

7.7 Clinical Pharmacokinetic Studies

Safety information from these studies were no integrated into assessments of clinical studies, because population, extent, and duration of exposure in these studies were variable and different for either the 12-week trials or the 52-week open label trials. Safety information is therefore presented below.

103 subjects received at least one dose of active study medication in the five PK studies: 38 subjects received both HFA flunisolide and CFC flunisolide, 55 subjects received only HFA flunisolide and 10 subjects received only CFC flunisolide. Mean age of all subjects in all five studies ranged from 24-32 years (range 24-32 years). The three single dose studies included only male subjects while the multiple dose studies included both sexes. The majority of subjects in each of the studies were White.

The five PK studies included a daily dose of 1000 mcg or 2000 mcg CFC flunisolide and a daily dose of 80 mcg, 170 mcg, 292, mcg, 340 mcg, 516 mcg, or 640 mcg HFA flunisolide. All CFC flunisolide doses were administered without a spacer. All HFA flunisolide doses were administered via a built in spacer: Bepak in 4 studies and Trudell in one study.

Subject Discontinuation, Deaths and SAEs: Of 103 subjects who received study medication, 7 (6.8%) discontinued prematurely. One subject discontinued due to an AE (mild tonsillitis considered unrelated to study drug), after treatment with single doses of 584 mcg HFA flunisolide and 1000 mcg CFC flunisolide in period one of the study (Study ANC-PK1-96-01). Other reasons for discontinuation included withdrawn consent, mis-dose, personal reason, other, and family reason.

No deaths or serious adverse events were reported in any of the five studies.

Adverse Events: Among 103 subjects, 44 (43%) had an adverse event(s) during treatment. In single dose studies, headache was the only adverse event reported in 2 or more subjects during any treatment period within a study. In multiple dose studies, adverse events reported in two of more subjects included headache (most common), bradycardia, hypotension, nausea and dizziness. There were no consistent differences between TEAE incidence or event between HFA flunisolide and CFC flunisolide, nor was there evidence of dose related increase in adverse events.

Clinical Laboratory tests and ECGs: No clinically significant values for routine hematology, chemistry, or U/A were observed. All ECGs were within the normal range.

Pulmonary Function: All pre and post-dose FEV₁ values were normal in the 4 studies where pulmonary function was assessed.

In conclusion, safety data in the 5 pharmacokinetic studies do not raise additional safety concerns for HFA flunisolide as compared to CFC flunisolide.

7.8 Summary of Forest Laboratories Literature Search and OPDRA Review

Potential systemic effects include glucocorticoid-related inhibition of bone formation with impact on growth in children and increased risk of osteoporosis in adults and suppression of the HPA axis. Other potential effects include cataract formation and glaucoma as well as local corticosteroid effects. Forest Laboratories and an Agency Safety Evaluator assessed the literature and post-marketing reports for adverse events.

Forest Laboratories on January 21, 2000, using MEDLINE, TOXLINE, EMBASE, BIOSIS conducted a literature search for flunisolide/Aerobid citations and International Pharmaceutical abstracts. In the US and Europe, inhaled aerosol formulations flunisolide, a corticosteroid is used as accepted first-line anti-inflammatory therapy for the maintenance treatment of asthma. In addition, topical nasal sprays are used to treat chronic allergic and non-allergic rhinitis. In literature reports, inhaled daily doses of up to 18 mg/day for 15 days was generally well tolerated by adult patients with asthma. Local adverse reported events included transient hoarseness and "bad taste". Literature reports of systemic effects include a 3 days study in normal volunteers suggesting that 2000mcg CFC flunisolide /day may result in adrenal suppression (decreased urinary cortisol/creatinine excretion). However, a 6-week study in asthmatic patients showed no adverse effects on the HPA axis at the same daily dose using ACTH stimulation testing (which may be a less sensitive test). Reported studies showed no statistically significant variation in bone density after up to 9 months treatment with 1000 mcg CFC flunisolide.

Joyce Weaver, PharmD, Safety Evaluator DDRE I, reports locating no medical literature identifying safety concerns specific for inhaled or nasal flunisolide, in a literature search conducted March, 2001 (see her April 6, 2001 review). As of March 16, 2001, there were 1168 adverse event (including duplicate reports) reported in the AERS database for flunisolide, including reports for inhalation spray and nasal spray. Events were reported more frequently for adults 17-60 years of age than for older adults or children. Events were reported more frequently in female patients than in males. 27.5% of reported events had a serious outcome, including 7 deaths, 45 hospitalizations, 3 life-threatening events, and 12 events resulting in disability. Causes of death were influenza and COPD (1), laryngospasm (1), liver failure in an alcoholic also taking acetaminophen,(1), overdose of unknown drug(1), ventricular fibrillation (1), and unknown (2). The most frequently reported post-marketing AEs among all 3 flunisolide products include in descending order: rhinitis, drug ineffective, parasomnia, epistaxis, nasal septum disorder, pain, application site reaction, taste disturbance, dyspnea, pharyngitis, headache, taste loss and asthma. Additionally, AERS contains 3 reports of osteoporosis, 3 reports of avascular necrosis, 7 reports of Cushing's syndrome, 4 reports of adrenal insufficiency, 2 reports of growth retardation, 5 reports of cataracts, and 13 reports of glaucoma. The event reports for flunisolide are similar to the event reports for other inhaled and nasal corticosteroids, and most of these are included in the labeling for one or more of the flunisolide products. There appeared to be no concerning signals in the overall profile of AERS data for flunisolide as compared to other inhaled and nasal corticosteroids.

