

GlaxoWellcome

September 19, 2000

Management Dockets, n/a
Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1-23
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

**Re: Docket No. 00D-1335, CDER 98146. Draft Guidance for Industry on Allergic Rhinitis: Clinical Development Programs for Drug Products; Availability. Page 38563 [FR Doc. 00-15632, published June 21, 2000
NAS; Not Product Specific
General Correspondence: Other**

Dear Sir or Madam:

Glaxo Wellcome endorses publication of the Draft Guidance for Industry on Allergic Rhinitis: Clinical Development Programs for Drug Products. In general, this guidance is extremely helpful. We do have some suggestions for consideration by the Agency. These are provided in the enclosed document and are divided into two sections. The first section provides general comments. The second section presents specific comments identified by section number and line number as they appear on the pdf published copy of the guidance.

Although we have recommended some revisions to this Guidance, we fully support its development and look forward to working with the Agency to finalize a document which provides sponsors with practical, high quality scientific advice that can be incorporated into their development programs.

This submission is provided in paper via duplicate copies with an additional copy on diskette (Word 97) and an electronic copy via email according to the instructions provided at <http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm>.

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Please contact me at (919) 483-4483 if you require clarification of any of these comments. Thank you for your consideration.

Sincerely,

A handwritten signature in black ink that reads "Alison Bowers". The signature is written in a cursive style with a prominent underline at the end.

Alison Bowers
Product Director
Regulatory Affairs

COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY: ALLERGIC RHINITIS: CLINICAL DEVELOPMENT PROGRAMS FOR DRUG PRODUCTS (APRIL 2000)

[Docket No. 00D-1335, CDER 98146. Draft Guidance for Industry on Allergic Rhinitis: Clinical Development Programs for Drug Products; Availability. Page 38563 [FR Doc. 00-15632, published June 21, 2000]

GENERAL COMMENTS

This draft guidance is extremely helpful and sets out a pragmatic, scientifically-based approach to development of these products. It is clear that many of the issues sponsors have faced over the last 8-10 years in development of first, second and third generation antihistamines and intranasal anti-inflammatory products have been taken into consideration during development of this guidance, and that the output reflects a consolidated approach to best practices in drug development. Our general comments are summarized below; detailed comments, referenced to the pdf version of the guidance by line number, are provided on subsequent pages:

- Reference to other widely used subjective symptom score measures such as the 0-100mm visual analogue scale should be included
- We suggest that there may be opportunities to examine use of objective endpoints such as peak nasal inspiratory flow (PNIF) as a primary endpoint (Wilson 2000, Bende 2000, Castel-Branco 2000, Penttila 2000)
- Additional guidance is required with respect to dose-ranging studies for intranasal corticosteroids
- Discussion of the potential for study of some of these products in other indications may be appropriate, e.g., nasal polyps, sinus conditions, nonallergic rhinitis
- More clarity is required with respect to the use of active controls in Phase II and III studies
- The reference to inclusion of oral prednisone in safety studies is unnecessary and should be deleted
- References to urinary cortisol should be clarified as being corrected for creatinine.

We appreciate the opportunity to comment on this draft guidance and look forward to its finalization and implementation.

SPECIFIC COMMENTS

I. INTRODUCTION

No comments.

II. BACKGROUND

Lines 35-36: We agree with the current definition of nasal and non-nasal symptoms of allergic rhinitis.

III. OVERALL CONSIDERATIONS - ADULT PROGRAM

A. New Molecular Entity

1. Number of Trials

Line 59: We support the approach taken to extrapolation of efficacy data generated in Phase III trials between seasonal and perennial allergic rhinitis studies. We suggest that the same approach would be appropriate for promotional claims e.g., references to individual symptoms.

2. Dose

Lines 70-71: Given the established importance of determining the lowest effective dose for new medicines and the difficulties experienced by sponsors in demonstrating this for intranasal corticosteroid products already on the market, additional guidance regarding the most appropriate study design for dose-ranging studies in allergic rhinitis would be helpful. It is especially difficult to develop low dose formulations of highly potent molecules for intranasal administration and it may be more meaningful to establish which of a range of doses or dosage regimens has the most favorable risk/benefit/convenience profile. Use of composite, subjective symptom scores as the primary endpoint also makes differentiation between doses of these products problematic.

