study, the majority of patients were Caucasian, and the mean age at time of enrollment was ~ 32-33 years of age (both treatment groups) [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:185-186]. The groups had moderate baseline nasal symptoms, with a mean baseline TNSS symptom range (defined as the 7:30 a.m. pre-treatment score on Day 2 of the study) of 9.6 for both treatment groups (overall p-value=0.87 for comparison of treatment groups based on the t-test) [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:34-35, 189, 192]. The majority of patients in both treatment groups manifested seasonal allergy to grass, tree, and weed pollen (incidence of 78-91% for both treatment groups) [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:195].

Using the change from baseline (pre-treatment with study medication) in patient hourly self-rated TNSS as the primary endpoint to determine onset of action, results of the 2 treatment groups are presented in Table I. Based on these data, the MFNS Nasal Spray treated patients demonstrated a sustained statistically significant decrease in TNSS when compared to placebo treatment **7 hours** post-initiation of treatment with MFNS Nasal Spray ($p<0.01$) which was demonstrated till the termination of symptom recording at 11.50 hours post-initial dosing with study medication [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:211]. The range in change from baseline in the TNSS for the MFNS treatment group was from -1.55 to -3.28 points (on a maximum scale of 12) and for the placebo group, this range was from -1.39 to -2.76 points for this 11.5 hour period duration [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:211]. Importantly, this numerical range of the change in symptom scores tended to differ by ~ 1 point between the 2 treatment groups, even though statistical significance was reached between these 2 treatments.

Review of the individual nasal symptoms and their relative contribution in determining the overall TNSS was performed by the medical officer, in order to rule out a disproportionate contribution of any one nasal symptom in determination of the TNSS. Based on the data provided for study P97-019 by the sponsor, a slightly greater contribution to the TNSS was afforded by the rhinorrhea and nasal congestion scores, closely followed by the nasal itching score [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:214-216]. The sneezing score was the least important nasal symptom in terms of contributing to the determination of the TNSS score [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:214-217]. Furthermore, review of the individual nasal symptoms indicated a similar degree of symptom decrease at 11.5 hours (~ a 1 point decrease) post-treatment with either MFNS or placebo nasal spray from baseline [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:214-217].

Review of the sponsor's analysis of onset of action using the Wilcoxon ranked test, indicated that statistical significance was not reached ($p=0.22$ for the ITT population) when comparing the 2 distributions of the percentiles of patients experiencing onset of relief (i.e. testing the equality of distributions) (see Table II. below) [Labeling

Supplement to NDA 20-762, 10/24/97, 18.1:201]. Nonetheless, at all assessments after the 1st hour, the cumulative proportion of patients experiencing a ≥ 35% reduction in total nasal symptoms (i.e. onset of relief) was only slightly higher in the MFNS group than in the placebo group. The median time to onset of relief, estimated using the method, was 4.0 hours for the MFNS group and 5.0 hours for the placebo group [Labeling Supplement to NDA 20-762, 10/24/97, 18.1:38, 201].

In summary, based on this onset of action study, MFNS Nasal Spray demonstrated onset of action within 12 hours, compared to placebo treatment when statistically significant differences between active treatment and placebo were compared using the change from baseline in the TNSS. Numerically however, the differences between MFNS Nasal Spray and placebo were small for the TNSS (an approximately 1 point difference between MFNS Nasal Spray and placebo on a 0-12 numerical scale) and even smaller when the individual nasal symptoms of SAR were reviewed (0.4-0.6 point difference).

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Table I.

Onset of Action of Mometasone Nasal Spray vs. Placebo Nasal Spray: Study I97-019; Hourly Patient Self-Rated Total Nasal Symptom Scores Intent-to-Treat (ITT) for 12 hours in a Park Study, Primary Efficacy Endpoint [Labeling Supplement to NDA 20-762, 18.1:211]

	TREATMENT GROUPS		
	[1]MFNS 200 µg qd	Placebo	P vs. MFNS 200 µg qd
Total Nasal Symptom Score (TNSS): Sum of nasal discharge + nasal stuffiness + nasal itching + sneezing scores			
Park Portion of the Study (Day 2)			
Baseline (t=0 hours) (n, mean score, std. dev.(SD))	120, 9.56, 1.68	119, 9.57, 1.57	**0.95**
1 hour post-Rx (n, mean Δ, SD)	120, -1.55, 2.09	119, -1.39, 2.12	**0.55**
2 hours " (n, mean Δ, SD)	120, -2.21, 2.32	119, -2.02, 2.40	**0.53**
3 hours " (n, mean Δ, SD)	120, -2.77, 2.66	119, -2.34, 2.42	**0.19**
4 hours " (n, mean Δ, SD)	120, -3.01, 2.71	119, -2.76, 2.72	**0.47**
5 hours " (n, mean Δ, SD)	120, -2.98, 2.79	119, -2.42, 2.48	**0.11**
6 hours " (n, mean Δ, SD)	120, -3.13, 2.84	119, -2.46, 2.61	**0.06**
7 hours " (n, mean Δ, SD)	120 -3.28, 2.83	119, -2.24, 2.59	[redacted]
8 hours " (n, mean Δ, SD)	120, -2.94, 3.07	119, -1.96, 2.44	[redacted]
9 hours " (n, mean Δ, SD)	120, -3.01, 3.05	119, -1.97, 2.42	[redacted]
9.75 hours " (n, mean Δ, SD)	120, -3.09, 3.13	119, -2.00, 2.63	[redacted]
10.75 hours " (n, mean Δ, SD)	120, -2.91, 3.32	119, -1.95, 2.83	[redacted]
11.50 hours (n, mean Δ, SD)	120, -3.06, 3.22	119, -2.02, 2.67	[redacted]
LAST EVALUATION (n, mean Δ, SD)	120, -3.06, 3.22	119, -2.02, 2.67	[redacted]

[1]MFNS=Mometasone Furoate Nasal Spray, Δ=Change, Std Dev (SD)=Standard Deviation

Baseline is the last pre-treatment reading at time t=0. All other times are post-treatment. The 'Last Evaluation' was each patient's last post-dosing evaluation. The p-values for comparison of treatment groups were based on the 2-sided t-test.

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Table II.

Onset of Action of Mometasone Nasal Spray vs. Placebo Nasal Spray:
Cumulative Distribution of Time to Onset of Relief for Total Nasal Symptom Score (defined as a ≥ 35% Reduction from Baseline in the Total Nasal Symptom Score Intent-to-Treat (ITT) for 12 hours in a Park Study, Secondary Efficacy Endpoint [Labeling Supplement to NDA 20-762, 18.1:201]

	TREATMENT GROUPS		
	[1]MFNS 200 µg qd (n=120)	Placebo (n=119)	P-Value Placebo vs. MFNS 200 µg qd
Time to Onset of Relief (defined as: ≥35 % reduction from Baseline in Patient Self-Rated Total Nasal Symptom Scores)			
≤ 1 hour	20 (16.7%)	21 (17.6%)	
≤ 2 hours	43 (35.8%)	36 (30.3%)	
≤ 3 hours	58 (48.3%)	49 (41.2%)	
≤ 4 hours	66 (55.0%)	56 (47.1%)	
≤ 5 hours	70 (58.3%)	62 (52.1%)	
≤ 6 hours	72 (60.0%)	62 (52.1%)	
≤ 8 hours	78 (65.0%)	65 (54.6%)	
≤ 10 hours	81 (67.5%)	66 (55.5%)	
≤ 12 hours	83 (69.2%)	71 (59.7%)	
NOT REACHED	37 (30.8%)	48 (40.3%)	
TOTAL	120	119	0.22
Estimate of Percentiles for Time of Onset Based on		**Method (Hours)**	
25%	2.0 hours	2.0 hours	
50%	4.0 hours	5.0 hours	
75%	Not Estimable	Not Estimable	

[1]MFNS=Mometasone Furoate Nasal Spray.
The p-value for comparison of the distribution was based on the Wilcoxon statistic. The method was used to estimate percentiles for time to onset of relief (in hours).