7.9 Conclusions on safety of HFA flunisolide

The data reviewed in this ISS support safety of HFA flunisolide at daily doses of 170mcg BID -340 mcg BID in mild-moderate asthmatic adult and adolescent patients ≥ 12 years of age. These data also support the safety of HFA flunisolide at daily doses of 85 mcg BID-170 mcg BID in mild-moderate asthmatic pediatric patients 4-11 years of age. Frequencies of several reported adverse events may be related to well documented local corticosteroid class effects and others may be more related to the age population studied rather than to the drug.

The frequencies of most of the adverse events were generally similar to active controls. HFA flunisolide dose related TEAE frequency was seen for dyspepsia and urinary tract infection in the combined 2 12-week placebo controlled studies, however, no other dose related effects in these combined studies were observed. Analysis of TEAE frequency by age, gender and race revealed no pattern of increased frequency of any TEAE in the HFA flunisolide group by comparison to placebo or active control treatment. Discontinuation due to adverse events occurred twice as frequently in the placebo group as in the HFA flunisolide group (largely due to an increased asthma exacerbation rate). There were no notable effects of HFA flunisolide on routine laboratory assessments or ECGs and no adverse effects on the HPA axis was determined in either the adult or pediatric studies. It should be recognized, however, that flaws in the pediatric study designs do not allow for clear interpretation of HPA axis function or growth in children.

8.0 INTEGRATED SUMMARY OF EFFICACY (vol. 1.87 et seq)

The efficacy database is supported by two adequate and well controlled pivotal trials: ANC-MD-01, a single adult/adolescent study in mild-moderate asthma patients ≥ 12 years and a single pediatric trial, ANC-MD-03 performed in children 4-11 years of age. The primary endpoint for both adult and pediatric studies was change from baseline in percent predicted FEV₁. Secondary endpoints in both trials included AM and PM peak flow rates, AM and PM asthma symptoms, rescue medication use, and discontinuation from the trial due to worsening asthma.

In the adult study, both 170 mcg BID and 340 mcg BID HFA flunisolide doses were statistically superior to placebo for the primary endpoint as well as most of the secondary endpoints. Premature discontinuation from the study due to lack of efficacy or asthma exacerbation, an important clinical measure of efficacy, was far more common in placebo treated patients than in HFA flunisolide treated patients. Treatment effect size differences did not reach 5% for the primary endpoint, which was the basis for powering the adult study, however, difference in actual FEV₁ versus placebo after 12 weeks treatment with HFA flunisolide of 161mL-186mL is nonetheless a reasonable clinical benefit. Numerical dose related effects, suggesting dose ordering, were also observed.

In the pediatric study, both 85 mcg BID and 170 mcg BID HFA flunisolide doses were statistically superior to placebo for the primary endpoint in 6-11 year old patients. Thus, efficacy was supported in this group. Patients 4-5 years of age were enrolled and randomized, but were not required to perform spirometry assessments secondary to their young age. No active treatment trends were observed for the diary recorded secondary efficacy parameters in 4-11 year old patients, nor did this trial demonstrate statistical superiority for in-clinic PEFR. Numerical superiority for in-clinic PEFR favoring HFA flunisolide over placebo was seen in a post-hoc observed case analysis for both the 4-11 year old population and the 6-11 year old population. However, the results for in-clinic PEFR in the 4-11 year old group were less favorable than the 6-11 year old group, suggesting less efficacy in 4-5 year old asthma patients. Difficulty demonstrating significant benefit for in-clinic PEFR may be related to the fact that PEFR assessment can be highly variable, PEFR was not corrected for height, and patients with very mild asthma were randomized. Placebo treated pediatric patients did not demonstrate any reduction in PEFR after randomization, as one would typically expect. Conversely, the lack of effect on in-clinic PEFR may reflect inadequate drug delivery in the very young pediatric population.

No dose response was observed or suggested in the pediatric trial for HFA flunisolide, and there are no PK data in children. Therefore, starting dose recommendations for pediatric patients that include the higher tested dose is not supported. A caveat however, is that these doses were not assessed in more severe asthma patients.

Treatment effect size did not reach 5% for the primary endpoint, which was the basis for powering the adult study. Difference in actual FEV₁ versus placebo after 12 weeks treatment with HFA flunisolide FEV₁ is uninformative in a pediatric trial, because of the wide range of height in children 6-11 years of age. It is therefore difficult to determine whether treatment with 85 mcg BID or 170 mcg BID HFA flunisolide demonstrated a reasonable clinical effect size benefit. Premature discontinuation due to lack of efficacy or asthma exacerbation was more frequently observed for placebo treated patients, however, this difference was not as robust as in the adult trial.

Results from both pivotal trials showed that HFA and CFC flunisolide were significantly superior to placebo treatment and not statistically different from each other in their ability to maintain asthma control over the duration of the trial. However, in the pediatric trial, there was an apparent dose-response relationship across the placebo, 250 and 500 mcg CFC flunisolide groups. The sponsor will therefore not be able to make dose comparability claims between specific HFA flunisolide and CFC doses, especially since there are no existing HFA pharmacokinetic data in children assessing dose comparability.

No important and consistent differences in efficacy response were observed, as analyzed post-hoc for race or gender, in either pivotal trials.

The purpose of this ISE is not to restate the data that support efficacy of HFA flunisolide in the maintenance treatment of asthma. The individual pivotal trials, as already reviewed, individually established those details. Efficacy was not established in the 4-5 year old sub-population, for either of the two doses of HFA flunisolide. Further, the pediatric study failed to demonstrate any additional benefit of the higher dose of HFA flunisolide in mild to moderate children with asthma, whereas, dose response was suggested in the adult/adolescent population.