The dose-ranging study should include a placebo control. We assume from the guidance that the dose-ranging study can be conducted either in SAR or PAR patients to establish the dose for both indications, but it may be helpful to state this.

3. Safety Monitoring

Lines 92-93: Instead of simply specifying that studies should be performed with both a macrolide and azole antibiotic, we suggest that insertion of a specific reference to the FDA guidances on Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro (April 1997) and In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling (November 1999) would be more appropriate, since this is a rapidly evolving area.

Insert after Line 111: Specific reference to liver function testing of drugs in the leukotriene class should be added. Specific reference to food interaction studies for all oral drugs, including the antihistamine class, should be added.

4. Corticosteroid Issues

Line 124: All references to timed urinary free cortisol level measurements should indicate that these must be corrected for creatinine. We are not convinced that urinary measures alone are appropriate for assessment of adrenal function in adult studies. Urinary measures corrected for creatinine are appropriate for pediatric studies.

Lines 127-128: We request deletion of the reference to inclusion of oral prednisone as a positive control to assess safety of corticosteroids. It is true that prednisone controlled studies were required during development of currently marketed products (Vargas 1998, study FLN-260 in NDA 20-121). However, other PK/PD models for assessing the HPA axis effects of inhaled and intranasal corticosteroids are now available and can be used to generate data that will be useful for product labeling purposes. Carefully conducted crossover design studies with frequent serial measurement of serum cortisol in adequately powered studies can detect relatively small changes in cortisol levels with confidence (e.g., 12 subjects in a crossover design (placebo vs. active), is powered to detect a 20% change), obviating the absolute need for positive controls. We do not believe that conduct of a prednisone-controlled study will add value to clinical development programs for new corticosteroids. Use of oral prednisone is a somewhat outdated approach to treatment of seasonal allergic rhinitis and so we do not think it is appropriate to randomize subjects to receive oral prednisone for a period of 6 weeks. Since oral prednisone is 80% bioavailable these subjects would likely experience HPA axis-related systemic effects and adverse events that would be unlikely to occur with the test drug.

We do agree that inclusion of a placebo control would be appropriate for these studies. Inclusion of an active control, selected from currently approved intranasal corticosteroid products, may be helpful but should not be obligatory.

Lines 130-134: We suggest that it would be sufficient to include the slit lamp examinations and intra-ocular pressure testing for cataracts and glaucoma in the protocols for long term clinical studies only. Inclusion of these measures in the shorter term efficacy studies will add little value and will increase development costs significantly. Such events should be carefully monitored during post-marketing surveillance/risk management programs and signals acted on as appropriate.

B. Change in Formulation and/or Device

1. Oral Formulations

No comments.

2. Topical Nasal Formulations

Lines 165-179: The guidance provided in this section with respect to a comparability or stand alone approach to validating a change to a product is helpful. It should be clearly stated that these study designs are not intended to establish bioequivalence between formulations that would be available to the public interchangeably i.e., they will not support substitution between a Test and Reference product or approval of an ANDA. This situation is the subject of separate draft guidance currently under development (Draft Guidance for Industry: June 1999: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action).

Line 173: After 'technically feasible', insert 'using current, sensitive, validated methodology with clearly stated limits of quantitation'.

Lines 183-184: We are not convinced that it is always necessary to conduct a dose-ranging study as part of a stand-alone program for a reformulated product. We do not believe, for example, that it would be necessary to reinvestigate the lowest effective dose for an active ingredient for which a safe and effective dose has previously been established. If systemic exposure is suitably elucidated through PK/PD studies, and local delivery studies confirm and define efficacy, we propose that the same dose range/regimens as previously marketed would be suitable for study. If there is a proven precedent for conducting such studies, we suggest that additional guidance, perhaps repetition of the advice provided in lines 168-171, be provided here.

3. Safety Monitoring

No comments.

