CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-121/S009

CORRESPONDENCE

Hillier

MEMORANDUM

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

DATE: October 20, 1998

/S/ 10/21/98

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

SUBJECT: Secondary Review Memo - Flonase Non Allergic Perennial Rhinitis Efficacy Supplement

Concur /S/ 10/25/98

TO: NDA 20-121

Flonase Nasal Spray is currently approved for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis (SAR and PAR, respectively) in patients age 4 years and older. The currently approved doses are the following:

> Adults: A starting dose of 200mcg daily (delivered as either 100mcg twice daily or a single dose of 200mcg daily) with the possibility of decreasing the dose to 100mcg as maintenance therapy.
> Children: A starting dose of 100mcg daily with the option of increasing the dose to 200mcg daily if the patient has not adequately responded to the lower dose.

This submission and medical officer review address extension of the Flonase Nasal Spray indications to include non-allergic perennial rhinitis (NAPR) in adults and children 4 years of age and older as well as the issue of the onset of action of the drug. With regard to the NAPR indication, the sponsor has conducted three clinical efficacy trials in adults with NAPR using the twice daily dosing regimen (200mcg per day). In addition, the sponsor has also submitted studies in patients with PAR in which both the once daily and twice daily regimens were used to demonstrate that in PAR both regimens are comparable. Thus, the sponsor reasons, since the diseases NAPR and PAR have similar symptomatology and in PAR twice daily dosing is comparable to once daily dosing, once daily dosing for NAPR should be supported by the twice daily dosing studies. These PAR studies will be termed "bridging studies" in this memo. With regard to onset of action, the sponsor, Glaxo Wellcome, Inc., had previously been requested to submit their onset of action data for this drug because questions had been raised as to whether the currently labeled onset of action (12 hours) is based on individual studies or a "meta-analysis" of a group of studies. This onset of action issue is discussed in the medical officer review and will be discussed in this memo as well.

NAPR Efficacy Trials

Three clinical efficacy trials were conducted in patients with NAPR. Study 3010 was a four week trial in which three doses of Flonase Nasal Spray (50, 100 and 200mcg twice daily) were evaluated vs placebo. The patients in this study were to rate, on a daily basis, the following four nasal symptoms reflectively over the previous 12 hours: (1) rhinorrhea, (2) nasal obstruction, (3) postnasal drip, and (4) sneezing. These symptoms were rated using a visual analog scale which ranged from a score of 0 (=absent symptoms) to 100 (most severe symptoms). Symptoms were scored in the AM (on awakening) and in the PM (at the end of each day). The total nasal symptom score (TNSS) was calculated by summing the individual reflective symptom scores for nasal obstruction, rhinorrhea, and postnasal drip. The primary efficacy variables were identified as change from baseline in the PM TNSS as well as change from baseline in patient rated overall evaluation of response to therapy. In this study, all three doses of Flonase Nasal Spray were statistically significant vs placebo on both the AM and PM TNSS for the study overall as well as based on a week by week analysis. Similarly, significant differences from placebo were seen on the overall response endpoint as well as for individual symptoms. Therefore, this study supports the efficacy of Flonase Nasal Spray for NAPR.

A second efficacy trial is study 351. Overall, this study was similar in design to study 3010, although only the two higher doses of Flonase Nasal Spray were evaluated. The results of this study demonstrate some significant differences between Flonase Nasal Spray and placebo for the 400mcg per day dose, but not for the 200mcg per day dose. Numerically, the effect of Flonase in this trial was smaller than that seen in study 3010. Therefore, this study does not support the efficacy of Flonase Nasal Spray for the treatment of NAPR.

The third efficacy trial is study 350 and is similar in design and doses to study 351. Of note, while study 3010 enrolled approximately 200 patients per treatment arm, in this study approximately 20 patients per treatment arm were enrolled. Nevertheless, on the primary endpoint of TNSS, the 200mcg per day dose was significantly better than placebo for weeks 1-3 of this 4 week study. While it was not statistically significantly better than placebo at week four, the numerical improvement from baseline was similar for weeks three and four. With regard to individual symptoms, there were trends and scattered time points of significant differences between the 200mcg per day dose and placebo. Numerically, the effects of the 200mcg per day dose in this study were similar to those seen in study 3010. As such, this study also supports the efficacy of the 200mcg per day dose in patients with NAPR.