Because these two trials were performed in very different populations, and because FEV₁ as an endpoint is difficult to integrate meaningfully across adult and pediatric populations, this reviewer does not believe that there is sufficient rationale to further integrate these data. Please refer to the individual study reviews for detailed interpretation of efficacy results.

Two open-label, long term trials assessing safety in adult and pediatric patients demonstrated that efficacy, as measured by FEV₁, PEF, prn albuterol use, asthma symptoms, and nocturnal awakenings due to asthma was generally maintained after 1 year of use. A slight decline in FEV₁ without decline in other measured parameters was observed in both trials, however, this open label trial was not designed to rigorously assess efficacy parameters.

8.1 Conclusions on efficacy of HFA flunisolide

These studies support the efficacy of HFA flunisolide for the maintenance treatment of mild-moderate asthma as prophylactic therapy in a range of doses in adult, adolescent and pediatric populations ≥ 6 years of age. These studies did not assess efficacy in a severe asthmatic population, steroid naïve, and oral steroid-dependant population, therefore efficacy in these populations cannot be evaluated.

9.0 DATA AUDITING

The integrity of the data for the two pivotal trials submitted in this NDA were assessed by two methods. This reviewer examined data line listings of patients and compared them with study report tables, and in some cases for study dropouts, against case report forms.

The Division of Scientific Investigations (DSI) conducted an audit of four centers chosen by this reviewer. Since no treatment by center interaction was identified, and no center seemed to drive the overall study outcome, two of the larger centers from each of the two pivotal trials were chosen to include sites that assessed HPA axis function. Sites were also chosen to include centers where financial disclosure information was incomplete and which were not recently audited by DSI. These sites were reviewed with James Gebert, PhD., Biometrics. This reviewer selected eight patients at random from each of two centers, from each of the adult and pediatric trials (ANC-MD-01 and ANC-MD-03, respectively). Five parameters (actual FEV₁, percent predicted FEV₁, and cortisol at baseline, and at 30 and 60 minutes post cortrosyn stimulation) on specific days were chosen for each patient from the line listings submitted as SAS transport data sets. These 40 data points were compared to original source data at each of the selected center sites.

In July, 2000, this reviewer was notified by DSI that one of the centers' principle investigator in Study ANC-MD-01 was unable to participate in the inspection, because he was terminated from employment at that site and was under investigation for possible fraud in other clinical studies. A For Cause Inspection was conducted that included 100% of patients randomized into Study ANC-MD-01 for the five selected parameters at that site.

9.1 Audit Findings

This reviewer did not identify any concerns about data integrity for the two pivotal trials submitted in this NDA.

DSI audit found that data generated by three principle investigators, including the center site that received a For Cause Inspection, were acceptable for support of the drug claim. However, one of the center sites in pivotal pediatric Study ANC-MD-03 was found to have evidence of data falsification. DSI recommended exclusion of these data from consideration in the NDA application. DSI findings are summarized below for each of the 4 selected sites (see GCP 1 Review authored by Dr. H.W. Ju, M.D.).

Study ANC-MD-03: 33 Study Centers; 863 enrolled patients, 669 randomized patients

1. Site # 34: 34 patients enrolled and 33 patients completed the study. Minor discrepancies were found in four submitted case report forms compared with source data. The data verification table and source data of eight subjects with were reviewed. No discrepancies were found. DSI recommended that data from this site are acceptable to support the NDA.
2. Site # 26: 22 patients enrolled and 16 patients completed the study. Pulmonary function test results were manually altered or otherwise misrepresented (data falsification); without these alterations or misrepresentations, these patients did not meet protocol specified criteria for study inclusion. Other violations included failure to conduct the study according to the approved protocol, and failure to maintain adequate and accurate records of all observations and other data pertinent to the investigation on each patient participating in the study. DSI recommended exclusion of these data from consideration in the NDA application.

Study ANC-MD-01: 51 Study Centers; 653 enrolled patients, 583 randomized patients

1. Site # 17: 43 patients enrolled and 19 patients completed the study. No discrepancies were found when the data verification table for 8 patients was compared with the source data. Deficiencies included failure to maintain adequate and accurate records in four patients, and failure to comply with all requirements of informed consent. DSI recommended that data from this site are acceptable to support the NDA.

2. Site # 10: 59 patients were enrolled and 31 patients completed the study. A for cause inspection was conducted at this site. Only minor violations were identified for specific parameters on all 59 patients were identified. DSI recommended that data from this site are acceptable to support the NDA.

9.2 Data Auditing Conclusions

Data from the Site # 26 cannot be used to support this NDA, because data integrity is uncertain.

9.3 Financial Disclosure

The NDA lacked adequate information addressing financial disclosure of all participating investigators, citing that where there was no information, investigators no longer worked or participated at the trial facilities. An amendment was submitted May 31, 2000, in which the Applicant states that multiple calls were made to those sites, but no information about those investigators could be obtained. The Applicant was asked to certify that there was no financial interest on form 3454 or disclose the financial arrangement of form 3455. Adequate response to the Agency request has not been clarified at the time of this Medical Officer Review.

10.0 REANALYSIS OF EFFICACY IN STUDY ANC-MD-03

Forest Laboratories submitted an NDA amendment March 9, 2001, which provided reanalysis of the primary efficacy endpoint in patients 6-11 year of age and in-clinic PEFr in patients 4-11 years of age, excluding data from the site identified with data falsification following DSI audit. There were no reanalyses provided by the Applicant for other endpoints.

