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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-704

Medical Review(s)

Medical Team Leader Review Memorandum

Memorandum to:	NDA 21-704 file
Product:	Fexofenadine HCl/pseudoephedrine HCl 180 mg/240 mg (Allegra D-24 Hour™ Extended Release Tablets)
Sponsor:	Aventis Pharmaceuticals, Inc
Memo Date:	October 8th, 2004
Memo From:	Lydia I. Gilbert-McClain, MD, FCCP, Medical Team Leader

This memorandum is to summarize the pertinent findings of the review of NDA 21-704 for fexofenadine HCl/pseudoephedrine HCl tablets 180 mg/240 mcg. For more details please see Dr. Charles Lee's excellent Medical Officer review.

Background/Administrative History

The application was submitted to the Agency under Section 505 (b) of the FD&C Act on December 19, 2003 and was received on December 19, 2003. The PDUFA due date is October 19, 2004. The application is submitted as a 505(b)2 application because the Applicant does not own the data for pseudoephedrine and was relying on the Agency's previous findings of efficacy and safety of pseudoephedrine. Given that this is a 505(b)(2) application, the Applicant provided patent certification as required under Section 505(b)(2)(A) of the FD&C Act. The Applicant obtained a patent license for Allegra-D 24 HOUR™ from ALZA corporation the owner of Patent No. 4801461 and was able to provide patent certification under paragraph IV pursuant to 21 CFR 314.50(h)(i)(6). Although the sponsor has an approved fexofenadine/pseudoephedrine drug product, (Allegra D tablets 60 mg fexofenadine/120 pseudoephedrine - NDA 20-786), a new NDA was required for the Allegra-D 24 hour product because this was a different formulation. In the acknowledgement letter to the Applicant (*Jan 5, 2004*) the Agency waived the requirement for pediatric studies for this application. This decision was based on the fact that the dose of the active drugs of this combination, and the formulation are not appropriate for use in children less than 12 years of age and that there are alternative fexofenadine and pseudoephedrine products available in suitable pediatric dosage forms.

The development program for this drug product was a bioequivalence program. Safety data are obtained from the clinical pharmacology studies, the literature, post-marketing and spontaneous adverse events reports for the other approved Allegra products, and from two controlled clinical studies that were previously submitted to NDA 20-872.

A brief overview of the application is presented below. For more detailed information please refer to Dr. Charles Lee's and Sayed Al Habet's excellent reviews. Although from a bioequivalence standpoint the drug product has demonstrated bioequivalence to the reference product, the Applicant changed the equipment at the manufacturing for the product during the review cycle and this change has affected the dissolution profile of the product.

OVERVIEW

The reference products for this 505(b)(2) application are fexofenadine HCl (Allegra®) tablets 180 mg developed by Aventis Pharmaceuticals, and pseudoephedrine HCl (Sudafed®) tablets 240 mg marketed by Pfizer Consumer Healthcare. Clinical efficacy studies were not required for this development program and the clinical studies submitted were previously reviewed in another NDA application [NDA 20-872; Allegra tablets] and were submitted to provide supporting safety information.

Clinical pharmacology and Biopharmaceutics

The sponsor conducted two clinical pharmacology studies. Study 106455S/1001 was a study conducted in the fasting state in 70 healthy male and female subjects age 18 -44 years that compared the bioavailability of the combination formulation of fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended-release tablets (Allegra-D 24 hour™) to the marketed fexofenadine HCl 180 mg immediate-release (Allegra®) and pseudoephedrine HCl 240 mg extended-release (Sudafed® 24 Hour) tablets after single and multiple doses. The 90% confidence intervals (CI) for the ratios of the $AUC_{0\text{-}inf}$ and C_{max} for the proposed and reference product were within the 80 -125% limits indicating that the proposed product was bioequivalent to the reference products for rate and extent of exposure when administered under fasting conditions for single dose and steady state conditions.

Study M106455S/1002 compared the effect of food on the bioavailability of the combination product in 24 healthy male and female subjects. Bioavailability was evaluated in the fasted state, and 0.5 and 1.5 hours after ingestion of a high fat breakfast. For fexofenadine, the 90% CI of the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values in the fed conditions to the values in the fasting condition fell below the 80 -125% confidence limits. Administration of the product 0.5 and 1.5 hours after ingestion of a high fat meal decreased the extent and rate of exposure to fexofenadine by approximately 42 and 54% respectively. The extent and rate of exposure of pseudoephedrine was not affected by food.

In addition to these 2 studies, the Applicant used a population modeling approach to analyze pharmacokinetic data from three pharmacology studies to estimate the effect of the concomitant intake of eight ounces of grapefruit or orange juice with fexofenadine HCl. The relative bioavailability with juice intake was reduced by a population mean of 36% when eight ounces of grapefruit or orange juice were administered concomitantly with a single dose of fexofenadine HCl 180 mg. Although the Applicant noted that the consumption of either grapefruit or orange juice did not alter the effects of fexofenadine on histamine-induced wheal and flare to any notable extent, it should be kept in mind that changes in skin test reactivity do not correlate with clinical.

Clinical

The Applicant submitted summary data from one controlled clinical efficacy and safety study (M106455B/3081) which was an SAR study conducted in 864 adults in the fall treated with fexofenadine 120 and 180 mg respectively, and one controlled clinical long-

term safety study (PJPR027) which evaluated the safety of fexofenadine 120 and 180 mg once daily in 469 adults treated for 1 year. Both of these studies were previously reviewed in NDA 20-872 and showed no safety signal of concern. In those studies, headache, followed by upper respiratory tract infection, pharyngitis, and back pain were the most common adverse events reported. In the clinical pharmacology studies pharyngolaryngeal pain (3.3%) and upper respiratory tract infection (2.2%) were the AEs reported in more than 2% of subjects receiving fexofenadine/pseudoephedrine. Additionally, vital signs, laboratory studies and ECG tracings were not indicative of safety concerns. The adverse events summarized in the postmarketing safety information and spontaneous adverse events reports for the currently approved Allegra-D product as well as a review of the literature did not reveal any new safety findings of concern.

INTERDISCIPLINARY ISSUES

Chemistry, Manufacturing, and Controls

The combination drug product is formulated to provide an immediate release of 180 mg of fexofenadine HCL and an extended release (over 24 hour) of 240 mg of pseudoephedrine [ ] The tablet is designed with an immediate-release outer layer of fexofenadine [ ] containing pseudoephedrine.

On Sept 22, 2004, the Applicant informed the Division that new equipment [ ] the pseudoephedrine [ ] had been installed at the manufacturing site and that the new equipment had affected the in-process dissolution profile for [ ] pseudoephedrine [ ] Because this change has altered the dissolution profile of the product, new data would be needed to ascertain that the tablets manufactured using the new equipment maintain bioequivalence to the reference products as was established for the products used to conduct the clinical pharmacology studies. Should an approval action be taken on this application during this review cycle without these data, the sponsor would need to submit a prior approval CMC supplement with these new data.

Non-clinical Pharmacology and Toxicology

The Agency did not require that the sponsor conduct nonclinical safety studies since single ingredient fexofenadine and pseudoephedrine have been previously studied and found to be safe at the proposed doses for the combination product. The Applicant did submit the results of two mouse reproductive studies which were conducted to evaluate the potential toxicity of fexofenadine to reproductive and development processes in mice. The studies demonstrated that fexofenadine was not teratogenic and did not have an effect on fertility or pre-and postnatal development.

Ethical and Statistical Integrity Issues

There was one study center and one analytical site for both of the clinical pharmacology studies and a DSI audit of the study center was conducted. The principal investigator was Dennis N.Morrison, D.O. of Bio-Kinetic Clinical Applications , 1816 West Mount Vernon, in Springfield, MO. Pharmacokinetic analyses were performed by [ ] [ ] There were 2 minor observations noted by DSI that resulted in the

issuance of a Form 483 however, DSI concluded that the data obtained from the 2 clinical pharmacology studies were not compromised and could be used in making a regulatory decision on the NDA.

The studies were conducted according to Good Clinical Practice and the sponsor certified that they did not use the services of any person debarred under Section 306 (a) and 306 (b) of the FD&C Act. Additionally, the sponsor certified that there was no financial arrangement with investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. Neither did any of the investigators have a proprietary interest in the proposed product.

Nomenclature

The proposed name is Allegra-D 24 hour and this is acceptable. It should be noted that the sponsor was asked to change the name of the currently marketed Allegra-D product (fexofenadine 60mg/pseudoephedrine 120 mg) to Allegra-D 12 hour to avoid confusion with the new product. The Applicant agreed to do this and submitted revised labeling in a supplement to NDA 20-786.

Pediatric considerations

This was a bioequivalence program and pediatric studies were not performed and were not required. The products are intended for use in patients 12 years of age and older and the use in this age group is appropriate since the reference products are approved for this age group as well. Additional clinical studies in children less than 12 years of age are not required because this formulation is not suitable for children below the age of 12 years. Therefore, in the acknowledgement letter for the NDA the Division granted the Applicant a waiver (under the requirements of the Pediatric Research Equity Act) for conducting studies in children less than 12 years of age.

Labeling considerations

1. Food effect

Although the proposed package insert mentions the food effect seen with fexofenadine, the Dosing and Administration (D&A) section recommends that the tablet be taken before a meal but this recommendation needs to be more specific. Given that the reduction in exposure of fexofenadine is quite significant (~50%) the tablet should be taken on an empty stomach. In addition, given the decrease in exposure noted with grapefruit and orange juice, the D& A section should state that the tablet should be taken with water. The package insert for the other fexofenadine products should be updated to uniformly reflect this information.

2. Co-administration with aluminum and magnesium-containing antacids

The Applicant should revise the Drug Interactions sub-section of the Clinical Pharmacology section of the label to include the decreased bioavailability of fexofenadine seen with co-administration of aluminum and magnesium-containing antacids. This information is in the Allegra® package insert.

Additionally, there are other sections of the package insert that need to be edited to maintain uniformity between the other Allegra package inserts: i.e., the Overdosage section, the Pharmacodynamic section, and the Drug Interactions Section. A "marked up" package insert has been sent to the Applicant with the Division's proposed changes.

SUMMARY/CONCLUSIONS

The sponsor has demonstrated bioequivalence of the test product fexofenadine HCl 180 /pseudoephedrine 240 mg tablets with the reference product Allegra® 180 mg tablets and Sudafed® 240 mg. The systemic exposure to fexofenadine was significantly reduced (~ 50%) by a high-fat meal. The safety profile was generally similar for the test and reference products and no safety signals of concern were noted. Finally because of the change in equipment at the manufacturing site and the new dissolutions issues, should this application be approved in this cycle, a prior approval supplement will need to be submitted to support bioequivalence of the product manufactured with the new equipment.

RECOMMENDATIONS

From a clinical standpoint I recommend that the drug be given an APPROVAL action pending submission of agreed upon labeling changes.

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/s/

Lydia McClain
10/13/04 04:32:43 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-704	**TRADE NAME:**	Allegra-D 24 Hour™
APPLICANT/SPONSOR:	Aventis Laboratories, Inc.	**USAN NAME:**	Fexofenadine HCl/pseudoephedrine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	H_1-antihistamine/decongestant
DATE:	9/27/04	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
12/19/03	12/19/03	NDA 21-704, N-000	NDA, electronic submission
4/9/04	4/9/04	NDA 21-704, N-000 SU	Safety update

RELATED APPLICATIONS

Document Date	Application Type	Comments
12/20/96	NDA 20-786, N-000	NDA for Allegra-D®, fexofenadine HCl/pseudoephedrine HCl
7/17/98	NDA 20-872, N-000	NDA for Allegra® Tablets, fexofenadine HCl
7/31/95	NDA 20-625, N-000	NDA for Allegra® Capsules, fexofenadine HCl

REVIEW SUMMARY: This application is an NDA for Allegra-D 24 Hour™ Extended Release Tablets. The sponsor is Aventis Pharmaceuticals, Inc. Each tablet of the proposed product contains 180 mg of immediate-release fexofenadine HCl and 240 mg of extended-release pseudoephedrine HCl. The proposed indication is the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. The proposed dose for adults and adolescents ages 12 years and older is one tablet once daily administered before a meal. The product is not recommended for children less than 12 years of age. Allegra-D 24 Hour™ is to be marketed as a prescription drug product. This application was filed under Section 505(b)(2) of the FD&C Act because the applicant does not own the data for pseudoephedrine. There are two pivotal bioequivalence and bioavailability studies in this application. The reference products for these studies are the applicant's Allegra® Tablets (fexofenadine HCl) (NDA 20-872) and Sudafed® (pseudoephedrine HCl) Non-Drowsy 24 Hour Nasal Decongestant Tablets (NDA 20-021). The application also relies on one controlled clinical efficacy and safety study and one controlled clinical long-term safety study. The clinical pharmacology studies in this application confirmed the bioequivalence of the applicant's product to the reference products. The 90% confidence intervals of the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values for the proposed and reference products fell within 80% to 125% limits, indicating that the proposed product is bioequivalent to the reference products for rate and extent of exposure in the fasted state after single dose administration and at steady state with multiple dose administration. Both of the controlled clinical studies were previously reviewed and supported the approval of NDA 20-872. These data support the efficacy of the applicant's product. A high fat meal, aluminum- and magnesium-containing antacids, and grapefruit and orange juices decrease the bioavailability of fexofenadine. Safety data in this application support the safety of the proposed combination product. Adverse events, vital signs, laboratory studies and ECGs in the pivotal clinical pharmacology studies identified no new safety signal. Safety data from the two controlled clinical studies included in this application were previously submitted to NDA 20-872 and revealed no safety signal. The commonly reported postmarketing spontaneous adverse events were similar to those noted in labeling for the currently approved Allegra-D product. The applicant's review of the medical literature and safety update reveal no new safety concerns. From a clinical perspective, this reviewer recommends an approval action. No phase 4 studies or specific risk management plans are recommended or are necessary at this time. The labeling should be revised to advise the prescriber that grapefruit juice, orange juice, and aluminum- and magnesium-containing antacids reduce the bioavailability of fexofenadine and that the product should be taken on an empty stomach with water. CMC changes that affect the dissolution profile were made during the review cycle and may prevent an approval action.