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1.2. Protocol P97-020: Onset of Action of Mometasone Furoate Nasal Spray vs. Placebo in Seasonal Allergic Rhinitis During an Acute Outdoor Exposure Study.

Principal Investigator: William E. Stricker, M.D.

Participating Centers: Clinical Research of the Ozarks, Inc., Rolla, Missouri

1.2.a. Objectives

As in study P97-019, the primary objective of this study was to define the onset of action after one dose of mometasone furoate nasal spray (MFNS) vs. one dose of placebo nasal spray in treating the nasal symptoms of seasonal allergic rhinitis (SAR).

1.2.b. Study Design

The study was a single-center, randomized, double-blind, placebo-controlled, parallel group onset of action park study of mometasone furoate nasal spray (MFNS) 200 μg qd, vs. placebo nasal spray qd conducted during the spring allergy season (March-May, 1997) in 200 patients with SAR which was identical in study design to study P97-019 previously reviewed. After a screening period (Visit 1) in which patients were required to have fulfilled certain pre-defined criteria (e.g. age between 12-60 years with a history of SAR for at least 2 seasons with a documented positive skin test within the prior 12 months to at least 1 relevant seasonal allergen prevalent in the local area, along with a total nasal symptom score ≥ 6 and a congestion score ≥ 2, on 6 of the 14 diary time points recorded during the 7 days prior to Visit 2) [specifics of skin testing described in: Labeling Supplement to NDA 20-762, 22.1:16, 58, 60-61], patients were randomly assigned to 1 of the 2 treatment groups: MFNS 200 μg qd or placebo nasal spray, for a 12 hour treatment period (Day 1) [Labeling Supplement to NDA 20-762, 10/24/97, 22.1:18, 65]. Hence, this study consisted of 2 visits, in which Visit 1 of the study was conducted in a clinic, whereas Visit 2 was conducted in a park [Labeling Supplement to NDA 20-762, 22.1:23, 58]. The protocol and case report form are provided in Appendix 1 and 2, respectively, of volume 22.2 [Labeling Supplement to NDA 20-762, 22.1:49-143].

Pollen counts were recorded at the investigational site as counts/m^3. Pollen counts were measured on at least 5 days during the week prior to Visit 2 and during Visit 2 [Labeling Supplement to NDA 20-762, 22.1:22, 60].

During Visit 1 (the screening visit), patients underwent the usual screening procedures seen in SAR trials [Labeling Supplement to NDA 20-762, 22.1:15-17, 24, 58-64, 71-73]. For the 7 days prior to Visit 2, prior to dosing at Visit 2, patients recorded on their diary cards nasal and non-nasal signs and symptoms of SAR every a.m. and p.m., along with adverse events, and concomitant medications.

Nasal symptoms of SAR were the same as those assessed during original review of NDA 20-762 and the other onset of action studies reviewed in this submission and included: rhinorrhea, nasal congestion, itchy nose, and sneezing. Non-nasal symptoms of SAR were likewise the same as those assessed during original review of NDA 20-762

(and the other respective onset of action studies in this submission) and included itchy eyes, watering eyes, red eyes, and itchy eyes/palate. Importantly, the non-nasal symptoms of SAR were not used to assess onset of action in the original NDA for mometasone furoate nasal spray as onset of action specifically focused on nasal symptoms of SAR and hence, will not be assessed here for onset of action. Each symptom was evaluated on a 0-3 (0=no symptoms, 1=mild, 2=moderate, and 3=severe symptoms) scale [Labeling Supplement to NDA 20-762, 22.1:20, 77].

The total nasal symptom score (TNSS=composite score comprised of the sum of the individual symptom scores of: rhinorrhea, nasal congestion, itchy nose, and sneezing was utilized in determining the primary efficacy endpoint or the time of onset of symptom relief. These 4 symptoms combined yielded a TNSS scale which could range from score of 0 to 12 (the maximum possible score). As in study P97-019, if the scores for one of the nasal or non-nasal symptoms was missing, then the total (i.e. total nasal, total non-nasal or total SAR symptom: the sum of nasal and non-nasal symptoms) was missing.

After recording nasal and non-nasal symptoms on a diary card at 7:30 a.m. on Day 2--the park portion of the study, patients were assembled in a park setting for a 12 hour period post-dosing with study medication for 1 day only. For patients admitted to the study, the 8:00 a.m. symptom scores on Day 2 of the study were used as the baseline. The dose of study medication was administered at 8:30 a.m. and patients were asked to refrain from blowing their noses for 30 minutes following administration of study medication but were allowed to wipe their noses as necessary [Labeling Supplement to NDA 20-762, 22.1:25, 75].

Patients were also instructed to remain outdoors at the park for 12 hours after dosing, eat only food provided by the investigator, consume no alcoholic beverages, and limit physical activity to mild, nonstrenous activities. Starting 1 hour post-dosing with study medication and continuing until 12 hours after dosing, patients completed diaries every hour in which they recorded nasal and non-nasal symptoms that were based on the patient's status over the previous hour (i.e. reflective scoring), along with recording of adverse events and concomitant medications [Labeling Supplement to NDA 20-762, 22.1:25, 76-82]. These hourly recordings were used to determine the onset of action. At the final hourly assessment (t=12 hours post-dosing or the time of early termination), patients recorded their evaluation of the response of their SAR to therapy. Patients who withdrew from the study were not replaced [Labeling Supplement to NDA 20-762, 22.1:17].

The primary efficacy endpoint for this study, as defined by the sponsor was the onset of symptom relief, defined as the first occurrence of a total nasal symptom score at least 35% lower than the baseline value (again, baseline score defined as the 7:30 a.m. score on Visit 2) [Labeling Supplement to NDA 20-762, 22.1:25, 88]. No mention is provided in the study protocol regarding whether the onset of action needed to be a sustained (i.e. more than one time point) difference between a given time point and baseline of 35% in the TNSS.

Reviewer's Note: As in study P97-019 previously reviewed, the medical officer did not deem this efficacy endpoint to be a primary efficacy endpoint, because this endpoint did state a priori that a comparison would be made of patients treated with active drug vs. those treated with placebo. This onset of action endpoint was treated as a secondary efficacy endpoint

The medical officer, for consistency sake, based on previous SAR onset of action studies reviewed for mometasone furoate and what the Pulmonary Division deems the best choice as a primary efficacy endpoint for onset of action in SAR, chose to use **the change from baseline in TNSS for the MFNS group vs. placebo as the primary efficacy variable** for this study [Labeling Supplement to NDA 20-762, 22.1:26]. A number of secondary efficacy variables were likewise determined, none of which were used to determine onset of action and will not be further discussed in this review.

The same statistical analysis conducted in study P97-019 was utilized in study P97-020. For the medical officer's chosen primary efficacy variable for the onset of action, the mean, the standard deviation, the median, and the change from baseline, were presented by treatment group and time for the TNSS, the total non-nasal symptom score, and total SAR symptom score. The difference between treatment groups at each time point was evaluated with the t-test [Labeling Supplement to NDA 20-762, 22.1:27-28, 88].

The sponsor's pre-defined onset of action was analyzed using the method of evaluating the distribution of onset times for relief of total nasal symptoms. In this analysis, the exact time of relief for each patient was analyzed, and the cumulative distribution of times was summarized at hourly intervals. Patients who had at least 1 diary assessment after dosing but did not experience symptom relief within 12 hours were considered to be censored at the last time of assessment at Visit 2. The between-group difference in onset time was evaluated for statistical significance with the Wilcoxon test [Labeling Supplement to NDA 20-762, 22.1:27, 88].