Results from this reanalysis, as assessed by this reviewer and by James Gebert, PhD., Biometrics, were similar to the original analysis. Efficacy in the 6-11 year old pediatric population at both 85mcg BID and 170 mcg BID HFA flunisolide doses continues to be supported by significant differences in change from baseline percent predicted FEV₁ after 12 weeks treatment with data from this site excluded. In-clinic PEFr in patients 4-11 years of age continued to show only a numerical trend favoring HFA flunisolide treatment groups over placebo when data from this site was excluded.

The excluded investigator enrolled 22 patients, of which 20 were randomized and 17 included in the ITT analysis. There were 14 patients in the 6-11 year old group. The following table describes the treatment means, treatment effect and p-values from ANCOVA for percent predicted FEV₁ in patients 6-11 years of age, excluding this investigator.

TREATMENT	BASELINE	12 WEEKS (LOCF)	CHANGE	TREATMENT EFFECT ^a	P- VALUE
PLACEBO (N=93)	84.9 (SD 14.36)	81.7 (SD 17.62)	-3.3 (SD13.52)	N/A	N/A
HFA 85 mcg BID	88.8 (SD 12.40)	90.0 (SD 17.44)	1.2 (SD 12.15)	4.82	0.010
HFA 170 mcg BID	87.6 (SD 14.03)	88.0 (SD 18.14)	0.4 (SD 12.18)	3.99	0.032
CFC 250 mcg BID	88.2 (SD 16.11)	88.6 (SD 16.97)	0.5 (SD 13.74)	4.56	0.015
CFC 500 mcg BID	87.6 (SD 14.76)	90.3 (SD 13.53)	2.7 (SD 9.62)	6.57	<0.001

^a least square mean of treatment minus least square mean of placebo

Mean change in in-clinic PEFR excluding data from this site was 0.9 L/min, 7.4 L/min, and 8.7 L/min for placebo, BID and 170 mcg BID HFA flunisolide respectively. As noted previously, these results did not reach statistical significance, and were similar to the results seen when data from this site were included.

10.1 Conclusions on reanalysis of efficacy

The reanalysis of the primary efficacy endpoint data excluding one pediatric site with questionable data continues to support 85 mcg BID and 170 mcg BID HFA flunisolide in the maintenance treatment of asthma as prophylactic therapy. Evidence of efficacy as demonstrated in in-clinic PEFR continues to fall short of statistical significance in the 4-11 year old population. Results from the reanalysis were very similar to the original analysis for both the primary efficacy endpoint and in-clinic PEFR. Therefore, this reviewer does not find that the reanalyzed data changes the previous conclusion that HFA flunisolide failed to demonstrate efficacy in 4-5 year old patients in this single study.

Dose response was not addressed in the March 9, 2001 amendment. However, since the results of the reanalysis of the primary endpoint are similar to the original analysis, it is assumed that dose response demonstrated by HFA and CFC flunisolide groups should also be similar. No dose response was seen in the original analysis for the HFA flunisolide groups. This reanalysis therefore does not change the original conclusion that there appeared to be no additional benefit for the higher HFA flunisolide starting dose in mild-moderate pediatric asthma patients. A caveat however, is that these doses were not assessed in more severe pediatric asthma patients.

11.0 LABELING REVIEW

A brief review of the label is provided below. This review outlines the major issues identified in the updated (October 19, 2001) draft label provided in the NDA submission. Line-by-line label edits will be provided to the sponsor following detailed interdisciplinary review.



3 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)



12. CONCLUSIONS AND APPROVABILITY

From a clinical perspective based on safety and efficacy data summarized in this medical officer review, Flunisolide HFA Inhaler System is approvable for the indication of maintenance treatment of asthma as prophylactic therapy in adults and children 6 years of age and older. By extrapolation, as a reformulation of marketed CFC flunisolide, Flunisolide HFA Inhaler System is also approvable for patients requiring oral corticosteroid therapy for asthma, where adding Flunisolide HFA may reduce or eliminate the requirement for oral corticosteroids over time.

Adult starting dose is as proposed in the draft label Dosage and Administration section and pediatric starting dose is as amended in the Dosage and Administration in the labeling section of this review.

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4/18/01 12:31:58 PM
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4/23/01 10:30:08 AM
MEDICAL OFFICER

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MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #: 21-247

APPLICATION TYPE: NDA

PROPRIETARY NAME: Flunisolide HFA Inhaler System

CATEGORY: Glucocorticoid

USAN NAME: Flunisolide hemihydrate

ROUTE: Oral inhalation

MEDICAL OFFICER:

REVIEW DATE: June 13, 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission Type</u>	<u>Comments</u>
27 April 2000	27 April 2000	Original New Drug Application	Full study reports for two one-year safety studies will be submitted with the 120-day safety update
31 May 2000	01 June 2000	Information request amendment	Revised detailed index for the pivotal studies and SAS transport dataset files
31 May 2000	06 June 2000	Information request amendment	Revised general index to all submitted NDA volumes
3 March 2000	10 March 2000	IND 51,456	Contains protocol, annotated CRF, content of SAS transport files, and the CDROM SAS transport file datasets for the two pivotal studies to be submitted to the NDA