OUTSTANDING ISSUES: Dissolution profile changes due to changes in manufacturing

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	X—APPROVAL	APPROVABLE	NOT APPROVABLE
OTHER ACTION:			

Note to RSS Staff:
This application was submitted before February 9, 2004. The end of the fifth month of this application's PDUFA review cycle had passed before the implementation date for the Clinical Review Template. The Clinical Review Template, which therefore was optional for this review, was not used.

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendations on approvability

The sponsor has demonstrated that their product is bioequivalent to approved 180 mg fexofenadine HCl and 240 mg pseudoephedrine HCl products. The sponsor's safety data support the safety of the product. From a clinical perspective, this reviewer recommends an approval action. However, changes in the manufacturing process that affect the dissolution profile of the pseudoephedrine tablet — were instituted late in the review cycle and, from the CMC perspective, may be sufficient to prevent an approval action for this application.

1.2. Recommendations on phase 4 studies and risk management steps

No phase 4 studies or specific risk management plans are recommended or are necessary at this time.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief overview of clinical program

This application is an NDA for Allegra-D 24 Hour™ Extended Release Tablets. The sponsor is Aventis Pharmaceuticals, Inc. Each tablet of the proposed product contains 180 mg of immediate-release fexofenadine HCl and 240 mg of extended-release pseudoephedrine HCl as active ingredients. The proposed indication is the relief of symptoms associated with seasonal allergic rhinitis (SAR) in adults and children 12 years of age and older. Allegra-D 24 Hour™ is to be marketed as a prescription drug product. The proposed dose for adults and adolescents ages 12 years and older is one tablet once daily administered before a meal. The product is not recommended for children less than 12 years of age. The product adds to the line of currently approved and marketed Allegra products, which includes Allegra® Capsules (fexofenadine HCl 60 mg, NDA 20-625), Allegra® Tablets (fexofenadine HCl 30, 60, and 180 mg, NDA 20-872), and Allegra-D® Tablets (fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg, NDA 20-786). The currently marketed Allegra-D® product is dosed twice daily.

This application was filed as a submission under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety and upon bioavailability and bioequivalence of the proposed new drug to approved reference products given that the applicant does not own the data for pseudoephedrine. The reference drug products for this application are:

- Allegra® (fexofenadine HCl) Tablets, 180 mg, Aventis Pharmaceuticals, Inc., NDA 20-872
- Sudafed® (pseudoephedrine HCl) Non-Drowsy 24 Hour Nasal Decongestant Tablets, marketed by Pfizer Consumer Healthcare, originally approved as Efidac® (pseudoephedrine HCl), 240 mg, Alza Corporation, NDA 20-021

There are two pivotal bioequivalence and bioavailability studies in this application:

- Study M106455S/1001, a pivotal clinical pharmacology study that compared the bioavailability of the combination formulation of fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended-release tablets (Allegra-D 24 Hour™) to the marketed fexofenadine HCl 180 mg immediate-release (Allegra®) and pseudoephedrine HCl 240 mg extended-release (Sudafed® 24 Hour) tablets after single and multiple doses.

- Study M106455S/1002, a pivotal clinical pharmacology study that compared the effect of food on the bioavailability of the combination formulation of fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended-release tablets (Allegra-D 24 Hour™).

The application also relies on one controlled clinical efficacy and safety study, M106455B/3081, and one controlled clinical long-term safety study, PJPR0027. Both of the controlled clinical studies supported the approval of NDA 20-872, and were previously reviewed [NDA 20-872, N-000, 7/17/98, Medical Officer Review, A. Worobec, M.D.].

The applicant supported the safety of their product with data from their clinical pharmacology studies, a summary of safety information from previously conducted controlled clinical studies, and an evaluation of safety information postmarketing and spontaneous adverse event reports for the currently approved Allegra-D product, a review of the literature of safety information relevant to fexofenadine and pseudoephedrine, and a safety update.

2.2. Efficacy

The sponsor's drug development program for Allegra-D 24-Hour™ Tablets was based on establishing that their combination fexofenadine/pseudoephedrine product produces equivalent exposures to that of their approved and marketed 180 mg single ingredient fexofenadine HCl product (Allegra® Tablets) and to an approved and marketed OTC 240 mg extended-release pseudoephedrine HCl product (Sudafed® 24 Hour Tablets). The clinical pharmacology studies in this application confirmed the bioequivalence of the applicant's product to the reference products. The 90% confidence intervals for the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values for the proposed and reference products fell within 80% to 125% limits, indicating that the proposed product is bioequivalent to the reference products for rate and extent of exposure in the fasted state after single dose administration and at steady state with multiple dose administration. These data support the efficacy of the applicant's product.

Administration of the product 30 minutes after ingestion of a high fat meal decreased the extent of exposure to fexofenadine by 42% and the rate of exposure by 54%. Administration of the product 1 hour after ingestion of a high fat meal decreased the rate and extent of exposure to fexofenadine to a similar extent. For pseudoephedrine, the 90% confidence intervals for the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values in the fed condition to values in the fasting condition fell within 80% to 125% limits, indicating that food does

not interfere with bioavailability of the pseudoephedrine component of the combination product. The applicant's proposed labeling notes the decrease in fexofenadine bioavailability associated with ingestion of a high-fat meal. The labeling should also be revised to state that the product should be taken on an empty stomach with water.

Co-administration of fexofenadine with Maalox® reduced the extent of exposure of fexofenadine by approximately 41% and the rate of absorption by 43%. This drug interaction is not noted in the proposed labeling. The labeling should be revised to advise the prescriber that aluminum- and magnesium-containing antacids reduce the bioavailability of fexofenadine.

The applicant used a population pharmacokinetics modeling approach to analyze data from the three clinical pharmacology studies to estimate the effect of concomitant intake of eight ounces of grapefruit or orange juice with fexofenadine HCl. The relative bioavailability for a juice effect was reduced by a population mean of 36% when eight ounces of grapefruit or orange juice was administered concomitantly with a single 180 mg dose of fexofenadine HCl. The estimated decrease in bioavailability of fexofenadine when taken with grapefruit or orange juices is only slightly less than the decrease in bioavailability noted when fexofenadine is taken with a high-fat meal or with aluminum- and magnesium containing antacids. Proposed labeling should be revised to include this interaction with grapefruit and orange juices.

Data from the innovator's NDA studies and the applicant's clinical pharmacology studies are sufficient to support the efficacy of fexofenadine.

2.3. Safety

Safety data in this application support the safety of the proposed combination product. Adverse events, vital signs, laboratory studies and ECGs in the pivotal clinical pharmacology studies identified no new safety signal. Safety data from the two controlled clinical studies included in this application were previously submitted to NDA 20-872 and were previously examined in detail. The safety data from these controlled clinical studies revealed no safety signal. Drug abuse and overdose data suggest that there is a low potential for risk to the consumer from abuse or overdose of fexofenadine. Although there is a risk of abuse and overdose for pseudoephedrine, the risk for this combination fexofenadine/pseudoephedrine prescription drug product would be expected to be less than more easily obtained and widely available OTC drug products. The commonly reported postmarketing spontaneous adverse events were similar to those noted in labeling for the currently approved Allegra-D product. The applicant's review of the medical literature and safety update reveal no new safety concerns.

2.4. Dosing

The proposed dose of Allegra-D 24 Hour™ Extended-Release Tablets is one tablet once daily administered before a meal for adults and children 12 years of age and older. The dose of fexofenadine HCl in this product is the same as the dose for the approved single ingredient product, Allegra Tablets, 180 mg. The proposed product given at the recommended dosing frequency, one tablet once daily, provides 240 mg of pseudoephedrine HCl, which is the same dose as the approved reference product and the

maximum daily dose of pseudoephedrine HCl specified by the OTC monograph [21 CFR 341.80 (d)(1)(ii)].

Co-administration of the product with food, aluminum- and magnesium-containing antacids, and grapefruit and orange juices decrease the bioavailability of fexofenadine. Co-administration of the product with a high-fat meal decreases the AUC and C_{max} of fexofenadine by 42% and 54%, respectively. Pseudoephedrine pharmacokinetics are unaffected when the product is co-administered with high-fat meal.

Co-administration of fexofenadine with Maalox® reduces the extent of exposure of fexofenadine by approximately 41% and the rate of absorption by 43%. The bioavailability of fexofenadine was reduced by a population mean of 36% (95% CI = 24% to 48%) when eight ounces of grapefruit or orange juice was administered concomitantly with a single 180 mg dose of fexofenadine HCl.

The applicant's proposed labeling notes the decrease in fexofenadine bioavailability associated with concurrent ingestion of a high-fat meal, but states that the product should be taken before a meal. Labeling does not address the co-administration of the product with aluminum- and magnesium-containing antacids or with grapefruit or orange juices. The estimated decrease in bioavailability of fexofenadine when taken with grapefruit or orange juices is only slightly less than the decrease in bioavailability noted when fexofenadine is taken with a high-fat meal or with aluminum- and magnesium containing antacids. Proposed labeling should be revised to include of these drug-drug and food-drug interactions and to state that the product should be taken on an empty stomach with water.

2.5. Special populations

The incidence of adverse events in the pivotal clinical pharmacology studies and in controlled clinical efficacy and safety study M106455B/3081 suggest that there are no gender-specific effects associated with the proposed product.

Data in this submission suggest that there are no differences in the safety profile for the product in patients of Caucasian and Black races. All subjects who experienced adverse events were of Caucasian race in the pivotal clinical pharmacology studies; there were no adverse events experienced by any of the six subjects of other races. In the controlled clinical study M106455B/3081, the frequency of adverse events for patients was similar for patients of Caucasian race and those of Black race. The numbers of subjects of Asian and Multiracial races were small, and conclusions cannot be drawn on these subgroups.

There were no subjects greater than 65 years of age in the pivotal clinical pharmacology studies. In the controlled clinical study M106455B/3081, only 3 subjects were greater than 65 years of age, making it difficult to draw definitive conclusions about the incidence of adverse events by age. In clinical pharmacology studies previously submitted to NDA 20-625, subjects greater than 65 years of age had peak plasma levels of fexofenadine that were approximately two-fold greater and mean elimination half-lives were similar to those observed in normal volunteers less than 65 years of age. Since approximately 43-96% of an orally administered dose of pseudoephedrine is excreted

unchanged in the urine, pseudoephedrine may accumulate in patients with renal insufficiency. Since patients greater than 65 years of age may have decreased renal function, proposed labeling appropriately suggests that it may be useful to monitor renal function.

No subjects were less than 18 years of age in the pivotal clinical pharmacology studies. The dose of active drugs in the product and its formulation are not appropriate for use in children less than 12 years of age, and the proposed labeling states that the product is not recommended for pediatric patients under 12 years of age. Alternative fexofenadine and pseudoephedrine products are available in suitable pediatric dosage forms. These products are available as either approved prescription products or as OTC monograph products. Accordingly, the Division waived the requirement for pediatric studies for this application.

Adverse event data in patients with renal impairment was collected in single dose pharmacology studies submitted in support of the application for Allegra Capsules, NDA 20-625. These studies showed that renal clearance of fexofenadine decreases as the severity of renal disease increases. Since approximately 43-96% of an orally administered dose of pseudoephedrine is excreted unchanged in the urine, pseudoephedrine may accumulate in patients with renal insufficiency. Because the doses of the individual components in the proposed combination fexofenadine/pseudoephedrine product cannot be individually titrated, and because renal insufficiency increases the bioavailability and prolongs the half-life of fexofenadine and pseudoephedrine, the proposed labeling appropriately recommends that the product should generally be avoided in patients with renal insufficiency.

The pharmacokinetics of fexofenadine were studied in subjects with hepatic impairment in studies previously submitted in support of the application for Allegra Capsules, NDA 20-625. The pharmacokinetics of plasma fexofenadine in hepatically impaired subjects were comparable to those observed in healthy volunteers. The sponsor states that the effect of hepatic impairment on pseudoephedrine pharmacokinetics is unknown, however, the OTC monograph specifies no warnings or precautions for the use of pseudoephedrine in patients with hepatic impairment. Proposed labeling appropriately contains no special instructions the use of the product in patients with hepatic impairment.

There are no adequate and well controlled studies of fexofenadine or fexofenadine/pseudoephedrine in pregnant women. Pregnancies occurring during clinical trials and in postmarketing adverse event reports for fexofenadine do not suggest a safety signal. The label appropriately states that the product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The sponsor states that it is not known if fexofenadine is excreted in human milk. Pseudoephedrine is excreted into breast milk of lactating human women and pseudoephedrine concentrations in milk are consistently higher than those in plasma. Proposed labeling states that a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The

applicant appropriately notes that caution should be exercised when the proposed product is administered to nursing women.