The study was powered such that 96 patients/treatment arm would provide at least 90% power to detect a 20% difference in relief rate (where relief is defined as a 35% decreased from baseline in total nasal symptom scores) with a significance level of α=0.05 (one-sided), assuming a relief rate of 25% in the placebo group *(Desu and Raghavarao, Sample size methodology. Academic Press. 1990)*. Hence, approximately 335 patients were to be screened to provide a total of 192 evaluable patients [Labeling Supplement to NDA 20-762, 22.1:15, 89].

1.2.c. Results

A total of 200 patients were randomized into the study, 99 patients to the MFNS group and 101 patients to the placebo group. Two placebo group patients terminated the study early (after dosing with study medication but before the 1st hourly symptom assessment, hence excluded from the ITT population), leaving 99 placebo to complete the double-blind treatment [Labeling Supplement to NDA 20-762, 22.1:29-30]. Hence, the safety and ITT populations for this study comprised 99 MFNS patients and 99 placebo patients.

No MFNS patients withdrew from the study, but a total of 2 placebo patients withdrew from the study, with 2 additional placebo patients (#4 and # 21) excluded from the efficacy population because of inadequate baseline symptom [Labeling Supplement to NDA 20-762, 22.1:30].

With regard to protocol violations, 4 MFNS group patients and 3 placebo group patients (in the efficacy population) took medications prohibited by the protocol [Labeling Supplement to NDA 20-762, 22.1:31]. These violations were reviewed by the sponsor before the blind was broken and were not considered likely to affect patients' eligibility for evaluation of treatment efficacy [Labeling Supplement to NDA 20-762, 22.1:31]. For the ITT population, 10 patients in the placebo (10.1%) and 11 patients in the MFNS group (11.1%) took concomitant medications such as various anti-inflammatory agents (acetaminophen, NSAIDS) [Labeling Supplement to NDA 20-762, 22.1:301].

Patient demographics and patient baseline rhinitis symptoms (including the TNSS) were similar at baseline and were comparable for the 2 treatment groups. Slightly more female than male patients were enrolled in the study, the majority of patients were Caucasian, and the mean age at time of enrollment was ~ 27-28 years of age (both treatment groups) [Labeling Supplement to NDA 20-762, 22.1:32]. The groups had moderate baseline nasal symptoms, with a mean baseline TNSS symptom range (defined as the 8:00 a.m. pre-treatment score on Day 2 of the study) of 8.36 for the MFNS treatment group and 8.30 for the placebo group (overall p-value=0.79 for comparison of treatment groups based on the t-test) [Labeling Supplement to NDA 20-762, 22.1:276]. Same as in study P97-020, the majority of patients in both treatment groups manifested seasonal allergy to grass, tree, and weed pollen (incidence of 76-93% for both treatment groups) [Labeling Supplement to NDA 20-762, 22.1:261].

Using the change from baseline (pre-treatment with study medication) in patient hourly self-rated TNSS as the primary endpoint to determine onset of action, results of the 2 treatment groups are presented in Table I. Based on these data, the MFNS Nasal Spray treated patients failed to demonstrate a sustained statistically significant decrease in TNSS when compared to placebo treatment at all time points throughout the 11 hour period post-dosing with study medication [Labeling Supplement to NDA 20-762, 22.1:276]. Indeed, for many of the time points, the placebo group demonstrated a greater numerical degree of change from baseline in TNSS than did the MFNS group (Table II.). The range in change from baseline in the TNSS for the MFNS treatment group was from -0.89 to
-2.99 points (on a maximum scale of 12) and for the placebo group, this range was from -0.96 to -3.25 points for this 11 hour period duration [Labeling Supplement to NDA 20-762, 22.1:276]. For both treatment groups, but especially more so for the MFNS group, the degree of change from baseline in the TNSS was smaller (~ 0.5 points) than in study P97-019.

Reviewer's Note: It is possible that the similarity of response rates and symptom scores between the 2 treatment groups may be attributable to environmental factors on the day of the 'park' visit (Day 2). These factors may have included the

following: the pollen count was noted to be relatively low (and had been falling for 2 days), the pollen types detected did not represent the full range of pollens that produced allergic responses in the study population, and the early part of the day was cold and overcast (possible weather-related factors that would tend to decrease the pollen count) [Labeling Supplement to NDA 20-762, 22.1:45-46].

In addition, study P97-020 was only carried out till 11 hours post-dosing with study medication which would make it impossible to make conclusions about efficacy at the 12 hour time point (though based on the noted trends in this study, it is not likely that a statistically significant difference in change from baseline in TNSS between MFNS and placebo would have been reached).

Again, review of the individual nasal symptoms and their relative contribution in determining the overall TNSS was performed by the medical officer, in order to rule out a disproportionate contribution of any one nasal symptom in determination of the TNSS. Based on the data provided for study P97-020 by the sponsor (and similar to the findings seen in study P97-019), a slightly greater contribution to the TNSS was afforded by the rhinorrhea and nasal congestion scores, closely followed by the nasal itching score [Labeling Supplement to NDA 20-762, 22.1:279-281]. The sneezing score was the least important nasal symptom in terms of contributing to the determination of the TNSS score [Labeling Supplement to NDA 20-762, 22.1:282]. Furthermore, review of the individual nasal symptoms indicated a similar degree of symptom decrease from baseline (~ a -0.6 to -0.8 points) post-treatment with either MFNS or placebo nasal spray [Labeling Supplement to NDA 20-762, 22.1:279-282]. Interestingly, despite the fact that these differences were not statistically significant, numerically they were slightly greater decrements in individual nasal symptom scores than those noted in study P97-019.

Review of the sponsor's analysis of onset of action using the Wilcoxon ranked test, indicated that statistical significance was not reached ($p=0.88$ for the ITT population) when comparing the 2 distributions of the percentiles of patients experiencing onset of relief (i.e. testing the equality of distributions) (see Table II. below) [Labeling Supplement to NDA 20-762, 22.1:266]. At the majority of assessments after the 1st hour, the cumulative proportion of patients experiencing a $\geq$ 35% reduction in total nasal symptoms (i.e. onset of relief) was not higher in the MFNS group than in the placebo group (a slightly greater response was seen for MFNS patients at 5 and 6 hours post-dosing with medication compared to placebo, however). The median time to onset of relief, estimated using the product-limit method, was 5.0 hours for the MFNS group and 6.0 hours for the placebo group [Labeling Supplement to NDA 20-762, 22.1:35]. Since at least 30% of patients did not achieve onset of relief by 12 hours, the 75th percentile for the distribution of onset time was not estimable in either treatment group. Hence, the comparison based on the Wilcoxon test may not be conclusive [Labeling Supplement to NDA 20-762, 22.1:266].

In summary, based on this onset of action study, MFNS Nasal failed to demonstrate onset of action within 12 hours, compared to placebo treatment when statistically significant differences between active treatment and placebo were compared

using the change from baseline in the TNSS. Similar to study P97-019, numerically the differences between MFNS Nasal Spray and placebo were small for the TNSS, and not vastly different from study P97-019, however a blunted response for the active treatment group compared to the placebo group obscured any demonstrable efficacy for the active treatment group. Reasons for this blunted response in the MFNS group may have been secondary to the low pollen counts and the particular weather conditions at the time of the park study. Furthermore, the study was only carried out till 11 hours post-dosing which would make it impossible to make conclusions about efficacy at the 12 hour time point (though based on the noted trends in this study, it is not likely that a statistically significant difference in change from baseline in TNSS between MFNS and placebo would have been reached).

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Table I.