Bridging Studies

The application contained two such studies which were 24 weeks in duration. In these studies, the treatment arms included Flonase Nasal Spray 100mcg twice daily or 200mcg once daily and placebo. Subjects rated four nasal symptoms (rhinorrhea, obstruction, sneezing and itch) on a 0 - 100 visual analog scale each evening prior to dosing and they also rated nasal obstruction each morning prior to receiving their next dose. In study FLN 310, both doses of Flonase were statistically superior to placebo on the primary endpoint of

patient scored TNSS for the entire duration of the study (24 weeks). Over the course of the trial, subjects in the twice daily dosing group tended to have symptom scores that were 8 - 10 points milder than those in the once daily dosing group, although at baseline there was an eight point difference between the two groups, with milder symptoms in the twice daily group. Statistically significant differences between once and twice daily dosing were seen at baseline, as well as at weeks 1, 2, and 6. Analysis of the end-of-dosing interval efficacy (or duration of drug effect) was only assessed by the AM nasal obstruction endpoint (assessed on awakening by study patients) which showed that the bid dosing was similar to daily dosing in terms of reducing the a.m. nasal obstruction symptom score; small numerical differences in the symptom scores between the 2 dosing regimens were seen (approximately 1-4 point magnitude of difference between scores).

In study FLN 311, while symptoms were again numerically somewhat milder in the twice daily group compared to the once daily group (7-12 points out of a composite maximal total of 400), there were no significant differences between the two treatment groups. Both groups were significantly better than placebo. Similar findings were seen for the nasal obstruction score in the AM.

Overall, these studies suggest a small numerical advantage for twice daily dosing compared to dosing Flonase Nasal Spray once a day, however there were no relevant statistically significant differences between the groups. Thus it does appear that outcomes are overall comparable between the two groups. Therefore, it is not likely that for NAPR, a related disorder, efficacy would be seen with twice daily dosing but not with once daily dosing. Thus, the NAPR studies and "bridging" PAR studies support the efficacy of once daily dosing of 200mcg of Flonase Nasal Spray for NAPR.

Onset of Action:

The medical officer review provides a detailed summary of the onset of action "park" studies and the longer duration clinical trials in which onset of action was evaluated. Using the criteria of achieving and maintaining a statistically significant difference from placebo, the two "park" studies, as well as 3 SAR and 1 PAR (note, the medical officer's label review states 4 SAR studies) do support a 12 hour onset of action for the 200mcg dose of Flonase.

Pediatric Dosing:

As noted above, Flonase Nasal Spray is currently indicated for use in children age 4 years and older. This application does support labeling the drug for use in NAPR in this age population based on the following rationale. Since NAPR could be considered the same disease in children and adults, and in adults it appears that the dose will be the same in NAPR as in allergic rhinitis, thus there is no reason to believe that in children the dose would differ between allergic rhinitis and NAPR.

Safety:

No safety issues were identified which would affect approvability of this indication.

Recommendation:

The indication of NAPR should be approved using the current dosing regimens for allergic rhinitis. The medical officer's labeling comments should be forwarded to the sponsor (they should state "In 4 allergic rhinitis studies" rather than "4 seasonal allergic rhinitis studies").

cc:

NDA 20-121 Division File
HFD-570: Jenkins, Himmel, Worobec
HFD-715: Wilson, Gebert
HFD-570: Hilfiker

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

December 17, 1997

DESK COPY

John Jenkins, M.D., Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Food and Drug Administration
HFD-570, Room 10B-3
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-121; Flonase® (fluticasone propionate) Nasal Spray, 50mcg/actuation
Supplemental Application: Labeling
A Labeling Revision to Add an Indication for the Management of the Nasal Symptoms of Perennial Nonallergic Rhinitis

Dear Dr. Jenkins:

Under the provisions of 21 CFR 314.70(b)(3) we are submitting a supplemental New Drug Application for the use of Flonase Nasal Spray, 50mcg/actuation, for the management of the nasal symptoms of perennial nonallergic rhinitis (PNAR). Flonase Nasal Spray (fluticasone propionate aqueous nasal spray) is currently indicated for the management of the nasal symptoms of seasonal and perennial allergic rhinitis in adults and pediatric patients 4 years of age and older.

This supplement presents safety and efficacy data generated in three adequate and well controlled clinical trials specifically conducted to support the use of this product in patients with PNAR (protocols FLTA3010, FLN-351 and FLN-350).

Data generated from these three studies demonstrate efficacy of fluticasone propionate aqueous nasal spray in patients with PNAR at the same daily dose (200mcg) as is currently approved for adults with allergic rhinitis; however the PNAR studies were carried out using a twice daily dosing regimen (FP 50mcg, 100mcg and 200mcg twice daily). In the absence of a clear dose response or difference in response to fluticasone propionate aqueous nasal spray between perennial rhinitis patients with an allergic or nonallergic causality, we propose to address the dosage regimen for PNAR without altering the existing Individualization of Dosage and Dosage and Administration sections of the package insert. This rationale is based in part on the Points to Consider document on Clinical Development Programs for New Nasal Spray Formulations (January 1996) which suggests that if comparability between two formulations can be established then data

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Five Moore Drive
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North Carolina 27709

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generated in one indication may be extrapolated to other indications - in this case it is proposed to extrapolate an existing administration regimen from one indication to another for an existing formulation.