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CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Introduction

This application is an NDA for Allegra-D 24 Hour™ Extended Release Tablets. The sponsor is Aventis Pharmaceuticals, Inc. Each tablet of the proposed product contains 180 mg of immediate-release fexofenadine HCl and 240 mg of extended-release pseudoephedrine HCl as active ingredients. The proposed indication is the relief of symptoms associated with seasonal allergic rhinitis (SAR) in adults and children 12 years of age and older. The proposed indication states that symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/ and/or throat, itchy/watery/red eyes, and nasal congestion. The product should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine are desired [labeling\proposed.pdf, page 004]. The proposed dose for adults and adolescents ages 12 years and older is one tablet once daily administered before a meal. The product is not recommended for children less than 12 years of age [labeling\proposed.pdf, page 007]. Allegra-D 24 Hour™ Tablets are to be marketed as a prescription drug product. The sponsor believes the product's once daily dosing regimen will provide for greater patient convenience and compliance [summary\summary.pdf, page 114].

Fexofenadine is an antihistamine with selective H_1-receptor antagonist activity. It is a "second generation" antihistamine with much lower potential for producing sedation than currently available "first generation" antihistamines, many of which are available as OTC drug products. Fexofenadine HCl 60 mg BID (NDA 20-625) and fexofenadine HCl 180 mg QD (NDA 20-872) were developed for the treatment of symptoms of seasonal allergic rhinitis (SAR) in adults and children 12 years of age and over, and were approved for marketing by the FDA as Allegra Capsules on July 25, 1996 and Allegra Tablets on February 25, 2000, respectively. Fexofenadine HCl 60 mg BID is also approved for treatment of skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 12 years of age and over. In addition to Allegra®, other approved second generation antihistamines include loratadine (Claritin®) and cetirizine (Zyrtec®). Pseudoephedrine is an orally active sympathomimetic amine that exerts a decongestant effect on the nasal mucosa [labeling\proposed.pdf, page 002]. Pseudoephedrine is recognized as an effective agent for relief of nasal congestion due to hay fever or other respiratory allergies, the common cold, or associated with sinusitis [21 CFR 341.80(b)(1)].

The fixed dose combination of fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg (NDA 20-876) for twice daily use was approved by the FDA on December 24, 1997 as Allegra-D for the treatment of SAR, including nasal congestion, in adults and children 12 years of age and over) [summary\summary.pdf, page 019]. Claritin-D® Non-Drowsy 24-Hour Tablets (NDA 20-470) is a currently marketed combination second generation antihistamine/pseudoephedrine drug product that is dosed once daily. Currently marketed combination second generation antihistamine/pseudoephedrine drug products that are

dosed twice daily include Allegra-D® Tablets, Claritin-D® Non-Drowsy 12-Hour Tablets (NDA 19-670), and Zyrtec-D 12 Hour® Extended Release Tablets (NDA 21-150).

The proposed product provides an immediate-release 180 mg dose of fexofenadine HCl and an extended-release 240 mg dose of pseudoephedrine HCl. The product is formulated with an immediate-release outer layer of fexofenadine HCl [redacted] containing pseudoephedrine. The pseudoephedrine [redacted] to effect the controlled release of the pseudoephedrine over 24 hours [summary\summary.pdf, page 021].

The sponsor's application originally referenced the Monograph for OTC Nasal Decongestant Drug Products for the pseudoephedrine component and the application was originally submitted under Section 505(b)(1) of the FD&C Act. Although labeling for Sudafed 24 Hour Tablets is based on the Monograph for OTC Nasal Decongestant Drug Products, which considers immediate-release pseudoephedrine to be generally recognized as safe and effective for the relief of nasal congestion, Sudafed 24 Hour Tablets is an extended-release formulation and an NDA product. Since the applicant does not have right of reference and must rely on the Agency's findings of efficacy and safety for the pseudoephedrine reference product, the application was filed as a 505(b)(2) submission. This section of the FD&C Act permits approvals to be based on the Agency's previous findings of efficacy and safety. This application relies on a comparison of the bioavailability/bioequivalence of the proposed new drug to approved reference products. The reference drug products for this application are:

- Allegra® (fexofenadine HCl) Tablets, 180 mg, Aventis Pharmaceuticals, Inc., NDA 20-872
- Sudafed® (pseudoephedrine HCl) Non-Drowsy 24 Hour Nasal Decongestant Tablets, Marketed by Pfizer Consumer Healthcare, originally approved as Efidac® (pseudoephedrine HCl), 240 mg, Alza Corporation, NDA 20-021

The effects of an antihistamine and decongestant are considered to be complimentary by the OTC Monograph for Cough, Cold and Bronchodilator Drug Products [21 CFR 341.40], which permits the OTC marketing of certain specified antihistamines and nasal decongestants.

1.2. Foreign marketing and regulatory history

Fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended-release tablets are not marketed in any country [summary\summary.pdf, page 019]. Fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg extended-release tablets are approved in 38 countries other than the United States, including countries in North, Central, and South America, the Caribbean, Asia, and Australia and New Zealand [clinstat\iss\iss.pdf, pages 159-161].

Fexofenadine HCl 60 mg BID and fexofenadine HCl 180 mg QD were developed for the treatment of symptoms of seasonal allergic rhinitis (SAR) in adults and children 12 years of age and over, and were approved for marketing in the United States as Allegra® Capsules (NDA 20-625) on 25 July 1996 and as Allegra® Tablets (NDA 20-872) on 25 February 2000, respectively [summary\summary.pdf, page 019]. Fexofenadine HCl 60

mg BID is also approved for treatment of skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 12 years of age and over. Allegra-D® (fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg), NDA 20-786, was approved for marketing in the United States on December 24, 1997. Pseudoephedrine HCl is generally recognized as safe and effective for the relief of nasal congestion under the Monograph for OTC Nasal Decongestant Drug Products [21 CFR 341.20, 21 CFR 341.80]. The recommended maximum dose in adults and children 12 years of age and older is not to exceed 240 mg in 24 hours.

An End of Phase 2 meeting was held with the sponsor on 1/29/02 [IND 48,486 N030 MR, 11/13/02, Meeting minutes; IND 48,486 N030 MR, 11/13/02, Medical Officer Review, Charles E. Lee, M.D.]. The Division recommended that females not be excluded from the pivotal clinical pharmacology studies and that sponsor study the effects of apple juice and grapefruit juice on fexofenadine bioavailability. The sponsor opened a new IND in early 2003, and included an updated protocol for a proposed pivotal bioequivalence study [IND 66,289, N-000, 11/25/02].

A Pre-NDA meeting was held with the sponsor on August 27, 2003 [IND 66,289 N003 GC, 7/25/03, Meeting minutes; IND 66,289 N003 GC, 7/25/03, Medical Officer Review, Charles E. Lee, M.D.]. The user fee, application structure and format, and CMC issues such as dissolution, stability, and measurement of impurities were discussed. The sponsor was advised to provide a review of the medical literature published since February 25, 2000, focusing on the safety of fexofenadine and pseudoephedrine. The sponsor was also advised to provide a summary, review, and analysis of worldwide postmarketing adverse event reports for fexofenadine and pseudoephedrine [IND 66,289 N003 GC, 7/25/03, Meeting minutes, IND 66,289 N003 GC, 7/25/03, Medical Officer Review, Charles E. Lee, M.D.].

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

2.1. Chemistry, manufacturing, and controls

The proposed product, Allegra-D 24 Hour™ (fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg) Extended Released Tablets provide an immediate-release 180 mg dose of fexofenadine HCl and an extended-release 240 mg dose of pseudoephedrine HCl. The product is formulated with an immediate-release outer layer of fexofenadine HCl [ ] containing pseudoephedrine. The tablet is designed to release pseudoephedrine over a 24-hour period [ ] [summary\summary.pdf, page 021]. Allegra-D 24 Hour is a round, white, film-coated, [ ] tablet printed with the coding "308 AV" [summary\summary.pdf, pages 035, 52-53].

Fexofenadine HCl drug substance is produced by Aventis Pharmaceuticals [summary\summary.pdf, page 025]. Pseudoephedrine drug substance is [ ] [summary\summary.pdf, page 026].

The drug product composition is displayed in Table 2.1. The pseudoephedrine [ ] tablets and [ ] delivery of pseudoephedrine are manufactured at [ ] tablets and all subsequent manufacturing and packaging are performed at Aventis Pharmaceuticals, Kansas City, MO [summary\summary.pdf, page 057].

Table 2.1. Composition of Allegra-D 24 Hour™ Extended Release Tablets [summary\summary.pdf, page 035].

Components	Composition Percentage (weight%)	Composition Weight/tablet (mg)	Function	Reference to standards
Tablet				
Pseudoephedrine HCl	[	240.00	active ingredient	USP
Microcrystalline Cellulose				NF
Microcrystalline Cellulose				NF
Sodium Chloride				USP
Polyethylene Glycol				NF
Povidone				USP
Magnesium Stearate				NF
Polyethylene Glycol				NF
Colloidal Silicon Dioxide				NF
Purified Water*				USP
Cellulose Acetate				NF
Cellulose Acetate				NF
Polyethylene Glycol				NF
Acetone*				NF
Methyl Alcohol*				NF
Methylene Chloride*				NF
Purified Water*				USP
Talc				USP
Copovidone				Ph.Eur.
Titanium Dioxide				USP
Brilliant Blue Aluminum Lake				non-compendial item (ref. supplier Letter)
Purified Water*				USP
Fexofenadine HCl		180.00		in-house NDA 20-625, S3-V1.2-P8 to P110)
Polyethylene Glycol				NF
Hydroxypropyl Methylcellulose				USP

Components	Composition Percentage (weight%)	Composition Weight/tablet (mg)	Function	Reference to standards
Croscarmellose Sodium	[			NF
Acetone*				NF
Isopropyl Alcohol*				NF
Purified Water*				USP
Opadry White				non-compendial item (ref. supplier DMF)
Black Ink				non-compendial item (ref supplier DMF)
Purified Water*			]	USP
TOTALS		760.00 mg		

* Removed during processing

The same batch of the to-be-marketed formulation of Allegra-D 24 Hour was used for both of the pivotal clinical pharmacology studies, M106455S/1001 and M106455S/1002. Marketed Allegra Tablets (180 mg fexofenadine HCl) and Sudafed 24 Hour (240 mg pseudoephedrine HCl) were used in the pivotal bioequivalence study M106455S/1001 [hpbio\biosum.pdf, page 010]. Lot numbers used in the pivotal clinical pharmacology studies are found in Table 2.2 below.

Table 2.2 Lot numbers of drug product in pivotal clinical pharmacology studies [hpbio\biosum.pdf, page 010].

Study	Product	Lot number	Batch size, Test product	Comments
M106455S/1001				
	F 180 mg/PSE 240 mg Allegra-D 24 Hour	1054547	—	To be marketed formulation Aventis
	F 180 mg Allegra Tablets	1053229	—	Marketed product Aventis
	PSE 240 mg Sudafed 24 Hour	0116052	—	Pfizer
M106455S/1002				
	F 180 mg/PSE 240 mg Allegra-D 24 Hour	1054547	—	To be marketed formulation Aventis

F = fexofenadine HCl
PSE = pseudoephedrine HCl

On September 22, 2004, the applicant notified the Division that new equipment for — the pseudoephedrine tablet — had been installed at the manufacturing site and that the new equipment has affected the in-process dissolution profile for [ ] pseudoephedrine — [NDA 21-704, N-000, 9/22/04, GC]. According the CMC review team, this manufacturing change late in the review cycle may prevent an approval action for this application. More information from the sponsor is pending at the time of finalization of this review.

A more detailed review of the CMC information in this application may be found in Dr. Edwin Jao's CMC review [NDA 21-704, N-000, 12/19/03, CMC Review, E. Jao, Ph.D.].

2.2. Non-clinical pharmacology and toxicology

Single ingredient fexofenadine HCl (NDA 20-625, NDA 20-872) and single ingredient pseudoephedrine HCl (NDA 20-021, 21 CFR 341.20, and 21 CFR 341.80) and the combination of fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg have been reviewed and found to be safe at doses including those recommended for the proposed product. No new non-clinical toxicology studies were required and none were performed with the proposed product [summary\summary.pdf, page 101].

The applicant submitted the results of two mouse reproductive studies, Study 6334-189 and Study 6344-190. Study 6334-189 was conducted to detect potential toxicity of fexofenadine to reproductive and developmental events in mice. Study 6334-190 was conducted to determine plasma concentrations of fexofenadine during different reproductive stages of development. The sponsor states that these studies demonstrated that fexofenadine had no effect on any stage of reproduction (no impairment on fertility, no teratogenic effect, and no impairment of pre- and postnatal development) at plasma concentrations (AUC) as high as 243,901 ng.hr/mL [summary\summary.pdf, pages 101-102].

A detailed review of the pharmacology-toxicology data in this application may be found in Dr. Lawrence Sancilio's pharmacology/toxicology review [NDA 21-704, N-000, 12/19/03, Pharmacology/Toxicology Review, L. Sancilio, Ph.D.].

2.3. Microbiology

No microbiology review was necessary for this application.

2.4. Statistics

No statistics review was necessary for this application.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The applicant's drug development program was based on establishing that their product produces equivalent exposures to that of the approved and marketed Allegra® 180 mg and Sudafed® 24-Hour (NDA 20-021) products.

This submission refers to two clinical pharmacology studies. The designs of these studies are described in Section 4 of this review, "Description of Clinical Data and Sources." A summary of the conclusions from the individual clinical pharmacology studies follows below. More detail on the pharmacokinetics of the product may be found in Dr. Sayed Al Habet's review [NDA[ ] N-000, 2/19/03, Clinical Pharmacology and Biopharmaceutics Review, S. Al Habet, Ph.D.].