Onset of Action of Mometasone Nasal Spray vs. Placebo Nasal Spray: Study I97-020; Hourly Patient Self-Rated Total Nasal Symptom Scores Intent-to-Treat (ITT) for 12 hours in a Park Study, Primary Efficacy Endpoint [Labeling Supplement to NDA 20-762, S-001, 07/24/98, 22.1:276]

	TREATMENT GROUPS		
	[1]MFNS 200 µg qd	Placebo	P vs. MFNS 200 µg qd
Total Nasal Symptom Score (TNSS): Sum of nasal discharge + nasal stuffiness + nasal itching + sneezing scores			
Park Portion of the Study (Day 2)			
Baseline (t=0 hours) (n, mean score, std. dev.(SD))	99, 8.36, 1.54	99, 8.30, 1.63	0.79
1 hour post-Rx (n, mean Δ, SD)	99, -0.89, 1.87	99, -0.96, 1.95	0.79
2 hours " (n, mean Δ, SD)	99, -1.57, 2.06	99, -1.58, 2.13	0.97
3 hours " (n, mean Δ, SD)	99, -1.86, 2.23	99, -1.82, 2.34	0.90
4 hours " (n, mean Δ, SD)	99, -1.94, 2.18	99, -2.14, 2.34	0.53
5 hours " (n, mean Δ, SD)	99, -2.07, 2.28	99, -2.17, 2.39	0.76
6 hours " (n, mean Δ, SD)	99, -2.37, 2.27	99, -2.52, 2.70	0.69
7 hours " (n, mean Δ, SD)	99, -2.87, 2.55	99, -2.95, 2.48	0.82
8 hours " (n, mean Δ, SD)	99, -2.79, 2.52	99, -3.02, 2.44	0.51
9 hours " (n, mean Δ, SD)	99, -2.99, 2.52	99, -3.25, 2.51	0.46
10 hours " (n, mean Δ, SD)	98, -2.59, 2.47	99, -2.74, 2.43	0.68
11 hours " (n, mean Δ, SD)	81, -2.57, 2.52	85, -2.80, 2.61	0.56
LAST EVALUATION (n, mean Δ, SD)	99, -2.65, 2.52	99, -2.82, 2.48	0.63

MFNS=Mometasone Furoate Nasal Spray, Δ=Change, Std Dev (SD)=Standard Deviation

Baseline is the last pre-treatment reading at time t=0. All other times are post-treatment. The 'Last Evaluation' was each patient's last post-dosing evaluation. The p-values for comparison of treatment groups were based on the 2-sided t-test.

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Table II.

Onset of Action of Mometasone Nasal Spray vs. Placebo Nasal Spray: Cumulative Distribution of Time to Onset of Relief for Total Nasal Symptom Score (defined as a ≥ 35% Reduction from Baseline in the Total Nasal Symptom Score Intent-to-Treat (ITT) for 12 hours in a Park Study, Secondary Efficacy Endpoint [Labeling Supplement to NDA 20-762, S-001, 07/24/98, 22.1:266]

	TREATMENT GROUPS		
	[1]MFNS 200 µg qd (n=99)	Placebo (n=99)	P-Value Placebo vs. MFNS 200 µg qd
Time to Onset of Relief (defined as: ≥ 35 % reduction from Baseline in Patient Self-Rated Total Nasal Symptom Scores)			
≤ 1 hour	12 (12.1%)	12 (12.1%)	
≤ 2 hours	27 (27.3%)	26 (26.3%)	
≤ 3 hours	37 (37.4%)	36 (36.4%)	
≤ 4 hours	43 (43.4%)	42 (42.4%)	
≤ 5 hours	50 (50.5%)	45 (45.5%)	
≤ 6 hours	54 (54.5%)	51 (51.5%)	
≤ 8 hours	64 (64.6%)	67 (67.7%)	
≤ 10 hours	68 (68.7%)	68 (68.7%)	
≤ 12 hours	69 (69.7%)	69 (69.7%)	
NOT REACHED	30 (30.3%)	30 (30.3%)	
TOTAL	99	99	0.88
Estimate of Percentiles for Time of Onset Based on		**Method (Hours)**	
25%	2.0 hours	2.0 hours	
50%	5.0 hours	5.0 hours	
75%	Not Estimable	Not Estimable	

[1]MFNS=Mometasone Furoate Nasal Spray.

The p-value for comparison of the distribution was based on the Wilcoxon statistic. The method was used to estimate percentiles for time to onset of relief (in hours).

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1.3. Protocol I97-341: Onset of action of mometasone furoate aqueous nasal spray (MFNS) vs. placebo in seasonal allergic rhinitis using the environmental exposure unit.

Principal Investigator: James H. Day, M.D.

Participating Center: Kingston, Ontario, CANADA

1.3.a. Objectives

The purpose of study C97-341 was to evaluate the onset of action of MFNS 200 μg qd vs. placebo in patients ≥ 16 years of age with a history of ragweed SAR of at least 1 year in duration using an environmental exposure unit (EEU) where patients were exposed to ragweed pollen in order to mimic the natural pollen season.

The rationale for conducting this study was to obtain additional clinical data to support a shorter 'onset of action' claim for NASONEX nasal spray. The current NASONEX label states that 'improvement generally occurs within 2 days after initial treatment' with NASONEX nasal spray treatment. Onset of action was determined based on the first time (in hours) at which a consistent statistically significant reduction in total nasal symptoms (MFNS vs. placebo) relative to baseline (pre-dose) symptoms was achieved [NDA 20-762, Labeling Supplement, 22.3:3].

1.3.b. Study Design

Study C97-341 was a single-dose, randomized, placebo-controlled, parallel group, double-blind, single-center study of the onset of action of MFNS (vs. placebo) in patients ≥ 16 years of age with a history of SAR due to ragweed allergen and with moderate symptoms of SAR (total nasal symptom score ≥ 6, with a nasal congestion score ≥ 1 at the baseline visit and end of the final priming session; using a subjective symptom score scale of 0-3, 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms; Table I below) [NDA 20-762, Labeling Supplement, 22.3:27]:

Table 1: SAR Severity Scale

0=None:	No sign/symptom.
1=Mild:	Sign/symptom is clearly present, but with minimal awareness; easily tolerated.
2=Moderate:	Definite awareness of sign/symptom which is bothersome but tolerable.
3=Severe:	Sign/symptom is hard to tolerate; patient desiring treatment or relief.

Patients were to complete up to 8 study visits, to include a screening visit, 1-6 allergen 'priming' visits, and 1 treatment visit. During the treatment visit, patients were to be exposed to allergen for up to 13.5 hours in the EEU.

Inclusion criteria for study C97-341 included the following [NDA 20-762, Labeling Supplement, 22.3:16, 100]

1. Patients must have a history of SAR for at least 1 year, documented by a positive skin test to short ragweed allergen within 1 year of study enrollment via skin prick testing

(wheal diameter ≥ 3 mm). The total severity of the total nasal symptoms (composite of rhinorrhea, sneezing, nasal itching, and nasal congestion (Table 2 below) at baseline and the end of the final allergen priming session baseline visit, is to be ≥ 6, with a nasal congestion score ≥ 1.

2. In females of child-bearing potential, the urine pregnancy test (HCG) must be negative on the screening and treatment visit (phase III of the study).
3. Patients must be at least 16 years of age, of either sex and any race.
4. Patients (and/or parent/guardian) must give written informed consent. Patients must be able to adhere to dose and visit schedules.

Pertinent exclusion criteria for Study C97-341 were as follows [NDA 20-762, Labeling Supplement, 22.3:17, 100-101]:

1. Patients must not have had an upper respiratory or sinus infection for at least 2 weeks prior to treatment.
2. Patients must not have asthma that required systemic or inhaled corticosteroids. In addition, patients must not have been dependent upon nasal, oral, or ocular decongestants and must not have had rhinitis medicamentosa.
3. Patients must not have had 'large' nasal polyps, marked septal deviations, or any other nasal structural abnormality that significantly interfered with nasal air flow.
4. Patients receiving escalating doses of immunotherapy, oral immunotherapy, or short course (rush) immunotherapy for treatment of rhinitis.

Permitted medications included those not restricted in the protocol, and those that would not be expected to interfere with the conduct of the study. Ocular symptoms may have been treated with Vascon A and saline eye drops. Chronic medications were to be dosed on a stable regimen.