4. Corticosteroid Issues

Lines 229-231: All references to timed urinary free cortisol level measurements should indicate that these must be corrected for creatinine. We are not convinced that urinary measures alone are appropriate for assessment of adrenal function in adult studies. Urinary measures corrected for creatinine are appropriate for pediatric studies. Specific guidance on the inclusion of active (old formulation, not oral prednisone) and placebo arms in these studies would be helpful.

IV. OVERALL CONSIDERATIONS - PEDIATRIC PROGRAM

A. New Molecular Entity or New Pediatric Indication

1. Drugs Not Previously Studied in Adults

Lines 245-249 and 259-261: We suggest that the two adequate and well controlled studies may be conducted in different age groups across the pediatric population selected for study and that this be stated by addition of a new sentence after the sentence that ends at line 261 as follows:

'These two studies may be conducted in different age groups'.

Line 251: A cross-reference to ICH guidance E11; clinical investigation of medicinal products in the pediatric population, would be helpful here.

Lines 261-263: We agree with the suggestion that a growth study is appropriate for intranasal corticosteroids and that this could be completed post-approval, providing that the pediatric clinical program and approximate timeline for completion of the program and submission of results is agreed with the Agency during drug development.

2. Drugs Already Studied in Adults

Lines 275-277: We accept the value of conducting clinical efficacy studies with intranasal formulations in the pediatric population. It would be helpful to provide guidance about the extent of dose-ranging work expected prior to initiation of Phase III studies in these patients. We suggest that pharmacokinetic data that provide reassurance of systemic safety, coupled with dose-ranging data generated in adults, would provide sufficient basis for selecting a reasonable pediatric dose for further evaluation in local bioavailability and topical efficacy studies for this group of products.

3. Safety Data

No comments.

4. Corticosteroid Issues

Lines 291-295: We strongly agree that ethical concerns should prevent use of oral prednisone as an active comparator in adrenal response studies in pediatric patients. We also agree that inclusion of an active comparator is appropriate for these studies and suggest that an additional placebo arm may not be necessary if an active control is included.

Lines 297-299: We agree that growth studies should be conducted with new molecular entity corticosteroids. Since these are complex studies that take some time to enroll and complete, we maintain that submission of the results of such studies as a Phase IV commitment is sufficient, especially if the pharmacokinetics of the compound are properly understood and efficacy/safety studies have been conducted in pediatric patients. The timing for initiation of these studies relative to submission of the NDA should be agreed with the Division on a case by case basis. It would be helpful for the Agency to develop published guidance about the detailed design of stadiometry studies.

Lines 299-302: We acknowledge that submission of a knemometry study in an NDA including a pediatric claim for an intranasal corticosteroid may provide an early assessment of the potential for gross growth effects, although the predictive value of these studies for long term growth is unproven. At present, these studies can only be conducted in a limited number of centers, using expensive equipment that requires validation and rigorous training of technicians to ensure that the studies are conducted successfully. It is not clear from the guidance what purpose a knemometry study is intended to serve within an NDA program for a new molecular entity. For example, is a

knemometry study a requirement for submission or is it an alternate to early initiation/completion of a stadiometry study? Is it appropriate for the results of a knemometry study to be reflected in the product label instead of, or in addition to, the current class labeling relating to pediatric patients and growth effects for these products?

B. Change in Formulation and/or Device

No comments.

V. PROTOCOL ISSUES AND ELEMENTS

A. Trial Design

Lines 338-341: We agree that superiority over placebo should be the primary requisite for establishing efficacy. While useful in some instances, we do not think that inclusion of a positive control is necessary for all Phase III clinical studies in SAR and PAR. However, a study intended to substantiate a promotional claim of superiority over an approved active control need not be placebo-controlled. We suggest revision of this paragraph as follows:

‘In the development programs for allergic rhinitis drugs, otherwise well-designed and well-conducted studies may occasionally fail to show effectiveness. This is due in part to the subjective nature of the assessments and spontaneous variability in the disease. This observation makes the use of a placebo control of paramount importance, since a positive control equivalence trial cannot be interpreted in such a situation. Therefore, superiority over placebo is the primary requisite for establishing efficacy. Inclusion of a positive control (any other product approved for the indication of allergic rhinitis) may be desirable but is not necessary and need not be included in all studies. However, replicate studies intended to substantiate a promotional claim of superiority over an approved active control need not be placebo-controlled, once efficacy over placebo has been established in separate studies.’