Study M106455S/1001 was a pivotal clinical pharmacology study that compared the bioavailability of the combination formulation of fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended-release tablets (Allegra-D 24 Hour™) to the marketed fexofenadine HCl 180 mg immediate-release (Allegra®) and pseudoephedrine HCl 240 mg extended-release (Sudafed® 24 Hour) tablets after single and multiple doses. Subjects received their first and last doses after a 10-hour fast. The remaining doses were

administered with a one hour fast before and after the dose. The 90% confidence intervals for the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values for the proposed and reference product fell within 80% to 125% limits, indicating that the proposed product was bioequivalent to the reference products for rate and extent of exposure, when administered under fasting conditions for both single dose and steady state conditions. The T_{max} at steady state for pseudoephedrine was longer (12.0 hours) for the proposed product than for the reference product (8.0 hours), but otherwise T_{max} and $T_{½}$ values for the test and reference products were similar [clinstat\clinsum.pdf, pages 023-024].

Study M106455S/1002 was a pivotal clinical pharmacology study that compared the effect of food on the bioavailability of the combination formulation of fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended-release tablets (Allegra-D 24 Hour™). Bioavailability was evaluated in the fasting state, 30 minutes and 1.5 hours after ingestion of a high fat breakfast. For fexofenadine, the 90% confidence intervals of the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values in the fed condition to values in the fasting condition fell below 80% to 125% limits. Administration of the product 30 minutes after ingestion of a high fat meal decreased the extent of exposure to fexofenadine by 42% and the rate of exposure by 54%. Administration of the product 1.5 hours after ingestion of a high fat meal decreased the rate and extent of exposure to fexofenadine to a similar extent [clinstat\clinsum.pdf, pages 031-033]. For pseudoephedrine, the confidence intervals of the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values in the fed condition to values in the fasting condition fell within 80% to 125% limits, indicating that the food does not interfere with bioavailability of the pseudoephedrine component of the combination product [clinstat\clinsum.pdf, page 034]. The proposed labeling notes the decrease in fexofenadine bioavailability associated with ingestion of a high-fat meal, but recommends [ ] The labeling should be revised to state that the product should be taken on an empty stomach with water.

Co-administration of fexofenadine with Maalox® reduces the bioavailability of fexofenadine by approximately 41% and the rate of absorption by 43% [clinstat\iss\iss.pdf, page 090]. This drug interaction is not noted in the proposed labeling. It is noted in the labeling for the currently marketed Allegra Capsules and Tablets products, but not for the currently marketed Allegra-D product. The labeling should be revised to advise the prescriber that co-administration of fexofenadine with aluminum- and magnesium-containing antacids reduces the bioavailability of fexofenadine.

The applicant used a population pharmacokinetics modeling approach to analyze pharmacokinetic data from the three clinical pharmacology studies to estimate the effect of concomitant intake of eight ounces of grapefruit or orange juice with fexofenadine HCl. The relative bioavailability for a juice effect was reduced by a population mean of 36% when eight ounces of grapefruit or orange juice was administered concomitantly with a single 180 mg dose of fexofenadine HCl [NDA 21-704, N-000 BM, 7/19/04, clinstat\PopPK.pdf, pages 023, 026]. The applicant noted that consumption of either grapefruit or orange juice did not appear to significantly alter the effects of fexofenadine on histamine-induced wheal and flare suppression and that fexofenadine efficacy is maintained under these conditions [NDA 21-704, N-000 BM, 7/19/04, response.pdf, page 013]. Changes in skin test reactivity, however, do not correlate with clinical efficacy of antihistamines. The estimated decrease in bioavailability of fexofenadine when taken

with grapefruit or orange juices is only slightly less than the decrease in bioavailability noted when fexofenadine is taken with a high-fat meal or with aluminum- and magnesium containing antacids. Proposed labeling should be revised to include this interaction with grapefruit and orange juices. The effect of grapefruit and orange juices on fexofenadine bioavailability is discussed in greater detail in Section 8 of this review, "Dosing, Regimen, and Administration Issues."

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

This submission refers to three clinical pharmacology studies. One study, KA467, was a pilot bioavailability study of the prototype of their proposed product. This pilot study is not reviewed in this document. There are two pivotal bioequivalence and bioavailability studies in this application, M106455S/1001 and M106455S/1002. The application also relies on one controlled clinical efficacy and safety study, M106455B/3081, and one controlled clinical long-term safety study, PJPR0027. Both of the controlled clinical studies supported the approval of NDA 20-872, and have been previously reviewed [NDA 20-872, N-000, 7/17/98, Medical Officer Review, A. Worobec, M.D.]. There were no new clinical efficacy or safety studies required to support this application.

These four studies are summarized in Table 4.1. More detailed descriptions of these studies follow below.

4.1. Study M106455S/1001

Study M106455S/1001 was a pivotal clinical pharmacology study that compared the bioavailability of the combination formulation of fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended-release tablets (Allegra-D 24 Hour™) to the marketed fexofenadine HCl 180 mg immediate-release (Allegra®) and pseudoephedrine HCl 240 mg extended-release (Sudafed® 24 Hour) tablets after single and multiple doses. The study was an open-label, randomized, two treatment, two period, two-way crossover bioavailability study conducted in 70 healthy male and female subjects from 18-44 years of age [hpbio\bio\1001\1001.pdf, pages 002-005]. Subjects received their first and last doses after a 10-hour fast. The remaining doses were administered with a one hour fast before and after the dose [hpbio\bio\1001\1001.pdf, page 030]. Samples were taken immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours for plasma fexofenadine and pseudoephedrine levels on Days 1 and 9. Trough samples were also drawn prior to dosing on Days 2 through 8. Subjects were housed at the study site from check-in on Day -1 until Day 3, and again from Day 9 until Day 10. Subjects returned to the clinic daily every morning from Day 4 until Day 9. A minimum washout period of eight days separated the treatment periods. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs. There were no withdrawals from the study. There were no serious adverse events [hpbio\bio\1001\1001.pdf, pages 002-005, 026, 066].

4.2. Study M106455S/1002

Study M106455S/1002 was a pivotal clinical pharmacology study that compared the effect of food on the bioavailability of the combination formulation of fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended-release tablets (Allegra-D 24 Hour™). The study was an open-label, randomized, single dose, three period, three treatment, three

way crossover bioavailability and food effect study conducted in 24 healthy male and female subjects. Bioavailability was evaluated in the fasting state, and 30 minutes and 1.5 hours after ingestion of a high fat breakfast. Samples were taken immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours for plasma fexofenadine and pseudoephedrine levels [hpbio\bio\1002\1002.pdf, page 058]. Patients were housed at the study site from check-in on Day -1 until after samples were drawn and procedures were completed on Day 3. A minimum washout period of six days separated each treatment period. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs. There was one patient who withdrew from the study because of adverse events of sore throat, URI, and fever. There were no serious adverse events [hpbio\bio\1002\1002.pdf, pages 002-006, 023].

4.3. Study M106455B/3081

Study M106455B/3081 was a controlled efficacy and safety study of fexofenadine HCl 120 mg and 180 mg once daily in the treatment of fall SAR. The study originally was submitted to provide support for the efficacy and safety of these products for NDA 20-872. The study was a double blind, randomized, parallel group, multiple center, efficacy and safety study conducted in 864 male and female patients with fall SAR, 12 to 65 years of age. There was a five to seven day, single blind, placebo run-in period. The primary efficacy endpoint was change from baseline in average 8 AM instantaneous Total Symptom Score over the two-week double blind treatment period. Secondary efficacy endpoints included among others, change from baseline in average 8 AM reflective Total Symptom Score change from baseline in average 8 AM 12-hour reflective Total Symptom Score, change from baseline in average 8 PM 12-hour reflective Total Symptom Score, and change from baseline in average individual 8 AM instantaneous symptom score over the two week double blind treatment period. Safety endpoints included adverse events, vital signs, physical examinations, and clinical laboratory studies. Seven of the 570 patients who were exposed to fexofenadine withdrew from the study because of adverse events. There were four of 293 placebo-treated patients who withdrew from the study because of adverse events. There were no deaths in the study [clinstat\other\M016455B 3081.pdf, pages 013-017, 023, 027, 062].

4.4. Study PJPR0027

Study PJPR0027 was a long term safety and tolerance study of fexofenadine HCl 240 mg once daily in normal healthy subjects. The study was originally submitted to provide support for the safety of fexofenadine HCl 120 mg and 180 mg once daily for NDA 20-872. The study was a double blind, randomized, parallel group, multiple center, safety study conducted in 469 healthy male and female subjects. The study treatment period was one year. The primary safety parameter was QTc. Other safety endpoints included adverse events, vital signs, clinical laboratory studies, and other ECG parameters. There were 15 of 234 fexofenadine-treated subjects (6.4%) and 16 of 234 placebo-treated subjects (6.8%) who withdrew from the study because of adverse events. Serious adverse events were reported with similar incidences in the two treatment groups. There was one death in the study in a placebo-treated subject due to a self-inflicted gunshot wound [clinstat\other\PJPR0027 synopsis.pdf, pages 001-004].

Table 4.1. Summary of studies, NDA 21-704 [clinstat\clinsum.pdf, page 013; clinstat\other\M016455B 3081, pages 013-017, 062; clinstat\other\PJPR0027 synopsis.pdf, pages 001-004].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted in this application
M106455S/1001	Pivotal bioavailability and bioequivalence study	F 180 mg plus PSE 240 mg BID F 180 mg/PSE 240 mg combination BID	8 days, single and multiple dose	Single center, randomized, open label, two period, two-way crossover	70	Healthy men and women, 18-44 years	Protocol Study report Tabulations Case report forms
M106455S/1002	Pivotal food effect study	F 180 mg/PSE 240 mg combination BID fasting F 180 mg/PSE 240 mg combination BID 30 min after high fat breakfast F 180 mg/PSE 240 mg combination BID 1.5 hr after high fat breakfast	Single dose	Single center, randomized, open label, two period, two-way crossover	70	Healthy men and women, 18-44 years	Protocol Study report Tabulations Case report forms
M106455B/3081	Controlled efficacy and safety study	F 120 mg QD F 180 mg QD Placebo QD	2 weeks	Multiple center, randomized, double blind, placebo controlled, parallel group	864	Men and women with fall SAR, 12-65 years	Protocol Study report
PJPR0027	Long-term safety study	F 240 mg QD Placebo QD	1 year	Multiple center, randomized, double blind, placebo controlled, parallel group	469	Healthy men and women, 12-65 years	Study synopsis

F = fexofenadine HCl
PSE = pseudoephedrine HCl

5. CLINICAL REVIEW METHODS

A summary of review methods, a description of the conduct of the review, and an assessment of data quality follows below.

5.1. Conduct of the review

The pharmacokinetic results of the two pivotal clinical pharmacology studies in this application were briefly reviewed and summarized in Section 3, "Human Pharmacokinetics and Pharmacodynamics." This review includes an abbreviated Integrated Review of Efficacy because the drug development program was based on clinical pharmacology studies and because there were no new clinical studies required to support this application. Safety data supporting this application was reviewed in depth and is presented in the Integrated Review of Safety. These data included integrated safety information from pivotal clinical pharmacology studies M106455B/1001 and M106455B/1002, safety information from controlled clinical studies in this application, M106455B/3081 and PJPR0027, postmarketing and spontaneous adverse event reports for fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg, a review of the literature for safety information relevant to fexofenadine and pseudoephedrine, and a 120 day safety update.

5.2. Data quality

There was one study center and one analytical site for both of the clinical pharmacology studies in this application. Division of Scientific Investigation (DSI) audit of the two pivotal clinical pharmacology studies and the study center was requested. There were no efficacy or safety studies in the development program for this drug product and therefore no clinical audit was requested.

The principal investigator was:

Dennis N. Morrison, D.O.
Bio-kinetic Clinical Applications
1816 West Mount Vernon
Springfield, MO 65802
Telephone: (417) 831-0456
Fax: (417) 831-0778
[hpbio\bio\1001\1001a.pdf, page 011; hpbio\bio\1002\1002a.pdf, page 003]

Pharmacokinetic analyses were performed by:

[

]

There were no objectionable findings noted at the audit of the clinical site, Bio-kinetic Clinical Applications. There were two objectionable findings noted at the audit of the analytical site, [ ] and a FDA Form 483 was issued. The first objectionable finding was that only two of the three fexofenadine quality control concentrations were representative of the subject's concentrations. The inspector noted that this finding would not be likely to affect the subject plasma concentration data. The second objectionable finding was that the lot number of the fexofenadine HCl 180 mg tablets used in M106455S/1001 and the lot number of the fexofenadine HCl 180 mg/pseudoephedrine 240 mg combination tablets used in M106455S/1002 were different from the lot reported by the sponsor. Despite the two objectionable findings, DSI concluded that data obtained from Studies M106455S/1001 and N106455S/1002 were acceptable for Agency review [NDA 21-704, N-000, 12/19/03, DSI Review, S. Subramaniam, Ph.D.].

5.3. Ethical standards and financial disclosure

The following items were included in this submission:

- Form FDA 356h [356h.pdf]
- Debarment certification [other\debar.pdf]
- Financial disclosure statement [other\financial.pdf]
- Statements of Good Clinical Practice [hpbio\bio\1001\1001.pdf, pages 001, 021; hpbio\bio\1002\1002.pdf, pages 001, 019; clinstat\other\M016455B 3081.pdf, page 018; hpbio\bio\ka467.pdf, pages 004, 034]

The applicant certified that they did not use and would not use the services of any person debarred under Section 306(a) and 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with their application [other\debar.pdf, page 002]. The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The applicant certified that the clinical investigators did not have a proprietary interest in the proposed product or a significant equity in the applicant. The applicant also certified that no investigator was the recipient of significant payments [other\financial.pdf, page 002].