The study consisted of 3 phases (I, II, and III). The screening visit (phase I) was approximately 28 days prior to study drug treatment during which patients were screened for inclusion and exclusion criteria, and underwent a routine physical exam (to include nasal exam) and assessment of vital signs. Skin prick testing to confirm hypersensitivity to ragweed allergen were performed and recorded unless previously done in the last year. No laboratory tests were performed for this study, however, all female patients of child-bearing potential were to undergo urine pregnancy testing during the screening visit.

During the priming phase (phase II), patients were exposed to ragweed pollen in the environmental exposure unit (EEU) for up to 3 hours, or until they experienced SAR symptoms. SAR symptoms were scored every 30 minutes until a positive response to priming (total nasal score ≥ 6 or a nasal congestion score ≥ 1) occurred or until 3 hours of exposure had elapsed. Immediately after pollen exposure, patients were transferred to a pollen-free room for up to 1 hour of observation. Patients underwent allergen priming from 1-6 times within 28 days of the screening visit. The number of priming visits required to induce an appropriate allergic response was determined by the investigator and based on the symptom score and physical exam. At least 1 priming resulting in a total nasal score ≥ 6 and a nasal congestion score ≥ 1 will needed to be completed to qualify the prospective patient for randomization to treatment. Patients with a positive

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response during the EEU priming visit(s), were asked to return on the treatment day (phase III of the study). Patients who did not achieve an adequate response during the priming session were asked to return for another session (for up to a maximum of 6 priming sessions). Patients who did not achieve an adequate response after 6 priming sessions were not deemed to meet the inclusion criteria for the study and did not qualify for treatment with study drug.

Pollen counts were measured in the EEU, expressed as 'pollen counts/meter^3, and tabulated for information purposes [NDA 20-762, Labeling Supplement, 22.3:36].

During the treatment phase (phase III), patients arrived at the EEU in the a.m. and completed pre-treatment symptom evaluations at 30 minute intervals for 3 evaluations pre-treatment. Sufficiently symptomatic patients were randomized to one of 2 treatment groups where all treatment units were to be identical in appearance for blinding purposes [NDA 20-762, Labeling Supplement, 22.3:19, 102]. They then received a single dose of medication, and symptom evaluations were performed at 1 hour intervals for the next 12 hours

Study Drug Treatment Groups:

GROUP	a.m. dose	TOTAL DOSE
1	MFNS 50 µg x 4 sprays	MFNS 200 µg qd
2	Placebo x 4 sprays	0 µg qd

Patients were to rate their nasal and non-nasal SAR symptoms per the scoring system delineated in Table I above and these ratings were to be based on the patient's 'instantaneous' symptoms at the time of evaluation.

Table 2: SAR Signs and Symptoms

Nasal signs/symptoms	[1]Non-nasal signs/symptoms
Nasal discharge (anterior of posterior)	Eye itching
Stuffiness/congestion	Eye tearing
Sneezing	Itching of ears/palate
Itching	

[1]NOTE: Eye redness not evaluated in this study.

The primary efficacy variable for study C97-341, the onset of action, was defined as the first time point (in hours) that mometasone furoate nasal spray treatment was statistically significantly superior to placebo, as measured by the change from baseline in total nasal symptoms; with consistent statistically significant superiority at subsequent time points [NDA 20-762, Labeling Supplement, 22.3:32-33]. Based on previous SAR studies with MFNS, where a difference of up to 1.0 points between the MFNS and placebo group (with regard to decrease in total nasal symptoms) with a 2.6 pooled standard deviation was evident within the first 12 hours after dosing with study drug, the sponsor has determined that a sample size of 132 patients/treatment group (a total of 264 randomized, ITT patients) would yield at least 80% power to detect a difference of at

least 0.9 points in change from baseline in the total nasal symptom scores between MFNS and placebo at a 2-sided significance level of α=0.05 [NDA 20-762, Labeling Supplement, 22.3:37].

The statistical method employed in this analysis of the primary efficacy endpoint consisted of a repeated measures analysis extracting treatment, time, and time-by-treatment interaction over the 12 hour post-dosing period for the change from baseline in total symptom scores in order to evaluate the overall treatment effect. If the overall treatment effect was significant, then Student's t test was to be performed at each time point post-dosing to determine the first (consistent) statistically significant result. This provision will allow for control of the type I error rate at an α=0.05.

Secondary time points, which were not the subject of this onset of action included non-nasal symptoms, individual diary symptom scores, and response to therapy. These endpoints were analyzed using the repeated measures model and t-tests at each post-dosing time point, as described above for the primary efficacy endpoint. Response to therapy was likewise analyzed using this model.

1.3.c. Results

A total of 279 patients with SAR due to ragweed allergy, 16-73 years of age were randomized into study I97-341: 139 into the placebo group and 140 into the MFNS group [NDA 20-762, Labeling Supplement, 22.3:40]. Patient demographics and patient baseline rhinitis symptoms (including the TNSS) were similar at baseline and were comparable between the 2 treatment groups [NDA 20-762, Labeling Supplement, 22.3:44]. The groups had moderate baseline nasal symptoms, with a mean baseline TNSS symptom (defined as the last of the pre-treatment symptom score readings obtained during the baseline period) for the MFNS group of 8.97 and for the placebo group: 9.19 (treatment comparison p-value=0.31) [NDA 20-762, Labeling Supplement, 22.3:39, 45-46].

A total of 3 (1%) of patients withdrew from the study: 1 (< 1%) from the placebo group and 2 (1%) from the MFNS group [NDA 20-762, Labeling Supplement, 22.3:40-41]. The 2 patients in the MFNS group discontinued treatment because of malaise or headache, respectively; and the one patient in the placebo group discontinued treatment because of migraine headache. Missing symptom scoring was handled by excluding the combined score that included the missing score. Potential use of specifically excluded medications during exposure in the EEU (e.g. antihistamines, corticosteroids) was not specifically discussed nor tabulated during the trial by the sponsor.

Using the change from baseline (pre-treatment with study medication) in patient hourly self-rated TNSS as the primary endpoint to determine onset of action, results of the 2 treatment groups are presented in Table III. In this study, the MFNS Nasal Spray treated patients demonstrated a statistically significant decrease in TNSS when compared to placebo treatment **at 11 and 12 hours post-treatment with MFNS Nasal Spray. Importantly, no further time points to assess TNSS were studied after 12 hours of treatment with either MFNS Nasal Spray or placebo.** The range of the change from baseline in the TNSS for the MFNS treatment group was from -1.75 to -2.14 points (-19.0

to -22.2% decrement in scores) for the 12 hour duration period (on a maximum scale of 12). For the placebo group, this range was from -1.02 to -2.17 points for the 12 hour period duration points (-9.6 to -22.7% decrement in scores) [NDA 20-762, Labeling Supplement, 22.3:46]. The numerical (and percentage) differences in TNSS between the MFNS group and the placebo group were similar to one another for the first 5 hours post-treatment, but tended to became more divergent between the 2 groups beginning with 6 hours post-treatment [NDA 20-762, Labeling Supplement, 22.3:46].

Reviewer's Note: Interestingly, in this study placebo group patients demonstrated a significant decrease in TNSS for the first 5 hours post-treatment, though the placebo response began decreasing at 6 hours post-treatment and became statistically significantly lower than the response to MFNS Nasal Spray at 11 and 12 hours post-treatment.