RELATED APPLICATIONS: not applicable

REVIEW SUMMARY: The applicant has submitted an NDA to support the efficacy and safety of the Flunisolide HFA Inhaler System for the maintenance treatment of asthma in adult and pediatric patients 4 years of age and older. The clinical development program primarily consisted of two 12 week DB, placebo and active controlled studies in patients with mild to moderate asthma (519 Flunisolide HFA Inhaler System exposed patients) and two one-year, open-label, long term safety studies (314 patients Flunisolide HFA Inhaler System exposed patients). The submission originally lacked an adequate index that cited the contents all submitted volumes. It further lacked an adequate detailed index for the two pivotal studies. Volume and page numbers for the after-text tables that were cited in the text were not originally included in either an index or in the text. These issues have been resolved with receipt of the May 31, 2000 amendments. The NDA further lacked adequate information addressing financial disclosure of all participating investigators, citing that those investigators no longer work or participate at the trial facilities. In the May 31, 2000 amendment cover letter, the applicant states that multiple calls were made to those sites but no information about those investigators could be obtained. The applicant will need to detail their efforts to get the information from investigators. For those investigators for which there is no information, the applicant must either certify that there was no financial interest on form 3454 or disclose the financial arrangement on form 3455. This review addresses the filing adequacy for the two pivotal efficacy studies, summarizes the 2 open label long-term safety studies that will be submitted with the 120-day safety update, by prior agreement with the Agency, gives a preliminary assessment of the integrated summary of efficacy and safety, identifies key elements of proposed labeling, and proposes a timeline for clinical review.

OUTSTANDING ISSUES: none from a clinical perspective.

RECOMMENDED REGULATORY ACTION

NDA/Efficacy/Label Supplements:

FILE

REFUSE TO FILE

SIGNATURES

Reviewer: _____

Date: _____

Team Leader: _____

Date: _____

NDA 21-247

MEDICAL OFFICER REVIEW
45 Day Filing Meeting
20 June 19, 2000

PRODUCT Flunisolide HFA Inhaler system
CATEGORY glucocorticoid
ROUTE oral inhalation
SPONSOR Forest Laboratories
Harborside Financial Center
Plaza Three, Suite 602
Jersey city, N.J. 07311
Lester Gibbs, Manager, Regulatory Affairs
201-386-2123, telephone
201-524-9711, facsimile
SUBMITTED 27 April 2000
CDER STAMP 27 April 2000
DAPDP Due 27 March 2000

OVERVIEW OF CLINICAL CONTENT

The applicant has submitted full study reports for 2 pivotal trials to support the efficacy and safety of the Flunisolide HFA Inhaler System for the maintenance treatment of asthma in adult and pediatric patients 6-years of age and older. The clinical development program primarily consisted of two pivotal 12 week DB, placebo and active controlled studies in patients with mild to moderate asthma (519 Flunisolide HFA Inhaler System exposed patients) and two one-year, open-label, long term safety studies (314 patients Flunisolide HFA Inhaler System exposed patients). Full study reports and an updated ISS for two long-term, open-label safety studies will be submitted with the 120-day safety update, by prior agreement with the Agency. As part of this agreement, the sponsor agreed to a 12 month review clock.

There are two ongoing supportive studies (ANC-MD-05 and ~~ANC-MD-04~~). Data from Study 05 (single center randomized, single dose 4-way crossover trial to assess taste in 52 patients with mild asthma) will be submitted with the four month safety update and will add to the safety database, but will not receive in depth review; ~~ANC-MD-04~~ will not be completed until ~~ANC-MD-04~~ and will not be reviewed.

ANC-MD01 and ANC-MD-03 will be reviewed in the most depth for both efficacy and safety because they are the two largest trials, and were fully blinded. ANC-MD-02 and ANC-MD-04 will be used to primarily serve to support safety.

SUMMARY OF CLINICAL TRIALS

◆ **S tudy ANC-MD-01(vol 47-66):** multicenter, double blind, double dummy, parallel group, placebo and active controlled efficacy and safety study in adults (≥ 18 years of age) and adolescents (12-18 years of age) with mild to moderate asthma. Patients meeting inclusion and exclusion criteria entered a 2-week, open-label run-in phase during which time they received CFC flunisolide 500 μ g BID (2 puffs BID without Aerochamber) and as needed albuterol. At the conclusion of the run-in phase, patients were then randomized into one of eight treatment groups to deliver 250, 500, and 1000mcg CFC flunisolide BID or 85, 170, and 340mcgHFA flunisolide BID according to the following: 85 μ g/puff HFA flunisolide formulation (with built-in spacer) given 1, 2, or 4 puffs BID with placebo CFC given 1,2 or 4 puffs BID; 250 μ g/puff CFC flunisolide formulation given 1,2,or 4 puffs BID with placebo HFA given 1,2,or 4 puffs BID; placebo HFA given 2 or 4 puffs BID with placebo CFC given 2 or 4 puffs BID. All patients received four canisters: CFC placebo and/or CFC flunisolide, and HFA placebo and/or HFA flunisolide. Each patient self-administered 1 or 2 puffs from each of the 4 canisters, depending on their group assignment. HFA canisters (active or placebo) were always administered prior to CFC canisters (active or placebo). During the treatment period, CFC Flunisolide was issued as an MDI without a spacer

The primary objective study was to demonstrate efficacy of the medium dose (170 μ g BID) and high dose (340 μ g BID) flunisolide hemihydrate HFA compared to placebo in patients with mild to moderate asthma patients. The primary efficacy parameter was change from baseline in percent predicted FEV₁ after 12 weeks of therapy.

Secondary efficacy parameters included change from baseline in actual FEV₁, prn inhaled agonist use, AM and PM peak flow rate (PEFR), daily, AM, and PM asthma symptom scores, and nocturnal awakenings requiring albuterol use. The study also compared the safety and efficacy of the HFA formulation with the CFC formulation with respect to both the primary and secondary parameters. It also evaluated the efficacy of low dose (85 μ g BID) flunisolide HFA for all parameters.