6. INTEGRATED REVIEW OF EFFICACY

Fexofenadine HCl 180 mg QD is approved for the SAR indication in adults and children 12 years of age and older (NDA 20-872). The Monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antihistaminic Drug products permits antihistamine/decongestant combinations [21 CFR 341.40]. Extended-release pseudoephedrine HCl was approved as an OTC decongestant in adults and children 12 years of age and older (NDA 20-021). Immediate-release pseudoephedrine HCl is considered to be generally recognized as safe and effective (GRASE) for nasal congestion in adults and children ≥12 years at the dose of 60 mg Q 4H to 6H, not to exceed (NTE) 240 mg/24 hours, under the Monograph for OTC Nasal Decongestant Drug Products [21 CFR 341.80].

This application was filed as a submission under Section 505(b)(2) of the FD&C Act because the applicant does not have right of reference and must rely on the Agency's findings of efficacy and safety for the pseudoephedrine reference product. This section of the FD&C Act permits approvals to be based on the Agency's previous findings of efficacy and safety. The application relies on a comparison of the bioavailability and bioequivalence of the proposed new drug to approved reference products. The reference drug products for this application are:

- Allegra® (fexofenadine HCl) Tablets, 180 mg, Aventis Pharmaceuticals, Inc., NDA 20-872
- Sudafed® (pseudoephedrine HCl) Non-Drowsy 24 Hour Nasal Decongestant Tablets, Marketed by Pfizer Consumer Healthcare, originally approved as Efidac® (pseudoephedrine HCl), 240 mg, Alza Corporation, NDA 20-021

The sponsor's drug development program for Allegra-D 24-Hour™ Tablets is based on establishing that their combination fexofenadine/pseudoephedrine product produces equivalent exposures to that of their approved and marketed 180 mg single ingredient fexofenadine HCl product (Allegra® Tablets) and to an approved and marketed OTC 240 mg extended-release pseudoephedrine HCl product (Sudafed® 24 Hour Tablets).

As such, only clinical pharmacology studies were included in this application. Clinical studies of the efficacy of the product were not required. The clinical pharmacology studies in this application confirmed the bioequivalence of the new drug to the reference products, Allegra® Tablets (fexofenadine HCl 180 mg) and Sudafed® 24-Hour Tablets (240 mg pseudoephedrine HCl), in the fasted state after single dose administration and at steady state with multiple dose administration.

The clinical pharmacology studies in this application and the Agency's prior findings of efficacy of the 180 mg fexofenadine HCl and 240 mg pseudoephedrine HCl products support the efficacy of the proposed product. The results of the clinical pharmacology studies are summarized in Section 3 of this review "Human Pharmacokinetics and Pharmacodynamics."

7. INTEGRATED REVIEW OF SAFETY

Integrated review of safety data supporting this application follows below.

7.1. Summary and conclusions

The applicant's Integrated Summary of Safety identifies no new safety concerns and supports the safety of the applicant's product.

Adverse events occurring in more than 2% of patients receiving the fexofenadine/pseudoephedrine combination product in the two pivotal clinical pharmacology studies included pharyngolaryngeal pain (3.3%, 3/92) and upper respiratory tract infection (2.2%, 2/92). It is difficult to draw conclusions based on these data because of the small number of adverse events. Vital signs, laboratory studies and ECGs identified no new safety signal.

Safety data from the two controlled clinical studies included in this application were previously submitted to NDA 20-872 and were examined in detail in the clinical review. The clinical reviewer concluded that fexofenadine HCl was safe and well-tolerated at a dose of 120 mg or 180 mg once a day in 570 patients in the controlled efficacy and safety study (M106455B/3081). No serious related adverse events occurred in patients treated with fexofenadine and no deaths were reported. Headache was the most common adverse event, followed by upper respiratory tract infection, pharyngitis, and back pain. No abnormal trends or worrisome laboratory findings or significant changes in vital signs were noted. For the long-term controlled safety study (PJPR0027), the incidence of most adverse events was comparable between the two treatment groups, with the exception of a slightly higher incidence of nasal irritation/inflammation in the placebo group. There was one death in the study in a placebo-treated subject due to a self-inflicted gunshot wound. Review of vital signs, laboratory studies, and ECGs showed no clinically meaningful difference between treatment groups. The safety data from the controlled clinical studies reveals no safety signal. Information on drug abuse and overdose suggest that there is a low potential for risk to the consumer from abuse or overdose of fexofenadine. Although there is a risk of abuse and overdose for pseudoephedrine, the risk for this combination fexofenadine/pseudoephedrine prescription drug product would be expected to be less than more easily obtained and widely available OTC drug products. The commonly reported postmarketing spontaneous adverse events were similar to those noted in labeling for the currently approved Allegra-D product. The applicant's review of the medical literature and safety update reveal no new safety concerns and support the safety of the proposed combination product.

7.2. Content

The following data were reviewed in preparation of this review of safety:

- Applicant's summary of safety information from pivotal clinical pharmacology studies in this application, M106455B/1001 and M106455B/1002 [clinstat\iss\iss.pdf, pages 008-063]
- Applicant's summary of safety information from controlled clinical studies in this application, M106455B/3081 and PJPR0027 [clinstat\iss\iss.pdf, pages 021-024; clinstat\iss\iss.pdf, pages 095-099]
- Adverse events in subgroups in clinical studies M106455B/3081 and PJPR0027 [clinstat\iss\iss.pdf, pages 031-038]
- Postmarketing and spontaneous adverse event reports for fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg [clinstat\iss\iss.pdf, pages 064-087]
- Drug-drug, drug-demographic, and drug-disease interactions [clinstat\iss\iss.pdf, pages 090-094]
- Drug abuse and overdose information [clinstat\drugabuseandoverdoseinf.pdf, pages 1-24]
- Review of the literature for safety information relevant to fexofenadine and pseudoephedrine [clinstat\clinsum.pdf, pages 044-047]
- Safety update [NDA 21-704, N-000 SU, 4/9/04, update\update.pdf, pages 001-044]

7.3. Integrated safety data, pivotal clinical pharmacology studies

Safety data from the applicant's pivotal clinical pharmacology studies are discussed below.

7.3.1. Description of pivotal clinical pharmacology studies

There were two pivotal clinical pharmacology studies in this application:

- M106455S/1001, a pivotal, single dose and steady state bioequivalence study of 180 mg fexofenadine HCl/240 mg pseudoephedrine HCl combination tablets in healthy subjects [clinstat\clinsum.pdf, page 013]
- M106455S/1002, an open label, randomized study to assess the effect of food on the pharmacokinetics of 180 mg fexofenadine HCl/240 mg pseudoephedrine HCl combination tablets in healthy subjects [clinstat\clinsum.pdf, page 013].

7.3.2. Demographics

Demographics in the pivotal clinical pharmacology studies are summarized in Table 7.1 [clinstat\iss\iss.pdf, page 16]. There were slightly more male subjects (59.6%, 56/94) than female subjects (40.4%, 38/94) in the pivotal clinical pharmacology studies. The mean age was 24.9 years, and ranged from 18 to 44 years. Patients of Caucasian race were represented most frequently, followed by patients of Black and other races.

Table 7.1. Demographics, pivotal clinical pharmacology studies [clinstat\iss\iss.pdf, page 016]

Characteristic	M106455S/1001 N = 70		M106455S/1002 N = 24		Total N = 94	
Gender	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Female	27	(38.6)	11	(45.8)	38	(40.4)
Male	43	(61.4)	13	(54.2)	56	(59.6)
Age, years						
Mean age	23.8		28.1		24.9	
Range	18-44		18-44		18-44	
Race	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Caucasian	66	(94.3)	21	(87.5)	87	(92.6)
Black	3	(4.3)	3	(12.5)	6	(6.4)
Other	1	(1.4)	0	(0)	1	(1.1)

7.3.3. Disposition

Subject disposition is summarized in Table 7.2 [hpbio\bio\1001\1001.pdf, page 68; hpbio\bio\1002\1002.pdf, page 059]. A total of 94 subjects were enrolled and randomized in the pivotal clinical pharmacology studies. The frequency of withdrawals was similar for both studies.

Table 7.2. Disposition, pivotal clinical pharmacology studies [hpbio\bio\1001\1001.pdf, page 068; hpbio\bio\1002\1002.pdf, page 059]

	M106455S/1001 N = 70		M106455S/1002 N = 24		Total N = 94	
	n	(%)	n	(%)	n	(%)
Enrolled	70	(100)	24	(100)	94	(100)
Randomized	70	(100)	24	(100)	94	(100)
Completed	64	(91.4)	22	(91.7)	86	(91.5)
Withdrawals	6	(8.6)	2	(8.3)	8	(8.5)
Reasons for withdrawal						

	M106455S/1001 N = 70 n (%)	M106455S/1002 N = 24 n (%)	Total N = 94 n (%)
Adverse event	0 (0)	1 (4.2)	1 (1.1)
Did not wish to continue	3 (4.3)	1 (4.2)	4 (4.3)
Lost to follow-up	0 (0)	0 (0)	0 (0)
Other reason	3 (4.3)	0 (0)	3 (3.2)

7.3.4. Exposure

Exposure to study medication is summarized in Table 7.3 [clinstat\iss\iss.pdf, page 24; hpbio\bio\1001\1001.pdf, pages 049-050, 068, 095]. More than 90% of patients completed all doses of study treatment in the pivotal clinical pharmacology studies.

Table 7.3. Exposure, pivotal clinical pharmacology studies [clinstat\iss\iss.pdf, page 24; hpbio\bio\1001\1001.pdf, pages 049-050, 068, 095]

	Complete course of study treatment	Subjects exposed N	Patients completing all doses of study treatment n (%)
M016455S/1001			
Fexofenadine/PSE	7 doses, once daily x 1 week	68	64 (94.1)
Fexofenadine plus PSE	7 doses, once daily x 1 week	68	66 (97.1)
M106455S/1002			
Fexofenadine/PSE	3 single doses, 3 study periods	24	22 (91.7)

PSE = pseudoephedrine HCl

7.3.5. Adverse events

Adverse events occurring in more 2% of patients treated with the combination fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg product are summarized in Table 7.4 [clinstat\iss\iss.pdf, page 24; hpbio\bio\1001\1001.pdf, page 095]. The frequency of adverse events was similar for patients receiving the fexofenadine/pseudoephedrine combination product in M016455S/1001 (10.3%, 7/68) and M016455S/1002 (8.3%, 2/24) and somewhat higher in patients who received one tablet of fexofenadine HCl 180 mg plus one tablet of pseudoephedrine HCl 240 mg concurrently (16.2%, 11/68). Adverse events occurring in more than 2% of patients receiving the fexofenadine/pseudoephedrine combination product included pharyngolaryngeal pain (3.3%, 3/92) and upper respiratory tract infection (2.2%, 2/92).

Reviewer comment:
It is difficult to draw conclusions based on these data because of the small number of adverse events.

Table 7.4. Adverse events occurring in >2% of subjects receiving fexofenadine/pseudoephedrine combination, data from pivotal studies [clinstat\iss\iss.pdf, page 24; hpbio\bio\1001\1001.pdf, page 095]

Adverse event	M016455S/1001				M106455S/1002			
	Fexofenadine/PSE N = 68		Fexofenadine plus PSE N = 68		Fexofenadine/PSE N = 24		Total Fexofenadine/PSE N = 92	
All adverse events	7	(10.3)	11	(16.2)	2	(8.3)	9	(9.8)
Pharyngolaryngeal pain	2	(2.9)	0	(0)	1	(4.2)	3	(3.3)
Upper respiratory tract infection NOS	1	(1.5)	0	(0)	1	(4.2)	2	(2.2)

PSE = pseudoephedrine HCl

7.3.5.1. Adverse events in subgroups

The overall incidence of adverse events was slightly higher for females (26.3%, 10/38) than for males 17.9%, 10/56). No adverse event occurred in more than 2 subjects in each gender group. No subjects were less than 18 years of age or greater than 65 years of age. All subjects who experienced adverse events were of Caucasian race; there were no adverse events experienced by any of the six subjects of other races [clinstat\iss\iss.pdf, pages 016, 031].

Reviewer comment:
It is difficult to draw conclusions from the subgroup data in these studies because of the small number of subjects.

7.3.6. Serious adverse events and deaths

There were no serious adverse events or deaths in the pivotal clinical pharmacology studies [clinstat\iss\iss.pdf, pages 040, 043].

7.3.7. Withdrawals due to adverse events

There was one patient who withdrew from the pivotal studies because of an adverse event (1.1%, 1/94). This patient, Subject 0001/01018 in Study M016455S/1002 withdrew because of an upper respiratory infection and pharyngeolaryngeal pain that started before dosing with the fexofenadine/pseudoephedrine combination product. The symptoms worsened after dosing, and the subject developed a fever. The adverse events resolved 3 days after withdrawal from the study [clinstat\iss\iss.pdf, page 041].

7.3.8. Vital signs

Descriptive statistics for vital signs in the pivotal clinical pharmacology studies showed no trends or clinically meaningful changes in vital sign values or changes from baseline to end of study. There were three subjects in the two studies that had changes in heart rate that met criteria for predefined abnormal changes (PCA). These subjects had decreases in heart rate from the high 80's at baseline to the low 50s/high 40's post-study [clinstat\iss\iss.pdf, pages 059-060, 155-156].