Review of the individual nasal symptoms and their relative contribution in determining the overall TNSS was again performed by the medical officer, in order to rule out disproportionate contribution of any one nasal symptom in determination of the TNSS. Based on the data provided for study I97-341 by the sponsor, the symptoms of nasal discharge, nasal congestion, and nasal itching numerically contributed approximately equally to determination of the TNSS [NDA 20-762, Labeling Supplement, 22.3:73-76], with again, a slightly greater contribution by the nasal congestion symptom [NDA 20-762, Labeling Supplement, 22.3:74]. Sneezing contributed least numerically to determination of the TNSS symptom [NDA 20-762, Labeling Supplement, 22.3:75]. Furthermore, for most time points post-dose, no differences were noted in the individual nasal (nasal discharge, nasal congestion, nasal itching, and sneezing) symptom scores. Only for the symptoms of nasal discharge and nasal congestion, was a statistically significant improvement in symptoms compared to placebo noted for the MFNS group at 11 and 12 hours post-dose [NDA 20-762, Labeling Supplement, 22.3:73-74].

In summary, based on this onset of action study, MFN Nasal Spray demonstrated onset of action by 12 hours post-dosing, though subsequent time points were not assessed post-dosing. A fairly strong trend in decreasing TNSS was noted at 6 hours post-dosing for the MFNS group, with statistical significance for the MFNS treatment group seen at 11 and 12 hours post-dosing, compared to placebo. The numerical differences in the change in TNSS for the MFNS treatment group compared to placebo were fairly small (~ 20% decrement in TNSS) compared to changes seen in other corticosteroid trials.

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Table III.

Onset of Action of Mometasone Nasal Spray vs. Placebo Nasal Spray: Study I97-341; Hourly Patient Self-Rated Total Nasal Symptom Scores Intent-to-Treat (ITT) for 12 hours in an Environmental Exposure Unit [NDA 20-762, Labeling Supplement, 22.3:46]

	TREATMENT GROUPS		
	[1]MFNS 200 µg qd	Placebo	P vs. MFNS 200 µg qd
Total Nasal Symptom Score (TNSS): Sum of nasal discharge + nasal stuffiness + nasal itching + sneezing scores			
DAY 1			
Baseline (t=0 hours) (n, mean score)	140, 8.97	139, 9.19	0.31
1 hour post-Rx (n, mean Δ, % Δ)	140, -1.84, -19.5%	139, -1.94, -20.1%	0.72
2 hours " (n, mean Δ, % Δ)	140, -2.14, -22.2%	139, -2.17, -22.7%	0.93
3 hours " (n, mean Δ, % Δ)	139, -1.96, -20.5%	138, -1.88, -19.8%	0.83
4 hours " (n, mean Δ, % Δ)	139, -1.97, -20.6%	138, -2.04, -21.4%	0.83
5 hours " (n, mean Δ, % Δ)	138, -1.88, -20.2%	138, -1.83, -19.3%	0.87
6 hours " (n, mean Δ, % Δ)	138, -1.78, -19.1%	138, -1.43, -15.1%	0.32
7 hours " (n, mean Δ, % Δ)	138, -1.91, -20.7%	138, -1.46, -14.8%	0.21
8 hours " (n, mean Δ, % Δ)	138, -2.02, -21.7%	138, -1.49, -15.1%	0.15
9 hours " (n, mean Δ, % Δ)	138, -1.80, -19.0%	138, -1.32, -12.7%	0.21
10 hours " (n, mean Δ, % Δ)	138, -1.79, -19.3%	138, -1.24, -12.2%	0.13
11 hours (n, mean Δ, % Δ)	138, -1.88, -20.2%	138, -1.08, -10.1%	[redacted]
12 hours " (n, mean Δ, % Δ)	138, -1.75, -19.1%	138, -1.02, -9.6%	0.05

[1]MFNS=Mometasone Furoate Nasal Spray, Δ=Change, %=Percent

Baseline is the last pre-treatment reading at time t=0. All other times are post-treatment. Means presented are unadjusted except for Average. The Baseline mean is based on the actual scores, all other means are based on the change from Baseline P-values are based on the t-test for the difference between MFNS and Placebo, except for the Average which is based on the repeated measures analysis (model: treatment + time + treatment x time).

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1.4. CONCLUSION

Based on review of the 2 'onset of action' park studies and the one environmental exposure unit (EEU) study, all of which evaluated a 12 hour time point post-initiation of treatment with FP Nasal Spray, a 12 hour onset of action of MFNS Nasal Spray (as defined by a sustained statistically significant reduction in TNSS compared to placebo treatment), was demonstrable in 2 of the 3 studies evaluated (1 park study (P97-019) and the environmental exposure unit (EEU) study). In the study that failed to demonstrate an onset of action within 12 hours (P97-020), a number of environmental factors may have attributed to blunting of clinical response in the MFNS group, along with failure to measure patient symptoms beyond the 11 hour time point post-dosing.

The medical reviewer recommends amending the NASONEX label to reflect an onset of action in decreasing TNSS of SAR within 12 hours post-dosing, compared to placebo treatment. Hence, the change in label for NASONEX should now read:

Clinical Studies section: "In patients with seasonal allergic rhinitis, NASONEX Nasal Spray, 50 μg demonstrated improvement in nasal symptoms (vs. placebo) **within 2 days in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic studies and within 12 hours after the first dose in one park study and one environmental exposure unit (EEU) study**. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing."

Information for Patients section: "Improvement in nasal symptoms of allergic rhinitis has been shown to occur **within 2 days after the first dose in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic studies and within 12 hours after the first dose in one park study and one environmental exposure unit (EEU) study**..."

Dosage and Administration section: "Improvement in nasal symptoms has been shown to occur **within 2 days after the first dose in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic studies and within 12 hours after the first dose in one park study and one environmental exposure unit (EEU) study**..."

Reviewed by:

/S/ 09/14/98

Alexandra S. Worobec, M.D.
Medical Officer, Division of Pulmonary Drug Products

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ON ORIGINAL

/S/ 9/15/98

Martin H. Himmel, M.D.
Deputy Director, Division of Pulmonary Drug Products

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-762/S001

STATISTICAL REVIEW(S)

Toyer

Statistical Review and Evaluation
Clinical

OCT 19 1998

NDA#:	20-762/S-001
APPLICANT:	Schering Corporation
NAME OF DRUG:	Mometasone Furoate
INDICATION:	Asthma
DOCUMENTS REVIEWED:	Volume 22.1 –22.4 dated July 24, 1998 .

Note: this reviewer did not have electronic datafiles for these studies, only the results from the sponsor are discussed in this review.

The submission contains 2 in-the-park studies (I97-019 and I97-020) and one environment chamber study (I97-341) to evaluate whether mometasone has an onset of effect within 12 hours. All three studies took a baseline assessment at time 0 and 11 or 12 hourly assessments (no 12-hour assessment in Study I97-020).

The two in-the-park studies were powered such that 96 patients/treatment arm would provide at least 90% power to detect a 20% difference in relief percentages (where relief is defined as a 35% decrease from baseline in total nasal symptom scores) with a significance level of 0.05 (one-sided), assuming a relief rate of 45% in the mometasone group and in the placebo group of 25%. However, the only statistical method described in the protocol is the Wilcoxon test of the onset of relief distributions.

The environment chamber study chose a sample size of 132 subjects per treatment to assure at least 80% power to detect a difference of 0.9 points in changes from baseline comparing the total nasal symptoms scores of the two treatments using a two-tailed 0.05 significance level. The sponsor stated that a repeated measures analysis (including factors for treatment, time and time by treatment interaction) would be performed to evaluate overall treatment effect. The protocol states that if the overall treatment effect is significant, then student t-tests will be performed at each time point post-dosing to determine the first consistent statistically significant result. It further stated that this would allow them to control type I error rate at the 0.05 level.

The medical officer, Dr. Worobec, indicated that total nasal system score should be considered the primary analysis measure. The primary analysis would then be t-tests of the mean changes from baseline at each hourly evaluation. One would look for the first hourly evaluation that showed statistical significance with continued significance for hourly evaluations after that time point.

The two in-the park studies failed to show efficacy in the predefined Wilcoxon test of onset distributions ($p=0.22$ in Study I97-019 and $p= 0.88$ in Study I97-020). The percentage of patients with relief as defined above were about 69% for mometasone in both studies with the placebo rates of 60% in Study I97-019 and 69% in Study I97-020.