Safety parameters included adverse events, hematology and serum chemistry, unanalysis, vital signs, physical examination, mouth and throat culture for *Candida*, 12 lead EKG, free urinary cortisol and creatinine, urine deoxyuridine, Cortrosyn stimulation and serum osteocalcin (HPA axis assessments were performed at 12 of 33 study sites, in 240 patients).

Additional analyses included evaluation of the dose response relationship for HFA flunisolide using change from baseline and change from screening in all efficacy parameters at 12 weeks, comparisons of drop-out rates for insufficient therapeutic effect between placebo and HFA flunisolide, and comparisons of HFA flunisolide with placebo for percent predicted FEV₁, actual FEV₁, and mean albuterol use after 6 weeks of treatment.

There were 650 planned patients, 863 enrolled patients, 669 randomized (age 12-78 years) including 66 12-15 years, 669 analyzed for safety and 661 analyzed for efficacy. Eight (1.2%) randomized patients did not have a follow-up assessment of the primary efficacy variable and were not included in the efficacy analyses. It should be noted that there were 30 patients age 12-17 years who were exposed to HFA Flunisolide

- ◆ **S** **study ANC-MD-03 (vol 67-85):** multicenter, double blind, double dummy, parallel group, placebo and active controlled efficacy and safety study in children 4-11 years of age with mild to moderate asthma. Patients meeting inclusion and exclusion criteria entered a 2-week, open-label run-in phase during which time they received CFC flunisolide 500µg BID (2 puffs BID without Aerochamber, unless they were 4-5 years of age) and as needed albuterol. At the conclusion of the run-in phase, patients were then randomized into one of five treatment groups to deliver the following: 85µg/puff HFA flunisolide formulation (with built-in spacer) given 2 puffs BID with placebo CFC 2 puffs BID; 85µg/puff HFA flunisolide formulation (with built-in spacer) given 1 puff BID with placebo HFA 1 puff BID and placebo CFC 2 puffs BID; or 250 µg/puff CFC flunisolide formulation given 2 puffs BID with placebo HFA given 2 puffs BID; 250 µg/puff CFC flunisolide formulation given 1 puff BID with placebo CFC 1 puff BID and placebo HFA 2 puffs BID; placebo HFA given 2 puffs BID with placebo CFC given 2 puffs BID. All patients received four canisters: CFC placebo and/or CFC flunisolide, HFA placebo and/or HFA flunisolide. Each patient administered 1 puff from each of the 4 canisters, depending on their group assignment. HFA canisters (active or placebo) were always administered prior to CFC canisters (active or placebo).

The primary objective study was to demonstrate efficacy of the 170µg BID flunisolide hemihydrate HFA compared to placebo in mild to moderate asthmatic patients. The primary efficacy parameter was change from baseline in percent predicted FEV₁ after 12 weeks of therapy (optional in 4-5 year old patients).

Secondary efficacy parameters for 170µg HFA flunisolide BID vs placebo change from baseline after 12 weeks of treatment included the following: change in in-clinic PEFR; change in prn inhaled albuterol use, change in AM and PM diary peak flow rate (PEFR), change in mean AM and PM asthma symptom scores, and change in mean number of nocturnal awakenings requiring albuterol use. The study also compared the safety and efficacy of the 170 µg HFA formulation with the 500µg CFC formulation with respect to both the primary and secondary parameters. It also evaluated the efficacy of low dose (85µg BID) flunisolide HFA vs placebo for all parameters.

Safety parameters included adverse events, hematology and serum chemistry, mouth and throat smear and culture for *Candida*, unanalysis, vital signs, physical

examination, 12 lead EKG, and Cortrosyn stimulation testing. HPA axis assessments were performed at 17 of 54 study sites.

Additional analyses included evaluation of the 250µg CFC flunisolide BID vs. placebo for both primary and secondary efficacy parameters, evaluation of the dose response relationship for HFA and CFC flunisolide using change from baseline and change from screening in percent predicted FEV1 and in-clinic PEFr at 12 weeks, and evaluation of safety with respect to dose-dependant differences, if any, between HFA and CFC flunisolide and placebo.

There were 510 planned patients, 583 randomized, including 61 patients aged 4-5 years of age. It should be noted that there were only 21 patients 4-5 years of age exposed to HFA flunisolide.

- ◆ **S tudy ANC-MD-02 (protocol-vol 86; final study report to be submitted with 120day safety update)** : a one year, multicenter, randomized, open label active controlled, flexible dose trial in adult and adolescent patients 12-60 years of age with mild to moderate asthma to assess safety. Enrolled patients entered a 1-week run-in period, during which time they continued to take their previous asthma medication. At the completion of the run-in period, patients were randomized into a 12-month, open label treatment period with either Flunisolide HFA Inhaler System 170µg - 340µg BID or beclomethasone dipropionate 168µg-336µg BID. Patients were also issued albuterol to use as needed. Patients were monitored for safety and efficacy at specified intervals during the treatment period. AEs, physical examination, vital signs, ECGs, laboratory examinations, and tests of HPA-axis function were the safety measures obtained during the study. Efficacy was assessed by patient diary of asthma symptom scores, AM PEFr, use of prn albuterol, number of night awakenings that required albuterol use, and percent predicted FEV1 determined by spirometry. 250 patients were randomized, 162 to the HFA flunisolide group and 53 to the beclomethasone group. 100 patients in the HFA flunisolide group completed the study and data analysis is now in progress.