Reviewer comment:
Vital signs data do not reveal any safety signal.

7.3.9. Physical examination

Physical examination was not a safety variable in the pivotal clinical pharmacology studies.

7.3.10. Laboratory studies

Laboratory studies revealed no clinically important changes in mean values or change from baseline. No changes meeting PCA criteria were clinically significant, and no abnormal laboratory values were reported as adverse events [clinstat\iss\iss.pdf, pages 048-050].

Reviewer comment:
Laboratory data do not reveal any safety signal.

7.3.11. ECGs

There were no trends or clinically meaningful changes in mean or individual values for ECG measurements in the pivotal clinical pharmacology studies. There were no adverse events reported for abnormal ECG results [clinstat\iss\iss.pdf, pages 056, 149-151].

Reviewer comment:
This reviewer's examination of ECG data did not reveal any clinically significant changes.

7.4. Safety data, controlled clinical studies

This application referred to two controlled clinical studies:

- M106455B/3081, a double blind, randomized, placebo controlled, parallel group study comparing the efficacy and safety of fexofenadine HCl 120 mg and 180 mg QD in the treatment of allergic rhinitis. Safety endpoints included adverse events, vital signs, and physical examinations. This study was completed as part of NDA 20-872 and was the pivotal study supporting the approval of fexofenadine HCl 180 mg QD in adults and children 12 years of age and older [clinstat\clinsum.pdf, page 042; clinstat\other\M016455B 3081.pdf, page 013; clinstat\iss\iss.pdf, page 009].
- PJPR0027, a double blind, randomized, placebo controlled, parallel group, twelve-month study comparing the safety and tolerance of fexofenadine HCl 240 mg QD with placebo in normal healthy subjects. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs. This study was also completed as part of NDA 20-872 and supported the safety of fexofenadine HCl 180 mg QD in adults and children 12 years of age and older [clinstat\clinsum.pdf, pages 043, 109; clinstat\other\PJPR0027 Synopsis.pdf, page 001; clinstat\iss\iss.pdf, page 009].

Safety data from these studies were previously submitted to NDA 20-872. The applicant resubmitted these data with this application in the form of a complete study report for M106455B/3081 and a study synopsis for PJPR0027 and summarized the safety data in the application's Integrated Summary of Safety.

There were 809 subjects exposed to fexofenadine HCl in the controlled clinical studies. The applicant concluded that adverse event rates were similar between the two treatment groups for both controlled clinical studies. The most commonly reported adverse event in both of these studies was headache. Serious adverse events were reported with similar incidences. There was one death PJPR 0027 in a placebo-treated subject due to a self-inflicted gunshot wound. Evaluation of adverse events in subgroups was performed in M106455B/3081. The overall frequency of adverse events was slightly higher in females (32.3%, 184/558) than in males (25.0%, 76/304). However, the frequency of adverse events in fexofenadine-treated females (34.3%, 126/367) was similar to that of placebo-treated females (30.4%, 58/191). The frequency of adverse events in fexofenadine-treated males (22.8%, 46/202) was similar to that of placebo-treated males (29.4%, 30/102).

There were no trends or clinically meaningful changes from baseline to study end in mean or individual vital signs data. There were no changes from baseline to study end in laboratory study results that were considered to be clinically important. ECG data from PJPR0027 showed no clinically important changes from baseline in ECG parameters, including QTc, QT, PR, QRS, and heart rate [clinstat\iss\iss.pdf, pages 010, 034-035; summary\summary.pdf, pages 110-113].

Reviewer comments:
Safety data from these studies were previously submitted to NDA 20-872 and were examined in detail in the clinical review. For M106455B/3081, the clinical reviewer concluded that fexofenadine HCl was safe and well-tolerated at a dose of 120 mg or 180 mg once a day in 570 patients. No serious related adverse events occurred in patients treated with fexofenadine, nor were any deaths reported. Headache was the most common adverse event, followed by upper respiratory tract infection, pharyngitis, and back pain. No abnormal trends or worrisome laboratory findings were noted in this study. No significant changes in vital signs were noted [NDA 20-872, N-000, 7/17/98, Medical Officer Review, A. Worobec, M.D.].

For PJPR0027, the clinical reviewer noted that the incidence of most adverse events was comparable between the two treatment groups, with the exception of a slightly higher incidence of nasal irritation/inflammation in the placebo group. Review of vital signs and laboratory studies showed no clinically meaningful difference between treatment groups. The reviewer concluded that PJPR0027 revealed no significant increase in QTc prolongation, other cardiac outliers, and no increased incidence of cardiac tachyarrhythmias in patients treated with fexofenadine HCl 240 mg QD, compared to placebo treatment [NDA 20-872, N-000, 7/17/98, Medical Officer Review, A. Worobec, M.D.].

The safety data from the controlled clinical studies reveals no safety signal.

7.5. Postmarketing and spontaneous adverse event reports for fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg

The applicant provided a summary and analysis of postmarketing adverse event reports for their currently approved product, fexofenadine HCl 60 mg/pseudoephedrine HCl 120

mg extended-release Tablets (Allegra-D). The product was approved in the United States in December 1997 and is now approved in 39 countries worldwide. Postmarketing data include information from clinical trials, spontaneous adverse event reports, and from the published medical literature. The summary and analysis of adverse event reports covers the period of time from December 1997 until December 2002, the cut-off date for the most recent annual report at the time of the NDA submission [clinstat\iss\iss.pdf, pages 063-064].

A total of 5080 adverse event reports occurring in 2908 patients have been submitted to the applicant over this period. The applicant estimates the postmarketing patient exposure to fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg to be ——— patient-treatment days over the period from 1998 to June 2003 [clinstat\iss\iss.pdf, page 064].

The most commonly reported spontaneous adverse events are presented below in Table 7.5.

Table 7.5 Most commonly reported postmarketing spontaneous adverse events for fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg (Allegra-D), January 1998-December 2002 [clinstat\iss\iss.pdf, page 066].

Adverse event	Number of adverse events	Number of cases
All adverse events	5080	2908
Drug ineffective	837	764
Medication in stool	581	572
Insomnia	424	421
Dizziness	158	148
Headache	154	154
Nausea	123	120
Somnolence	103	100
Dry mouth	99	99
Back pain	97	93
Diarrhea	93	93

The most commonly reported adverse events included "drug ineffective", "medication in stool", insomnia, dizziness, headache, and nausea, among others. The applicant notes that the majority of the most commonly reported adverse events were not serious and consistent with the known safety profile for the combination product [clinstat\iss\iss.pdf, page 066].

Reviewer comment:
Reports of "drug ineffective" and "medication in stool" have been previously noted in annual reports for Allegra-D and Allegra [NDA 20-786, P-013, 3/1/02 and NDA 20-872, P-101, 9/11/02, Medical Officer Reviews, Charles E. Lee, M.D.]. Most of the other most commonly reported postmarketing adverse events are similar to those noted in labeling for the currently approved Allegra-D product.

7.5.1. Postmarketing adverse events of special interest

The applicant reviewed adverse events of special interest relating to the cardiac, nervous, psychiatric, general, gastrointestinal, hepatic system organ classes, and deaths. The applicant also reviewed postmarketing adverse events for drug exposure during pregnancy. The most commonly reported adverse events for these items of special interest are consistent with the known safety profile of Allegra-D and many are noted in

labeling for the currently marketed product. Serious, unlabeled events were relatively infrequent, given the large patient exposure to the drug. Many serious unlabeled events were confounded by pre-existing disease or concomitant medication, and some did not include enough information to assess any causative role of the drug product. The applicant concluded that these data do not provide evidence for new safety signal or concerns.

Adverse events of special interest are discussed in greater detail below.

Reviewer comment:
This reviewer concurs that these data do not provide evidence of new safety concerns.

7.5.1.1. Cardiac adverse events

The majority of commonly reported cardiac events included palpitations and tachycardia. There were 18 serious cardiac events of which five were considered to be labeled. These labeled adverse events included palpitations and tachycardia. There were 13 unlabeled events that occurred in nine patients. Unlabeled events included supraventricular tachycardia (2 events), ventricular tachycardia (1 event), first degree AV block (1 event), cardiac failure NOS (1 event), cardiac arrest (3 events), and myocardial infarction (1 event). Pre-existing cardiac disease and use of concomitant medication were confounding factors in the majority of these reports. The applicant points out that the there are relatively few cardiac reports, considering the prevalence of cardiac disease in the population and the large patient exposure to the product [clinstat\iss.iss.pdf, pages 067-071].

7.5.1.2. Nervous system adverse events

The most commonly reported nervous system adverse events included dizziness, headache, and somnolence. The applicant notes that these adverse events are consistent with the safety profile for the combination product. Serious, unlabeled nervous system adverse events included benign intracranial hypertension (1 event), facial palsy (1 event), loss of consciousness (4 events), migraine (1 event), cerebrovascular accident (1 event), syncope (2 events), and speech disorder (1 event). The majority of these cases were associated with other concomitant medical conditions or alternative etiologies. Some of the cases did not have a sufficient amount of information to permit a causal assessment. The applicant concluded that the serious, unlabeled nervous system adverse events did not reveal any new safety concern [clinstat\iss\iss.pdf, pages 072-077].

7.5.1.3. Psychiatric adverse events

The most commonly reported psychiatric adverse events included insomnia, nervousness, and anxiety. The applicant notes that these adverse events are consistent with the safety profile for the combination product. Serious, unlabeled psychiatric adverse events included disorientation (2 events), paranoia (1 event), and confusion (1 event). No new safety signal or concerns were identified by these events [clinstat\iss\iss.pdf, pages 078-080].

7.5.1.4. General disorder and administration site adverse events

The most commonly reported adverse events in this category included "drug ineffective" and "medication in stool." The applicant notes that with a patient exposure of [ ] treatment days, that the reporting rate for "drug ineffective" is approximately 1 event per 1 million treatment days. The applicant notes that the pseudoephedrine component of the drug product is contained in [ ] matrix, and that the appearance of the medication in the stool is not unexpected. As noted previously, both of these adverse events have been previously noted in annual reports for Allegra-D and Allegra [NDA 20-872, P-101, 9/11/02 and NDA 20-786, P-013, 3/1/02; Medical Officer Reviews, Charles E. Lee, M.D.].

Serious, unlabeled adverse events in this category included dysphagia (1 event), vomiting and sensation of foreign body (1 event), and chest pain (1 event). The patient with dysphagia had a tablet stuck in her throat, which had resolved by the time she had endoscopy, five days after the event. The patient with vomiting and a sensation of foreign body ingested half of an Allegra-D tablet that had been split in half. The tablet dissolved prior to surgical intervention. The applicant concluded that there were no new safety signals or concerns revealed [clinstat\iss\iss.pdf, pages 080-082].

7.5.1.5. Gastrointestinal adverse events

The most commonly reported gastrointestinal adverse events included nausea, diarrhea, dry mouth, and fecal abnormality, which are compatible with the known safety profile of the product. There were seven serious, unlabelled events, which included vomiting and diarrhea (1 event each), esophageal disorder (1 event), ischemic colitis (1 event), pseudointestinal obstruction and constipation (1 event each), and intestinal obstruction (1 event). The patient with esophageal disorder had a tablet lodged in the esophagus and a pre-existing history of esophageal stenosis. The patient with pseudointestinal obstruction and constipation had pre-existing constipation and presented after only one day of treatment with Allegra-D. The patient with intestinal obstruction had a prior history of small bowel obstruction and ulcer at the ileocecal junction. The applicant concluded that there were no new safety signals or concerns revealed [clinstat\iss\iss.pdf, pages 082-085].

7.5.1.6. Hepatic adverse events

There were only two non-serious hepatic adverse events (liver disease and liver enlargement) reported from the same patient. The patient was reported to be asymptomatic and doing well. The applicant concluded that this isolated case report does not present any safety issue [clinstat\iss\iss.pdf, page 085].

7.5.1.7. Deaths

There were two cases of death reported in patients taking Allegra-D. One case, a 60-year old male who had cardiac arrest and QT prolongation had concomitant hypokalemia and metabolic acidosis. The second case was a 65-year old woman who developed anaphylactic shock 15-20 minutes after receiving one dose of Allegra-D. She suffered

cardiac arrest and was resuscitated and placed on a ventilator, but expired two days later. She had a prior history of asthma and allergies, and was also taking fluticasone, enalapril, budesonide, and salmeterol. The applicant concluded that these two individual cases do not have any proven causal relationship with the combination product [clinstat\iss\iss.pdf, pages 085-086]. Labeling for Allegra-D notes that rare cases of systemic anaphylaxis has been reported.

7.5.1.8. Pregnancy

There are four spontaneous adverse event reports of pregnancy and drug exposure to the fetus for the currently approved combination fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg product. One mother required emergency Caesarian section because of fetal distress. There was one case of pregnancy on an oral contraceptive and insomnia, one case of a missed abortion, and one case of spontaneous abortion [clinstat\iss\iss.pdf, page 86].

7.6. Drug-drug, drug-demographic, and drug-disease interactions

The applicant notes that fexofenadine peak plasma levels following erythromycin or ketoconazole co-administration increased 80% and 130%, respectively. No notable differences in adverse events were reported when fexofenadine HCl was administered alone or in combination with either erythromycin or ketoconazole. There was no statistically significant increase in QTc when fexofenadine HCl was administered alone or in combination [clinstat\iss\iss.pdf, page 090]. Information on interactions of fexofenadine, erythromycin, and ketoconazole are noted in the labeling for the currently marketed Allegra-D product.