The placebo rate is surprisingly high considering the sponsor's assumption of a 25% relief rate.

However, Study I97-019 did show a significant difference ($p<0.01$, two tailed) in the mean changes from baseline in total nasal symptom scores between mometasone and placebo from Hours 7 through 12, with about a 1 point difference between treatments in the mean changes. Study I97-020 failed to show any significant differences between treatments at any hour. Placebo showed numerically more mean improvement than mometasone in changes in total nasal symptom score from baseline at all hours except Hour 3. At the end of 11 hours, both groups were showing mean changes of about -2.7. The sponsor stated that this study may have failed due to low pollen counts and because the early part of the test day was cold and overcast.

The environment chamber study, I97-341, showed a significant difference between the two treatments at 11 hours ($p=0.03$) and 12 hours ($p=0.046$) in the mean changes from baseline in total nasal symptom score. The difference in means changes was about 0.7-0.8. At 12 hours the mean change in total symptom scores was –1.75 for mometasone and –1.02 for placebo. The repeated measures analysis was not significant for the average treatment effect ($p=0.28$).

The overall p-value of the repeated-measures test should not be used to control the type I error rate at 0.05. With results such as the sponsor's (only at 11 and 12 hours did a significant effect occur), *a priori,* it appears likely that the overall repeated measures p-value for treatments would not be significant. The sponsor already has a control on type I error by the necessity that significance must be consistently obtained after some hour.

Reviewer's comments

This reviewer agrees with the medical officer that it is appropriate to use changes from baseline in total nasal symptom score as the primary variable to assess onset of effect. The sponsor did not accurately estimate the percentages of relief that would be obtained in the in-the-park studies (using relief as a 35% decrease in total nasal symptom scores). [In planning the trials, the sponsor assumed that 25% of placebo patients would get relief whereas 60% of placebo patients in Study I97-019 and 69% of placebo patients in study I97-020 got relief. The mometasone percentages were also inaccurate.] This reviewer does not know why Study I97-020 failed. (The sponsor stated that it might be due to low pollen counts). The results of the in-the-park studies were thus inconsistent. Study I97-019 showed efficacy at hour 7 through hour 12 in changes in total nasal symptom scores whereas Study I97-020 showed results numerically favoring placebo for this measure.

The environment chamber study, I97-341, showed efficacy at hours 11 and 12 in mean changes in total symptom score.

Though the evidence is not strong, the sponsor has presented results from two studies demonstrating onset of effect within 12 hours.

/S/

James R. Gebert, Ph. D.
Mathematical Statistician

/S/ 10/19/98

Concur: Dr. Wilson
This review contains 3 pages of text.
CC:
NDA 20-762/S-001
HFD-570
HFD-570/Dr. Worobec
HFD-570/Ms. Toyer
HFD-715/Div. File,Chron
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-762/S001

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20762	**Trade Name:**	NASONEX NASAL SPRAY (MOMETASONE FUROATE)
Supplement Number:	1	**Generic Name:**	MOMETASONE FUROATE NASAL SUSPENSION
Supplement Type:	SE8	**Dosage Form:**	AER
Regulatory Action:	AP	**Proposed Indication:**	For the prophylaxis and treatment of the nasal symptoms of seasonal allergic rhinitis and the treatment of the nasal symptoms of perennial allergic rhinitis, in adults and children 12 years of age and older.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:
This supplement SE8 is to revise the onset of action and is not a pediatric supplement.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DENISE TOYER

/S/ 11/18/98

Signature Date

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EXCLUSIVITY SUMMARY FOR NDA # N20-762 SUPPL # SE-08

Trade Name Nasonex Nasal Spray, 50 mcg 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 /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE8

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:

The clinical data supports an onset of action of eleven hours based on data from a park study and a chamber study.

_____

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?

No

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 /_X_/ NO /___/

If yes, NDA # 20-762 Drug Name Nasonex Nasal Spray, 50 mcg

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 /___/

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 /__/ 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 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 /___/ 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 /___/ 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:

_____

(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:

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 /___/
Investigation #2	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:

_____ _____

_____ _____

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 /___/

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"):

_____ _____

_____ _____

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: _____

_____

Signature /S/ **Date** 11/18/98
Title: Project manager

Signature of Office/ Division Director /S/ **Date** 11/22

cc: Original NDA
HFD-570/Division File
HFD-93/Mary Ann Holovac

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-762/S001

CORRESPONDENCE

Memorandum of Telephone Facsimile Correspondence

Date: ~~10/27/98~~ 10/28/98 /S/

To: Ms. Elin Krhon
Drug Regulatory Affairs

From: Dr. Denise P. Toyer
Project Manager /S/

Thru: Cathie Schumaker
Chief, Project Management Staff

Subject: Labeling Comments for NDA 20-762/SE-01

Attached are the Division's comments which were discussed in the October 22, 1998, telephone conversation. The first page, of the document, contains the Division's response and recommendations for the CLINICAL STUDIES Section, INFORMATION FOR PATIENTS Section, DOSAGE AND ADMINISTRATION Section, and PATIENTS INSTRUCTIONS FOR USE Section. Pages 2-6 describe the place where the Division's comments should be inserted. Please review the labeling and amend your efficacy supplement with revised labeling by November 3, 1998. (S1)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

/S/
Denise P. Toyer
Project Manager
Division of Pulmonary Drug Products

APPEARS THIS WAY
ON ORIGINAL

NDA 20-762/SE-01
Nasonex Nasal Spray
Schering Pharmaceuticals

FDA Response to 'CLINICAL STUDIES' Section:
In patients with seasonal allergic rhinitis, NASONEX Nasal Spray, 50 mcg demonstrated improvement in nasal symptoms (vs. placebo) within 11 hours after the first dose based on one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study, and within 2 days in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing.

FDA Response to 'INFORMATION FOR PATIENTS' Section:
Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing...

FDA Response to 'DOSAGE AND ADMINISTRATION' Section:
Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks. Patients should use NASONEX Nasal Spray, 50 mcg only once daily at a regular interval.

FDA Response to 'PATIENTS INSTRUCTIONS FOR USE' Section:
Based on single day studies done in a park during pollen season or in a controlled pollen exposure room, improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose. In other studies that lasted up to 2 weeks, improvement in nasal symptoms of seasonal allergic rhinitis was shown to occur within 2 days after the first dose. The full benefit of NASONEX Nasal Spray, 50 mcg is usually achieved within 1 to 2 weeks.

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: November 3, 1998

To: Ms. Bernadette Knott
Drug Regulatory Affairs

From: Dr. Denise P. Toyer
Project Manager /S/

Thru: Cathie Schumaker
Chief, Project Management Staff

Subject: Labeling Comments for NDA 20-762/SE-01

Attached is the Division's additional labeling comment which pertains to the ADVERSE REACTIONS section of the labeling. We recommend adding this sentence as a new paragraph after the last paragraph of the ADVERSE REACTIONS section.

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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Thank you.

/S/

Denise P. Toyer
Project Manager
Division of Pulmonary Drug Products

NDA 20-762/SE-01
Nasonex Nasal Spray
Schering Pharmaceuticals

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ADVERSE REACTIONS. . . . . .Rare cases of nasal ulcers and nasal and oral candidiasis were also reported in patients treated with NASONEX Nasal spray, 50 mcg, primarily in patients treated for longer than 4 weeks.

cases of nasal burning and irritation, and nasal septal perforation among users have been reported in post-marketing surveillance of this product.