Lines 344-345: Revise ‘adolescents (older than 12 years) and children (younger than 12 years)’, to ‘adolescents (12 years of age and older) and children (under 12 years of age)’, to be clear which group a 12 year old patient belongs to, and for consistency with the age ranges quoted in the FDA guidance on Content and Format for Pediatric Use Supplements.

Line 348: It is usually impractical to include a vehicle placebo run-in period in a SAR study. Some study seasons are not long enough to establish symptomatology during a no drug run-in, then conduct a vehicle placebo run-in, during which an intranasal vehicle placebo would provide some benefit, and then initiate and complete a 2-week treatment period.

Line 358 –362: If the clinical trial program includes more than one SAR study, it should not be necessary to measure pollen counts at all centers for all studies or to conduct separate pollen days analyses. For the purpose of documenting the exposure of patients to

relevant allergens during the study period, provision of pollen counts obtained from an appropriate source in each area where the study is conducted should be sufficient.

It is unlikely that the extent of patient exposure to outdoor air or number of rain days can be reliably documented or be used to generate meaningful data for large multicenter studies. Collection of such data is unlikely to yield information that would be useful for developing product labeling. We recommend that the sentence ‘It may also be helpful....outdoor air’ be deleted.

Line 364: We accept that in SAR trials in geographical areas where pollen seasons are well defined e.g., Texas Mountain Cedar, there are advantages associated with randomizing patients within each center over a relatively short time period. However, this is not practical for all SAR studies or for multinational trials. We note that patients included in spring pollen studies will have an allergic response to one or several allergens and the onset of symptoms for all patients local to a particular site will not be synchronous, thus randomization over a longer period will be more representative of the SAR population under study. The variability in allergen exposure between patients will not necessarily be reduced through a short randomization period approach, which would introduce significant practical difficulties for study centers. Academic centers may not be resourced to manage very short randomization phases and will be discouraged from conducting studies.

Lines 368-370: We appreciate the intent to restrict the conduct of PAR studies to periods when SAR allergens are less abundant. However, many parts of the US have pollen year-round and a blanket restriction would preclude some States from participating in PAR studies. In addition, this will not be practical for studies intended to collect long term safety data (e.g., the 6-12 month studies referenced under III.A.3. above). Provided that efficacy data collected during ‘concomitant SAR/PAR allergen periods’ of the study are not used as the sole evidence of efficacy in PAR, conduct or continuation of long term studies in all geographic regions and through seasonal allergen periods should not be a problem. Patients who suffer symptoms of both diseases might reasonably expect relief throughout exposure to allergens, although an abnormal allergen load might necessitate additional access to rescue medication e.g., for eye symptoms. For example, a 12 month safety study in PAR might initiate in the fall in the northern US and Canada and include primary efficacy assessments after 4 weeks, but safety data would be collected after 6 months of treatment (in the spring) and after 12 months of treatment (the following fall). We propose revision of this bullet point as follows:

‘Many patients with PAR may have concomitant SAR. Therefore, 4-week primary efficacy data from PAR trials should be collected during a time when seasonal allergens relevant to that geographic area are less abundant and therefore less likely to influence results of the trial. Long term safety studies will necessarily continue through concomitant SAR/PAR allergen periods.’

B. Inclusion Criteria

Lines 374-375: After ‘effectiveness trials’, insert ‘in adults and adolescents’. A 2 year history of SAR may not be demonstrable for pediatric patients.

Line 378: Revise ‘within 12 months of enrollment’ to ‘within 24 months of enrollment’.

C. Exclusion Criteria

Lines 416-420: It would be helpful to identify the washout periods for more recently approved antihistamines such as fexofenadine and cetirizine.

D. Blinding

Line 440: It is true that the endpoints that have been traditionally used in allergic rhinitis studies are somewhat subjective. We suggest that more objective endpoints such as Peak Nasal Inspiratory Flow (PNIF) warrant further study (Wilson 2000, Bende 2000, Castel-Branco 2000). These references suggest that domiciliary measurements of nasal peak flow can be correlated with symptoms of SAR and may be a useful objective marker of treatment response in the same way as PEFr measurements are accepted as a marker of asthma symptoms.