The applicant notes that co-administration of fexofenadine with Maalox® reduced the bioavailability of fexofenadine by approximately 41%. A corresponding decrease in rate of absorption of 43% was also observed [clinstat\iss\iss.pdf, page 090]. This drug interaction is noted in the labeling for the Allegra Capsules and Tablets products, but not for the currently marketed Allegra-D product.

The OTC Monograph labeling for oral nasal decongestant drug products containing pseudoephedrine instructs consumers not must use the product if they are taking a monoamine oxidase (MAO) inhibitor or for two weeks after stopping a MAO inhibitor [21 CFR 341.80(c)(1)(i)(D); clinstat\iss\iss.pdf, page 092].

Reviewer comments:
The applicant's proposed labeling notes the drug interactions of fexofenadine with erythromycin and ketoconazole and pseudoephedrine with MAO inhibitors. It does not note the interaction with aluminum- and magnesium-containing antacids. The labeling should be revised to advise the prescriber that co-administration of fexofenadine with aluminum- and magnesium-containing antacids reduces the bioavailability of fexofenadine. Such labeling would be consistent with current labeling of the approved single-ingredient fexofenadine products.

Adverse events in males and females in the pivotal clinical pharmacology studies and the controlled clinical study M106455B/3081 have been discussed previously in Sections 7.3.5.1 and 7.4 of this review. Adverse event rates did not appear to differ significantly across subgroups of subjects defined by gender for any of the studies. In the pivotal clinical pharmacology studies and the controlled clinical study M106455B/3081, only 3 subjects were greater than 65 years of age, making it difficult to draw definitive conclusions about the incidence of adverse events by age [clinstat\iss\iss.pdf, pages 092-093]. In the controlled clinical study M106455B/3081, the frequency of adverse events for patients was similar for patients of Caucasian race (31.1%, 157/505) than for those of Black race (28.2%, 11/39). The numbers of Asian and Multiracial races were small [clinstat\iss\iss.pdf, pages 037, 092-093].

Fexofenadine-disease interactions have been previously studied in renal and hepatic insufficiency and data has been previously submitted to NDA 20-625. Renal clearance of fexofenadine decreases as the severity of renal disease increases. Based on these data, fexofenadine HCl 60 mg QD is recommended for renally-impaired patients. Because the doses of the fexofenadine and pseudoephedrine in the combination product cannot be individually titrated and because renal insufficiency increases the bioavailability and prolongs the half-life of fexofenadine and pseudoephedrine, the combination product should be avoided in patients with renal insufficiency [clinstat\iss\iss.pdf, pages 093-094]. Both the labeling for the currently approved Allegra-D product and the proposed product include this information on use in patients with renal insufficiency [labeling\labeling\proposed.pdf, page 005]. The pharmacokinetics of fexofenadine in hepatically-impaired patients were similar to those observed in healthy volunteers [clinstat\iss\iss.pdf, page 094]. No precautionary labeling is necessary for use of fexofenadine in patients with hepatic impairment. Accordingly, neither the current labeling for the approved Allegra-D and Allegra products nor the proposed labeling for the Allegra-D 24-Hour product include precautions for patients with hepatic disease.

Labeling specified by the OTC monograph cautions consumers to avoid pseudoephedrine if they have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a physician [21 CFR 341.80(c)(1)(c)].

Reviewer comment:
The applicant's proposed labeling appropriately instructs prescribers to avoid use of the proposed combination fexofenadine/pseudoephedrine product in patients with renal disease. No precautions for use of the proposed product are necessary for patients with hepatic impairment.

7.7. Drug abuse and overdose

The applicant notes that there are no reports of drug abuse for the currently approved Allegra-D product, and that preclinical and clinical use of fexofenadine have not demonstrated evidence suggesting a potential for abuse. The applicant notes that pseudoephedrine has been abused. At elevated dosages of pseudoephedrine, subjects experience an elevated mood, a sense of increased energy and alertness, and decreased

appetite. Anxiety, irritability, and an enhanced sense of physical strength and mental capacity may also be experienced. Tolerance may develop with continued use and depression may follow rapid withdrawal [clinstat\drugabuseandoverdoseinf.pdf, page 001].

The applicant states that most reports of fexofenadine overdose contain limited information, but that dizziness, drowsiness, and dry mouth have been reported. Single doses of fexofenadine HCl up to 800 mg and doses of fexofenadine HCl up to 690 mg BID for one month and 240 mg once daily for one year have been studied without evidence of clinically important adverse events. Pseudoephedrine in large doses may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, hypertension difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness, and insomnia. Some individuals may develop a toxic psychosis with delusions and hallucinations. Cardiac arrhythmias, circulatory collapse, convulsions, coma, and respiratory failure may also occur with high doses [clinstat\drugabuseandoverdoseinf.pdf, page 001].

Reviewer comment:
This reviewer did not identify any case reports in a search of the literature using PubMed with search terms "fexofenadine" AND "overdose." This reviewer also searched the AERS database with AERS DataMart to determine the extent that drowsiness was noted in cases of overdose. Search terms were: "fexofenadine HCl" AND ("accidental overdose" OR "chemical injury, overdose and poisoning," OR "intentional overdose," OR "multiple drug overdose," OR "multiple drug overdose accidental," OR "multiple drug overdose intentional," OR "overdose," OR "overdoses," OR "prescribed overdose"). There were 83 adverse event reports identified. Of these, 23 reports were large intentional or accidental overdoses or were overdoses for which the amount ingested was not recorded. The remaining cases were smaller overdoses (in the range covered by in clinical trials) or were medication errors. Recorded doses in the 23 large overdose reports ranged from 600 mg to 7000 mg. Of these 23 reports, only three were coded as having adverse events for sedation or coma. One of these cases was a 15 year old female who intentionally took an overdose of cisapride, flecainide, and fexofenadine. She had QT prolongation, torsade de pointes, and ventricular tachycardia, in addition to sedation [ISR #3146368]. Another case was a 19 year old female who intentionally took an overdose of phenytoin, carbamazepine, clonazepam, and fexofenadine. She was reported as having coma [ISR# 1926394]. The last case was a 25 year old male who was reported as having dizziness, dry mouth, and sedation with an overdose of fexofenadine. No other concomitant medications are listed for this case. The ingested dose was not recorded [ISR# 1921932]. The adverse events listed for this case are the similar to those noted in the OVERDOSAGE section of the proposed label and the labels for the currently approved Allegra-D and Allegra products. It is possible that the overdose labeling in the labels is based on this single case.

These drug abuse and overdose data suggest that there is a low potential for risk to the consumer from abuse or overdose of fexofenadine. The risk of abuse and overdose with

pseudoephedrine for this prescription drug product would be expected to be less than more easily obtained and widely available OTC drug products.

7.8. Review of the literature for safety information relevant to fexofenadine and pseudoephedrine

The applicant performed searches of the medical literature on the safety of fexofenadine and pseudoephedrine. The results of these searches are discussed below.

The applicant searched the medical literature for articles relevant to the safety of fexofenadine published from February 25, 2000 (the date of the approval of Allegra Tablets, 180 mg) until September 30, 2003. The applicant identified ten articles of interest [clinstat\clinsum.pdf, pages 044-046]. Of these ten articles, one article addressing the cardiovascular safety of fexofenadine is of note. Scherer, et. al. found that a 67-year old male patient reported in the literature as having QTc prolongation and ventricular dysrhythmia temporally associated with the use of fexofenadine, in fact, had a mutant HERG protein, which produced I_{kr} currents that were not blocked by fexofenadine at concentrations far exceeding those found in human plasma.[1] This patient, reported by Pinto, et. al., had other risk factors for QTc prolongation, including hypertension and sudden withdrawal of an antihypertensive.[2]

The applicant searched the medical literature published between June 1992 and September 2003 for articles relevant to the safety of pseudoephedrine. There were two articles of interest identified by the applicant [clinstat\clinsum.pdf, page 047]. Beck, et. al., noted no statistically significant increases in cardiovascular parameters in a study of 28 patients with hypertension when administered pseudoephedrine 120 mg twice daily for 72 hours.[3] There were minimal increases in mean arterial pressure and heart rate. The authors concluded that extended-release pseudoephedrine appears to be safe for the majority of medically controlled hypertensive patients. The applicant notes that a study comparing the efficacy and safety of fexofenadine HCl 60 mg BID, pseudoephedrine HCl 120 mg BID, and the fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg combination product BID in patients with SAR showed no serious adverse events in any treatment group.[4] The most common adverse events in each of the treatment groups were headache and insomnia. The overall frequency of adverse events in the combination fexofenadine/pseudoephedrine group (34.9%) and the pseudoephedrine group (36.7%) were similar and greater than that in the fexofenadine group (16.5%). Insomnia, nausea, dry mouth, and dizziness were more common in the fexofenadine/pseudoephedrine and pseudoephedrine groups than in the fexofenadine group.

The applicant concluded that the literature survey provides evidence that fexofenadine is safe and lacks any deleterious effects on the central nervous and cardiovascular systems. The applicant also concluded that the literature review of the safety of pseudoephedrine did not alter the currently known risk and benefit profile of the drug [clinstat\clinsum.pdf, page 047].

Reviewer comments:
The case of prolonged QTc and ventricular arrhythmia reported by Pinto, et. al. has previously been examined by this reviewer, and there is substantial evidence suggesting pre-existing cardiac disease as a causative factor in the patient's dysrhythmia [NDA 20-872, N-000 AZ, 8/26/99, Medical Officer Review, Charles E. Lee, M.D.]. The adverse events noted in the efficacy and safety study reported by Sussman, et. al. revealed no new safety information. Adverse events noted in the fexofenadine/pseudoephedrine combination and pseudoephedrine groups were consistent with the known safety profile of pseudoephedrine. The applicant's review of the medical literature reveal no new safety concerns and supports the safety of the proposed combination product.

7.9. Safety update

The 120-day safety update for this application consisted of a review and analysis of spontaneous adverse event reports received during the period from September 27, 2003 until February 25, 2004 for the currently approved Allegra-D product. There were a total of 237 adverse event reports in 141 patients reported over this period [NDA 21-704, N-000 SU, 4/9/04, update\update.pdf, pages 005-007]. The most commonly reported adverse events included "drug ineffective", "stool analysis abnormal", and insomnia [NDA 21-704, N-000 SU, 4/9/04, update\update.pdf, page 008]. A change in the MedDRA dictionary in January 2002 led to the previous term "medication in stool" to be coded as "stool analysis abnormal" [NDA 21-704, N-000 SU, 4/9/04, update\update.pdf, page 006]. The most common adverse events were consistent with those noted in the review of postmarketing spontaneous adverse events submitted with the NDA application and discussed in Section 7.5 of this review.

The applicant also reviewed adverse events of special interest relating to the cardiac, nervous, psychiatric, general, gastrointestinal, hepatic system organ classes, and deaths that were reported during the period covered by the safety update. Non-serious adverse events for the organ classes of special interest were consistent with those previously reported and were part of the known safety profile for the product. There were no new serious unlabeled events reported for the cardiac, nervous, psychiatric, gastrointestinal, and hepatic system organ classes. One serious event was reported for general disorders, an individual who had dizziness associated with tachycardia. Both of these adverse events are labeled and are consistent with the safety profile of the product. There were no deaths reported during the period of time covered by the safety update [NDA 21-704, N-000 SU, 4/9/04, update\update.pdf, pages 008-015].

The applicant concluded that there were no new safety concerns noted in the review and analysis of the safety data received during the period covered by the safety update [NDA 21-704, N-000 SU, 4/9/04, update\update.pdf, page 016].

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The proposed dose of Allegra-D 24 Hour™ Extended-Release Tablets is one tablet once daily administered before a meal for adults and children 12 years of age and older.
The proposed labeling states that the product should generally be avoided in patients with renal insufficiency. The product is not recommended for pediatric patients under 12 years

of age [labeling\proposed.pdf, pages 007, 009]. The dose of fexofenadine HCl is the same as the dose for the approved single ingredient product, Allegra Tablets, 180 mg. A single dose of the proposed product dosed once daily provides 240 mg of pseudoephedrine HCl, the maximum daily dose of pseudoephedrine HCl specified by the OTC monograph [21 CFR 341.80 (d)(1)(ii)].

In the Pharmacokinetics subsection of CLINICAL PHARMACOLOGY, the proposed label notes that co-administration of the product with a high-fat meal decreased the AUC and C_{max} of fexofenadine by 42% and 54%, respectively [labeling\proposed.pdf, page 002]. This section also states that pseudoephedrine pharmacokinetics were unaffected when co-administered with high-fat meal.

Co-administration of fexofenadine with Maalox® reduces the bioavailability of fexofenadine by approximately 41% and the rate of absorption by 43% [clinstat\iss\iss.pdf, page 090]. This drug interaction is not noted in the proposed labeling. It is noted in the labeling for the Allegra Capsules and Tablets products, but not for the currently marketed Allegra-D product.

Reviewer comment:
The labeling notes the decrease in fexofenadine bioavailability associated with concurrent ingestion of a high-fat meal, but recommends [redacted]. *The labeling should be revised to state that the product should be taken on an empty stomach with water. The labeling should also be revised to advise the prescriber that co-administration of fexofenadine with aluminum- and magnesium-containing antacids reduces the bioavailability of fexofenadine.*

The Division asked the applicant to study the effects of grapefruit and apple juices on fexofenadine bioavailability at the End-of-Phase 2 meeting on January 29, 2002. The Division reiterated this request in the March 2, 2004 filing letter. The sponsor provided a response in a submission to this NDA, dated July 19, 2002 [NDA 21-704, N-000 BM, 7/19/04]. The response discussed the results of three clinical pharmacology studies, Study M106455A/4141, Study M106455A/4143, and Study M106455A/4144. These studies are briefly described below.