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cc
ORIG NDA 20-762/SE-8
DIV. FILE
HFD-570/WOODBEC/TOYER

Toyer

Memorandum of Telephone Facsimile Correspondence

Date: 10/8/98

To: Ms. Elin Krhon
Drug Regulatory Affairs

From: Dr. Denise P. Toyer
Project Manager
/S/

Thru: Cathie Schumaker
Chief, Project Management Staff

Subject: Labeling Comments for NDA 20-762/SE-01

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

/S/

Denise P. Toyer
Project Manager
Division of Pulmonary Drug Products

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Draft

Labeling

Toyer

RECORD OF TELEPHONE CONVERSATION

NDA:	20-762/SE-01	**DATE:**	10/22/98
APPLICANT:	Schering-Plough		
DRUG:	Nasonex Nasal Spray		
INITIATED BY:	**_X_APPLICANT**	**___FDA**	
NAMES AND TITLES OF PERSONS WITH WHOM CONVERSATION WAS HELD:			
FDA:	Ms. Joan Hankin, Dr. Martin Himmel, Dr. John Jenkins, Dr. Denise Toyer and Dr. Alexandra Worobec		
APPLICANT:	Ms. Mary Jane Boyle, Ms. Elin Krhoun, Dr. Richard Lorber, and Ms. Lucy Shneyer		

BACKGROUND

The Division faxed labeling comments to Schering on October 9, 1998. Schering requested a telecon to discuss the Division's labeling recommendations.

TELECON

The telecon began with the Division providing an explanation of our approach to onset of action information in the labeling. In general, applicant's may submit data from several types of studies to support an onset of action claim. These studies include: data from the pivotal Phase 3 efficacy trials, data from park studies, and data from inhalation chamber studies. Any onset of action claims must be reproduced in two studies. Data, pertaining to onset of action, contained in the pivotal Phase 3 trials will generally remain in the labeling. Any subsequent data from single-dose studies which provide for changes in the onset of action claims will be added to the labeling (i.e., onset of action data found in the Phase 3 trial will continue to be included in the labeling in addition to data from new trials).

The Division noted that Schering conducted two park studies and one chamber study. The onset of action for one park study was seven hours (statistically significant) and for the chamber study eleven hours (statistically significant). The second park study did not provide data to substantiate Schering's onset of action claims. Therefore, the Division determined that Schering has two studies which reproduced an eleven hour onset of action. At this time the hour onset of action has not been reproduced and therefore will not be added to the labeling. Since the hour onset of action has not been reproduced, the Division will not allow Schering to use a range of 11 hours as the onset of action in the labeling.

Schering requested that the onset of action information pertaining to the park and chamber study be listed in the labeling prior to the Phase 3 onset of action data. The Division agreed with this modification.

Information for Patients section

The Division agrees, with Schering, that the information provided in this section may be confusing to patients, however physicians use this section to provide additional information to patients. The information in this section should be consistent with the information provided in the CLINICAL STUDIES section.

Patient's Instructions for Use section

This section should contain information which provides patients with a reasonable expectation of the performance of this medication. The Division agrees that providing information regarding Phase 3 trials, park studies, and chamber studies may be confusing to patients. However, the Division feels it is inappropriate to provide limited information (i.e., onset of action of eleven hours only) if the patient use conditions will be substantially different than what is displayed in the labeling. This section of the labeling should provide information to the patient that will reflect the patient's actual use conditions.

Action Items

1. The Division will revise the wording for the Patient's Instructions for Use section and the other sections. The revised labeling will be faxed to Schering by October 27, 1998. Schering will respond to the labeling by October 30, 1998.

/S/

Denise Toyer
Project Manager

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ON ORIGINAL

M E M O R A N D U M

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

DATE: September 28, 1998

FROM: Martin H. Himmel, MD, Deputy Division Director, HFD-570

/S/ 9/28/98

SUBJECT: Secondary Review of NDA 20-762 Onset of Action Labeling Supplement

TO: NDA 20-762

This labeling supplement was submitted to support an onset-of-action of Nasonex earlier than 2 days, as is currently described in the package insert. This supplement includes the results of 2 park studies and one EEU (environmental exposure unit) study in which Nasonex, at a dose of 200mcg per day, was administered to patients with seasonal allergic rhinitis.

The definition of onset-of-action that has been adopted by the Division is the time at which the treated subjects statistically differ from placebo subjects on symptom scores and that the difference from placebo is maintained at subsequent assessments. In the trials included in this supplement, in one park study, an onset of action for Nasonex was seen at hours and in the EEU study it was seen at 11 hours. In the second park study efficacy was not seen. Based on these data, this supplement does support the onset of action of Nasonex by 12 hours. As such, this information can be included in the package insert, however, the onset-of-action data from the trials used to support the approval of Nasonex (onset-of-action was seen within two days) should also be included in the package insert.

cc: HFD570/NDA 20762, Himmel, Worobec, Jenkins, Wilson, Gebert

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NDA SUPP AMEND
SE8-001 BL

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

October 19, 1998

John Jenkins, M.D., Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
HFD-570, Room 10B03
5600 Fishers Lane
Rockville, MD 20857

NDA 20-762/SE-01
NASONEX (mometasone furoate) Nasal Spray, 50 mcg

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 20 1998
HFD-570

SUBJECT: RESPONSE TO FDA REQUEST/DRAFT LABELING

Dear Dr. Jenkins:

We refer you to the October 8, 1998 fax from Ms. Toyer regarding the labeling comments for NDA 20-762/SE-01, our supplement for onset of action.

We are setting up a conference call to discuss the Agency's comments and reach agreement on the labeling.

We are providing responses and revised draft labeling in which deletions and additions to the Agency's recommendations are indicated by ~~strikethroughs~~ and underlines, respectively. For each section of the labeling involved, the FDA comment is repeated below following by Schering's response.

Clinical Studies section:

Comment:

"in patients with seasonal allergic rhinitis, NASONEX Nasal Spray 50 µg demonstrated improvement in nasal symptoms (vs. placebo) within 2 days in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic studies and within hours after the first dose in one single-dose parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study. Maximum benefit is usually achieved with 1 to 2 weeks after initiation of dosing."

Response:

The description of improvement of nasal symptoms for the 'park' and environmental exposure unit studies was moved to the beginning of the sentence since the early time points (<12 hours) were not studied in the 2 randomized, double-blind seasonal allergic studies. The time of improvement in nasal symptoms for each study was included to provide complete information. The second paragraph of this section was revised to

> "In patients with seasonal allergic rhinitis, NASONEX NASAL Spray, 50 mcg demonstrated improvement in nasal symptoms (vs. placebo) within hours after the first dose in one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and 11 hours in one environmental exposure unit (EEU) study and within 2 days in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic studies. Maximum benefit is usually achieved with 1 to 2 weeks after initiation of dosing."

Information for Patients section:

Comment:

"Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 2 days after the first dose in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic studies and within hours after the first dose in one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study..."

Response:

The revised time to improvement in nasal symptoms, 11 hours after the first dose," was included to be consistent with the CLINICAL STUDIES section. The expanded descriptions of the studies were omitted as most patients would not understand this detail if it were provided to them. However, the information is available to healthcare providers since it is included in the CLINICAL STUDIES section. The fifth sentence of this section was revised to

"Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose."

Dosage and Administration section:

Comment:

"Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 2 days after the first dose in 2 randomized, double-blind, placebo-controlled, parallel group seasonal allergic studies and within hours after the first dose in one single-dose, parallel group study of patients in an outdoor 'park' setting (park study) and one environmental exposure unit (EEU) study..."

Response:

The information regarding the time for improvement of nasal symptoms and achievement of maximum benefit was deleted from this section, as it does not pertain to the dosage and administration of the drug. As indicated above, it is described fully in the Clinical Studies, Information for Patients and Patient's Instructions for Use.

Patient's Instructions for Use:

The time for improvement of nasal symptoms to occur was revised to 11 hours" to be consistent with the rest of the package insert. (Note: No FDA comment was received on this section).

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

/S/

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

EK:
Enclosures

Desk Copy: Denise Toyer (via FAX), HFD-570, Room 10B03

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Labeling