Glaxo Wellcome sought advice from the Agency (General Correspondence of July 10, 1997) on the acceptability of proposing a once daily claim (FP 200mcg) for this indication based on clinical trials conducted in allergic rhinitis patients which compared once and twice daily dosing regimens. The Agency considered that this proposal was reasonable, since an extrapolation of dosing regimens between indications had been allowed for in prior actions, provided that suitable evidence of comparable efficacy of the two dosing regimens in allergic rhinitis studies could be provided (facsimile of July 25, 1997).

The original NDA presented full reports of six studies which compared once and twice daily dose regimens (four in seasonal allergic rhinitis, two in perennial allergic rhinitis); the current supplement references all of these, but concentrates on the two most relevant studies; FLN-310 and FLN-311. These are considered more important because they were conducted in patients with perennial allergic rhinitis (PAR), a condition closely allied with PNAR, and were studies which generated long term efficacy and safety data (6-month treatment period) with dosing intervals which could be compared with PNAR studies. The results from FLN-310 and FLN-311 are discussed in the Integrated Summary of Effectiveness in this supplement.

Several studies conducted outside the U.S. in perennial rhinitis (mixed allergic and nonallergic) populations are also relevant to this submission, either because of the dosing regimen studied (once daily, FLNT43), the study duration (1 year, FLIT11 and FLIT08), or the patient population (pediatric patients 4-11 years of age, FLNT60, FLNT61). These non-U.S. studies are presented as supportive data, but are pertinent since in clinical practice it is not always possible for the physician to differentiate between allergic and nonallergic rhinitis. Additionally, the product is already indicated for use in pediatric patients 4-11 years of age with seasonal allergic rhinitis or PAR, and while there is limited evidence of safety and efficacy in young children with PNAR, the course of the disease and the safety profile of the compound suggest that it is not necessary to introduce a distinction between allergic and nonallergic causality in this subpopulation.

Full clinical study reports with appendices, data listings and case report form tabulations are provided for the three U.S. studies in PNAR. Full clinical study reports without individual patient data listings are provided for U.S. studies in PAR and non-U.S. studies in adults with perennial rhinitis. Summary clinical study reports are provided for the two non-U.S studies in pediatric patients with perennial rhinitis for which full reports were submitted to the Pulmonary Division in 1996 (approved S-005 to NDA 20-121, October 31, 1997).

The data presented in this supplement provides:

- Clear evidence of efficacy and safety of FP 200mcg daily in patients with PNAR
- Evidence of the comparability of FP 100mcg twice daily and FP 200mcg once daily in patients with PAR
- Reassurance of safety and efficacy in all patients with perennial rhinitis (allergic and nonallergic), including children.

Taken together, these data support extension of the indications for Flonase Nasal Spray to include management of the nasal symptoms of nonallergic rhinitis. It is appropriate to align the dose regimen and age group to which this claim applies with the existing approved product.

Glaxo Wellcome certifies that it has not used in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

If you have any questions or require additional information regarding this application, please contact me at (919) 483-4483.

Sincerely,

/S/

Alison Bowers
Project Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-121/S-009

DEC 23 1997

GLAXO WELLCOME
FIVE MOORE DRIVE
RESEARCH TRIANGLE PARK, NC 27709

Attention: ALLISON BOWERS
PROJECT DIRECTOR
REGULATORY AFFAIRS

Dear:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: FLONASE NASAL SPRAY

NDA Number: 20-121

Supplement Number: S-009

Date of Supplement: DECEMBER 17, 1997

Date of Receipt: DECEMBER 18, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on FEBRUARY 16, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Attention: Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

FOR Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Memorandum of Telephone Facsimile Correspondence

Date: 11/05/98

To: Alison Bowers
Product Director
Regulatory Affairs

From: David Hilfiker
Project Manager

/S/

Through: Cathie Schumaker
Chief, Project Management Staff

Subject: Labeling Recommendations for S-009

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/ 11-5-98

David Hilfiker
Project Manager
Division of Pulmonary Drug Products

cc: Orig NDA 20-121/S-009
HFD-570/div file
HFD-570/Hilfiker
/Schumaker

November 5, 1998

Alison:

I have enclosed a revised package insert for Flonase Nasal Spray which shows the revisions that we recommend following our review of pending supplement S-009, submitted to FDA on December 17, 1997. This supplement provides for the additional indication of perennial nonallergic rhinits for patients 4 years and older.

If you accept our recommended changes, please submit an amendment to your pending supplement incorporating the recommended changes in a clean copy. If you wish to propose alternate language, please call me to discuss your proposal and you may send your proposed language via facsimile for our consideration.

As always, if you have any questions, contact me at (301) 827-1046.

Dave Hilfiker
Project Manager
Division of Pulmonary Drug Products

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Draft

Labeling