- ◆ **S tudy ANC-MD-04 (protocol-vol 86; final study report to be submitted with 120 day safety update)**: a one year, multicenter, randomized, open label active controlled, flexible dose trial in pediatric patients 4-11 years of age with mild to moderate asthma to assess safety (including growth). At the conclusion of a one week run-in period in which patients received their usual stable dose of asthma medication, enrolled patients aged 4-5 years of age received HFA flunisolide for the remaining 12 month treatment phase. Patients 6-11 years of age were randomized to receive HFA flunisolide, beclomethasone dipropionate, or cromolyn. 253 pediatric patients were randomized. 152 to the HFA flunisolide group, 39 to the beclomethasone group and 44 to the cromolyn group. 106 patients in the HFA flunisolide group completed the study and data analysis is now in progress.

INTEGRATED SUMMARY OF EFFICACY (vol 87)

Subgroup analyses based on age, gender, race and disease severity were assessed in Studies ANC-MD-01 and ANC-MD-03 were performed in addition to primary and secondary analyses or efficacy parameters. These analyses were performed on the percent predicted FEV₁ in Study ANC-MD-01 and the in-clinic PEF_R in Study ANC-MD-03 and overall, appears to be of adequate quality on its face. It should be noted that there are only nine 4-5 year old patients in the 85µg HFA Flunisolide group and only twelve 4-5 year old patients in the 170µg HFA Flunisolide group, sample sizes that are too small to meaningfully evaluate. FEV₁ was not evaluated in the 4-5 year old population. No treatment related trends were demonstrated for the diary recorded secondary efficacy parameters in Study ANC-MD-03, however, subgroup analyses by age for the 4-5 year old patients were not included in the submission. Labeling to include 4-5 year old patients will likely be a review issue. It should further be noted in Study ANC-MD-01, there were only 10 patients age 12-17 year in the 85mcg HFA Flunisolide group, 8 patients age 12-17 years in the 170mcg HFA Flunisolide group, and 12 patients age 12-17 years in the HFA flunisolide group.

INTEGRATED SUMMARY OF SAFETY (vol87)

The safety database is primarily based on 583 pediatric patients and 669 adult and adolescent patients in the two identified pivotal trials and is adequate on its face in patients older than 6years of age. This database will be updated to include long term assessment of safety 152 patients (age 4-11years) randomized to HFA flunisolide in the long term pediatric trial, and 162 patients (age 12-60 years) randomized to HFA flunisolide in the long term adult/adolescent trial. Additionally, the safety data base also includes a total of 103 subjects who received at least one dose of active medication in five PK studies, including 55 subjects who received HFA flunisolide only and 38 subjects who received both HFA and CFC flunisolide. Safety information in these PK studies are based on daily dose exposure up to 2000µg CFC flunisolide and up to 680µg of HFA flunisolide. The applicant also included a literature review summary of other studies conducted in the USA and Europe addressing safety of topical flunisolide nasal spray and inhaled CFC flunisolide at dose up to 20 mg/day. Forest reports that no formal drug-drug interaction studies involving flunisolide are published in the literature, and that drug-disease interactions were not investigated in either pivotal trials.

SUMMARY OF LABELING

- ◆ The following preliminarily highlights labeling to be addressed in the review:

F

J

nilar

FOREIGN MARKETING HISTORY

Marketing approval for Flunisolide HFA Inhaler System has not been sought in any country except the US. Two flunisolide-containing products are marketed outside of the USA. The applicant states that no product containing flunisolide was ever withdrawn from marketing due to safety or effectiveness.

FILING DECISION ISSUES

This application was initially submitted without a complete index to all volumes, and lacked a detailed index for the two pivotal studies in the clinical section. Volume and page numbers for the after-text tables that were cited in the text were not originally included in either an index or in the text. Forest Laboratories subsequently submitted both an adequate general index and an improved detailed index that is adequate for this reviewer. It should be noted, however, that after-text table 3.1.A cited in the text on page 06054 in volume 67 cannot be found. Sandra Barnes, Agency Project Manager spoke with the

Forest representative and was told that this reference was an error. Until these studies are reviewed in depth, it will be unclear if this type of error is an aberration.

The NDA further lacked adequate information addressing financial disclosure of all participating investigators, citing that those investigators no longer work or participate at the trial facilities. In the May 31, 2000 amendment cover letter, the applicant states that multiple calls were made to those sites but no information about those investigators could be obtained. The applicant will need to detail their efforts to get the information from investigators. For those investigators for which there is no information, the applicant must either certify that there was no financial interest on form 3454 or disclose the financial arrangement on form 3455.

The pivotal trials were not conducted with any disqualified investigators and were conducted with the to-be marketed HFA formulation, designed to deliver a minimum of 120 doses of 85µg flunisolide HFA ex-spacer. The to-be marketed formulation and device has minor differences from those used in clinical trials, but are not likely to impact safety or efficacy. Please see the Chemist's Review for evaluation of the to-be-marketed device and formulation changes.

DSI AUDIT

Two of the larger centers from each of the two pivotal trials that assessed HPA-axis parameters were selected. Two of the four selected sites were missing financial disclosure information for all sub-investigators. These sites were reviewed with James Gebert, Biometrics, to assess whether or not efficacy trends appeared to be going in the right direction. Eight patients from each of the two centers, from each of the two pivotal trials, were chosen and five parameters on specific days were selected for each patient from the line listings submitted as SAS transport data sets. At each center, 40 original data points will be compared to the electronic line listings. Copies of the audit instructions and check lists are attached to this document and will be given to the Project Manager.