E. Formulations and Dosage Regimens

Lines 453-456: We agree that the NDA should make it clear how the formulation studied in clinical trials compares with the to-be-marketed formulation and that bridging studies may need to be conducted if the formulation has evolved during development. It should be noted that the relationship between the studied formulation and to-be-marketed formulation might not be known when an individual clinical study conducted early in development is reported. Thus this discussion is more appropriately addressed in the CMC, Integrated Summaries of Safety and Efficacy and the Human Pharmacokinetics/Bioavailability sections of the NDA. We suggest replacement of ‘study report’ in line 453 with ‘NDA’. In line 457, since the purpose of a bridging study is to link formulations, it is appropriate for the study report to include comparative details of formulation composition and study lots.

F. Evaluation

1. Assessment of Patient Compliance

No comments.

2. Assessment of Rescue Medication Use

No comments.

3. Rating System

Line 480: Replace ‘composite’, which refers to a single score, with ‘total’.

Line 482: We suggest that the visual analogue scale is another suitable, validated allergic rhinitis rating system (Linder 1988). After ‘0-3 scale of severity’, insert ‘or the 0-100mm visual analogue scale for symptom scores’.

Line 482-486: We do not believe that nasal congestion should automatically be excluded from a composite or total nasal symptom score for antihistamines. We suggest that the two sentences included in lines 482-486 be deleted and replaced with a single sentence as follows:

‘Addition or deletion of symptoms to/from the composite or total score, e.g., non-nasal symptoms, based on the drug’s mechanism of action, should be discussed with the Division on a case by case basis.’

4. Recording Scores

No comments.

VI. DATA ANALYSIS ISSUES

A. Collection of Data

Line 526-528: For seasonal allergens where the start of the maximum exposure to pollen period is less well defined and determination of the baseline is problematic, determination of the change from baseline in the total nasal symptom score over the last week of treatment may be a more appropriate primary endpoint than over the overall double-blind period. Both the entire double-blind period and weekly periods should be included as endpoints, as referenced in lines 551-552.

Lines 546-548: It may also be appropriate to assess onset of effect in the clinic over the first few hours of the first day of treatment in these clinical studies. This may permit a more complete comparison with the results of Park or EEU studies.

B. Time to Maximal Effect

No comments.

C. Duration of Effect (End-of-Dosing Interval Analysis)

No comments.

D. Onset of Action

Lines 582-583: The requirement for maintenance/consistency of a statistically significant difference, which should also be a clinically relevant difference, should be further defined. It should apply to all measurements through the dosing interval and be consistent

for a minimum of 24 hours for a once daily product and for at least 12 hours for a twice-daily therapy.

VII. SAR PROPHYLAXIS TRIALS

No comments.

REFERENCES

Wilson A, Dempsey OJ, Sims EJ, Coutie WJR, Paterson MC, Lipworth BJ. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. *Clinical & Experimental Allergy*. June 2000; 30(6):833-838.

Bende M, Carrillo T, Vóna I, da Graça Castel-Branco M, Arheden L. Efficacy of two doses of budesonide aqueous nasal spray and mometasone aqueous nasal spray in patients with perennial allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 2000;105;1(2); abstr. 1143 (AAAAI 2000).

Castel-Branco M G, Bende M, Carillo T, Vona I, Arheden L. Budesonide aqueous nasal spray (bans) compared to mometasone furoate (MF) in patients with perennial allergic rhinitis. *Allergy*. 2000;55 (suppl 63);Abst 769 (EAACI 2000).

Penttila M, Poulsen P, Hollingworth K, Holmstrom M. Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 mcg once daily and twice daily in the treatment of bilateral nasal polyposis: a placebo-controlled randomized study in adult patients. *Clinical & Experimental Allergy*. Jan 2000; 30(1):94-102.

Vargas R, Dockhorn, RJ, Findlay SR et al. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. *J. Allergy Clin. Immunol*. 1998; 102(2): 191-197.

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