TIME LINE

July, 2000 Study ANC-MD-01
Mid September, 2000 Study ANC-MD-03
Mid October, 2000, Study ANC-MD-02
Mid November, 2000, Study ANC-MD-04
End November, 2000, Study ANC-MD-05
Mid January, 2000, Integrated Safety Summary
Mid February, 2000, label review
Mid March, 2000, complete

**PROTOCOL ANC-MD-01 INVESTIGATOR: Jay Grossman CENTER: 10, Vivra Research Partners
Tucson, AZ**

INSPECTORS

The patient identification number, initials and date of the sixth visit are in the left-most column. Find the cortisol-baseline, cortisol-30 min, cortisol-60 min from the blood sample obtained on that date. Also find the Fev-actual and Fev-% of predicted from the spirometry performed on that date. If the value is the same, check the neighboring box in the adjacent column. If the value is not the same, please fill in the correct value.

PROTOCOL ANC-MD-01		INVESTIGATOR: Grossman				CENTER: 10, Tucson, AZ					
Patient ID Number/Initials/Date		Visit 6				Visit 6					
		Cortisol - Baseline		Cortisol - 30 minutes		Cortisol - 60 minutes		Fev-actual		Fev-% of predicted	
		Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry
1024/	'13July98	8		25		27		2.79		76	
1022/	11July98	13		20		24		2.64		91	
1023/	10July98	13		23		25		2.37		102	
1020/	/06July98	14		21		23		2.39		67	
1005/	/04May98	21		28		24		3.02		74	
1009/	13May98	16		23		29		2.54		72	
1007/	15May98	9		6		4		2.26		77	
1006/	'22May98	11		19		22		2.67		64	

PROTOCOL ANC-MD-01 INVESTIGATOR: Harold Nelson CENTER: 17, National Jewish Medical and Research Center, Denver, CO.

INSPECTORS

The patient identification number, initials and date of the sixth visit are in the left-most column. Find the cortisol-baseline, cortisol-30 min, cortisol-60 min from the blood sample obtained on that date. Also find the Fev-actual and Fev-% of predicted from the spirometry performed on that date. If the value is the same, check the neighboring box in the adjacent column. If the value is not the same, please fill in the correct value.

PROTOCOL ANC-MD-01		INVESTIGATOR: Nelson		CENTER: 17, Denver, CO		Visit 6					
Patient ID Number/Initials/Date	Cortisol - Baseline			Cortisol - 30 minutes		Cortisol - 60 minutes		Fev-actual		Fev-% of predicted	
	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	
1724	17		18		22		3.42		89		
1713	11		24		27		3.01		74		
1710	15		23		25		3.11		72		
1716	18		24		30		2.9		67		
1731	11		23		29		2.56		68		
1739/ /24September98	25		17		29		3.05		84		
1725/ /06July98	32		38		38		3		92		
1740/ /01October98	8		17		21		3.1		91		

PROTOCOL ANC-MD-03 INVESTIGATOR: Leonardo Caputo CENTER: 26, Asthma and Allergy Institute, Mobile AL.

INSPECTORS

The patient identification number, initials and date of the sixth visit are in the left-most column. Find the cortisol-baseline, cortisol-30 min, cortisol-60 min from the blood sample obtained on that date. Also find the Fev-actual and Fev-% of predicted from the spirometry performed on that date. If the value is the same, check the neighboring box in the adjacent column. If the value is not the same, please fill in the correct value.

PROTOCOL ANC-MD-01		INVESTIGATOR: Caputo				CENTER: 26, Mobile, AL				Visit 6			
Patient ID Number/Initials/Date		Cortisol - Baseline		Cortisol - 30 minutes		Cortisol - 60 minutes		Fev-actual		Fev-% of predicted			
		Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry		
2606/	/10May99	14		24		25		1.47		53			
2605/	/29March99	11		23		31		1.81		84			
2614/	/21May99	6		15		20		1.34		89			
2607/	/16April99	8		19		22		1.75		73			
2617/	6June99	14		24				2.07		79			
2609/	21May99	9		19		27		1.85		109			
2608	07May99	5		20		23		1.93		120			
2621	02July99	12		21		23		1.12		54			

PROTOCOL ANC-MD-03 INVESTIGATOR: Paul Chervinsky CENTER: 31 New England Clinical Studies, North Dartmouth, MA.

INSPECTORS

The patient identification number, initials and date of the sixth visit are in the left-most column. Find the cortisol-baseline, cortisol-30 min, cortisol-60 min from the blood sample obtained on that date. Also find the Fev-actual and Fev-% of predicted from the spirometry performed on that date. If the value is the same, check the neighboring box in the adjacent column. If the value is not the same, please fill in the correct value.

PROTOCOL ANC-MD-01		INVESTIGATOR: Chervinsky				CENTER: 31, North Dartmouth, MA				Visit 6			
Patient ID Number/Initials/Date		Cortisol - Baseline		Cortisol - 30 minutes		Cortisol - 60 minutes		Fev-actual		Fev-% of predicted			
		Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry	Correct value	Check or correct entry		
3105	/22Feb99	11		23		25		1.61		68			
3111	/19Feb99	17		28		33		1.4		80			
3116	/17March99	8		19		23		2.6		87			
3119	/22March99	4		24		26		1.77		83			
3129	/19May99	7		23		28							
3102	/02Feb99	16		21		24		1.68		92			
3126	/13May99	7		26		25							
3121	/29March99	7		26		29		1.08		74			

CC: NDA 21-247
HFD 570/Division Files
HFD 570/Himmel
HFD 570/Birenbaum
HFD 570/Rogers
HFD 570/Sancilio
HFD 570/Gebert
HFD 570/Borders
HFD 570/Barnes

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