Study M1061455A/4141 was a randomized, open label, single dose, crossover study designed to determine the effect of eight ounces of grapefruit juice on the inhibition by fexofenadine HCl 180 mg of histamine-induced wheal and flare. There were 20 healthy subjects. There was no pharmacokinetic sampling performed in this study. Concomitant administration of fexofenadine and grapefruit juice resulted in a statistically significant decrease in wheal size of 31%. There was a decrease in flare size of 16%, which was not statistically significant [NDA 21-704, N-000 BM, 7/19/04, response.pdf, pages 006, 010].

Study M106455A/4143 was a double-blind, randomized, crossover, placebo controlled study designed compare histamine-induced wheal and flare after administration of grapefruit juice and fexofenadine HCl 180 mg with grapefruit juice and placebo. There were 23 evaluable subjects. Sparse blood sampling methodology was used for population

pharmacokinetic analysis. In subjects given eight ounces of grapefruit juice, fexofenadine HCl 180 mg suppressed histamine-induced wheal and flare to a greater extent than placebo [NDA 21-704, N-000 BM, 7/19/04, response.pdf, pages 006-007, 010].

The design of Study M106455A/4144 was similar to that of Study M106455A/4143, except that eight ounces of orange juice was administered instead of eight ounces of grapefruit juice. There were 21 evaluable subjects. Sparse blood sampling methodology was used for population pharmacokinetic analysis. In subjects given eight ounces of orange juice, fexofenadine HCl 180 mg suppressed histamine-induced wheal and flare to a greater extent than placebo [NDA 21-704, N-000 BM, 7/19/04, response.pdf, pages 007, 011].

The applicant used a population pharmacokinetics modeling approach to analyze pharmacokinetic data from three clinical pharmacology studies to estimate the effect of concomitant intake of eight ounces of grapefruit or orange juice with fexofenadine HCl. The relative bioavailability for a juice effect was estimated to be 0.64 (SE = 0.056), suggesting that the bioavailability of fexofenadine was reduced by a population mean of 36% (95% CI = 24% to 48%) when eight ounces of grapefruit or orange juice was administered concomitantly with a single 180 mg dose of fexofenadine HCl [NDA 21-704, N-000 BM, 7/19/04, clinstat\PopPK.pdf, pages 023, 026].

The applicant states that the degree and duration of suppression for both flare and wheal in the three studies was comparable to that observed in a previous study performed under identical design conditions that compared fexofenadine HCl 180 mg versus placebo versus loratadine in the absence of grapefruit juice. Based on these pharmacodynamic data, the applicant states that the consumption of reasonable quantities of either grapefruit or orange juice does not appear to significantly alter the effects of fexofenadine on histamine-induced wheal and flare suppression and that the reduction of fexofenadine exposure associated with concurrent intake of these juices may not be clinically relevant. The sponsor concludes that these pharmacodynamic data indicates that fexofenadine may be safely administered without regard to consumption of reasonable quantities of these juices and that efficacy is maintained under these conditions [NDA 21-704, N-000 BM, 7/19/04, response.pdf, page 013].

Reviewer comment:
The sponsor's conclusion that the efficacy of fexofenadine is maintained when co-administered with grapefruit or orange juices relies on the assumption that suppression of histamine-induced wheal and flare is a valid surrogate for clinical efficacy in SAR. This assumption is incorrect, as changes in skin test reactivity do not correlate with clinical efficacy of antihistamines. Bousquet, et. al. demonstrated that astemizole produced a greater degree of skin reactivity to histamine and allergen than did loratadine in a natural exposure study, but astemizole and loratadine had the same clinical effect on nasal and ocular symptoms of SAR.[5] Persi, et. al. showed that cetirizine suppressed skin reactivity to histamine to a greater degree than loratadine, but there was no significant difference in a nasal challenge study between the two drugs in symptom scores and threshold number of pollen grains to produce a positive challenge.[6]

Berkowitz, et. al. demonstrated that 5 mg and 10 mg cetirizine once daily were numerically, but not statistically superior to astemizole 10 mg once daily for patient-assessed symptom scores.[7] Astemizole, however, produced a much greater degree of suppression of skin test reactivity to histamine and allergen. In fact, astemizole has been shown to produce suppression of skin test reactivity for up to 60 days after discontinuation.[8,9] The duration of skin test suppression is much longer any residual clinical efficacy that would be expected after astemizole is stopped.

The estimated decrease in bioavailability of fexofenadine when taken with grapefruit or orange juices is only slightly less than the decrease in bioavailability noted when fexofenadine is taken with a high-fat meal or with aluminum- and magnesium containing antacids. All of these food-drug interactions should be noted in CLINICAL PHARMACOLOGY section of the label.

The proposed DOSAGE AND ADMINISTRATION section of the label states [redacted] *This statement should be revised to state that the product should be taken on an empty stomach with water.*

9. USE IN SPECIAL POPULATIONS

The incidence of adverse events in the pivotal clinical pharmacology studies and controlled clinical efficacy and safety study M106455B/3081 suggest that there are no gender-specific effects associated with the proposed product. In the pivotal clinical pharmacology studies in this application, the overall incidence of adverse events was slightly higher for females (26.3%, 10/38) than for males (17.9%, 10/56). No adverse event occurred in more than 2 subjects in each gender group. In the controlled clinical efficacy and safety study M106455B/3081, the overall frequency of adverse events was slightly higher in females (32.3%, 184/558) than in males (25.0%, 76/304). However, the frequency of adverse events in fexofenadine-treated females (34.3%, 126/367) was similar to that of placebo-treated females (30.4%, 58/191). The frequency of adverse events in fexofenadine-treated males (22.8%, 46/202) was similar to that of placebo-treated males (29.4%, 30/102) [clinstat\iss\iss.pdf, page 093].

Data in this submission suggest that there are no differences in the safety profile for the product in patients of Caucasian and Black races. All subjects who experienced adverse events were of Caucasian race; there were no adverse events experienced by any of the six subjects of other races [clinstat\iss\iss.pdf, pages 016, 031]. The frequency of adverse events for patients was similar for patients of Caucasian race (31.1%, 157/505) than for those of Black race (28.2%, 11/39). The numbers of patients of Asian and Multiracial races were small.

No subjects were greater than 65 years of age in the pivotal clinical pharmacology studies. In controlled efficacy and safety study M106455B/3081, only 3 subjects were greater than 65 years of age making it difficult to draw definitive conclusions about the incidence of adverse events by age [clinstat\iss\iss.pdf, pages 037, 092-093]. The pharmacokinetics of fexofenadine HCl in the elderly population (>65 years old) were different from healthy male subjects (19 to 45 years) following a single dose of

fexofenadine HCl 80 mg (capsule formulation) in Study PJPR0020, previously submitted to NDA 20-625. Peak plasma levels of fexofenadine were approximately 2-fold greater and mean elimination half-lives were similar to those observed in normal volunteers (<65 years old) [clinstat\iss\iss.pdf, page 93]. Since approximately 43-96% of an orally administered dose of pseudoephedrine is excreted unchanged in the urine, pseudoephedrine may accumulate in patients with renal insufficiency [labeling\proposed.pdf, page 003]. Since patients greater than 65 years of age may have decreased renal function, proposed labeling appropriately suggests that that it may be useful to monitor renal function [labeling\proposed.pdf, page 007].

No subjects were less than 18 years of age in the pivotal clinical pharmacology studies. The dose of active drugs in the product and its formulation are not appropriate for use in children less than 12 years of age, and the proposed labeling states that the product is not recommended for pediatric patients under 12 years of age. Alternative fexofenadine and pseudoephedrine products are available in suitable pediatric dosage forms. These products are available as either approved prescription products or as OTC monograph products. Accordingly, the Division waived the requirement for pediatric studies for this application [Correspondence: NDA Acknowledgement Letter, dated 1/14/04].

Adverse event data in patients with renal impairment was collected in single dose pharmacology studies submitted in support of the application for Allegra Capsules, NDA 20-625. These studies showed that renal clearance of fexofenadine decreases as the severity of renal disease increases. Fexofenadine was well tolerated in patients with renal impairment irrespective of the severity of renal disease [hpbio\bio\PJPR0013 Synopsis.pdf, page 4]. Since approximately 43-96% of an orally administered dose of pseudoephedrine is excreted unchanged in the urine, pseudoephedrine may accumulate in patients with renal insufficiency [labeling\proposed.pdf, page 003]. However, because the doses of the individual components in the proposed combination fexofenadine/pseudoephedrine product cannot be individually titrated, and because renal insufficiency increases the bioavailability and prolongs the half-life of fexofenadine and pseudoephedrine, the proposed labeling appropriately recommends that the product should generally be avoided in patients with renal insufficiency [labeling\proposed.pdf, pages 007, 009].

The pharmacokinetics of fexofenadine were studied in clinical pharmacology studies submitted in support of the application for Allegra Capsules, NDA 20-625. The pharmacokinetics of plasma fexofenadine in hepatically impaired subjects were comparable to those observed in healthy volunteers. The sponsor states that the effect of hepatic impairment on pseudoephedrine pharmacokinetics is unknown, however, the OTC monograph specifies no warnings or precautions for the use of pseudoephedrine in patients with hepatic impairment [clinstat\iss\iss.pdf, page 94]. Proposed labeling appropriately contains no special instructions the use of the product in patients with hepatic impairment.

In long-term safety study PJPR0027, which was reviewed in NDA 20-872, there were five patients exposed to fexofenadine HCl 240 mg once daily who became pregnant

during the study. These patients were exposed to fexofenadine from 13 days to 36 days. Of these five patients, one had a spontaneous abortion, three had induced abortions, and one delivered an infant with a congenital shallow hip socket [clinstat\iss\iss.pdf, page 99]. There have been four postmarketing spontaneous reports of pregnancy and drug exposure to the currently approved Allegra-D product. Of these four reports, there was one report of missed abortion, one report of spontaneous abortion, once report of insomnia and pregnancy occurring while taking an oral contraceptive, and one case of fetal distress and cardiac arrest during delivery that required emergency caesarian section. The infant was resuscitated, had Apgar scores of 1 at one minute and 9 at five minutes, and recovered. These data do not suggest a safety signal for fexofenadine use during pregnancy. The proposed label notes that terfenadine, a pro-drug for fexofenadine, was not teratogenic in rats and rabbits, and that terfenadine doses that produced fexofenadine AUC values 24 times the human AUC at the daily dose of the proposed product. There are no adequate and well controlled studies in pregnant women. The OTC monograph requires no specific warning for the use of pseudoephedrine in pregnancy [21 CFR 341.80]. Since no specific warning is required, the labeling for the pseudoephedrine reference product for this application recommends that the pregnant or breast-feeding consumer ask a doctor before use, as detailed in the labeling requirements for OTC drugs [21 CFR 201.63]. The applicant's product is considered to be Pregnancy Category C and the proposed label appropriately states that the applicant's product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [labeling\proposed.pdf, pages 006-007].

The sponsor states that it is not known if fexofenadine is excreted in human milk. The proposed label note that many drugs are excreted in human milk, and therefore caution should be used when fexofenadine hydrochloride is administered to a nursing woman [labeling\proposed.pdf, page 007]. The sponsor states that pseudoephedrine is excreted into breast milk of lactating human women and that pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by AUC is 2 to 3 times greater than the plasma AUC. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to 0.7% [labeling\proposed.pdf, page 007]. Proposed labeling states that a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The applicant appropriately notes that caution should be exercised when the proposed product is administered to nursing women [labeling\proposed.pdf, page 007]. Proposed labeling is similar to that of the currently approved Allegra-D product.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions

The sponsor's drug development program for Allegra-D 24-Hour™ Tablets was based on establishing that their combination fexofenadine/pseudoephedrine product produces equivalent exposures to that of their approved and marketed 180 mg single ingredient fexofenadine HCl product (Allegra® Tablets) and to an approved and marketed OTC 240 mg extended-release pseudoephedrine HCl product (Sudafed® 24 Hour Tablets). The

clinical pharmacology studies in this application confirmed the bioequivalence of the applicant's product to the reference products. The 90% confidence interval of the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values for the proposed and reference products fell within 80% to 125% limits, indicating the proposed product is bioequivalent to the reference products for rate and extent of exposure in the fasted state after single dose administration and at steady state with multiple dose administration. These data support the efficacy of the applicant's product.

Administration of the product 30 minutes after ingestion of a high fat meal decreased the extent of exposure to fexofenadine by 42% and the rate of exposure by 54%. Administration of the product 1.5 hours after ingestion of a high fat meal decreased the rate and extent of exposure to fexofenadine to a similar extent. For pseudoephedrine, the 90% confidence interval for the ratios of the $AUC_{0\text{-}inf}$ and C_{max} values in the fed condition to values in the fasting condition fell within 80% to 125% limits, indicating that food does not interfere with bioavailability of the pseudoephedrine component of the combination product. The applicant's proposed labeling notes the decrease in fexofenadine bioavailability associated with ingestion of a high-fat meal, but recommends [ ] The labeling should be revised to state that the product should be taken on an empty stomach with water.

Co-administration of fexofenadine with Maalox® reduces the bioavailability of fexofenadine by approximately 41% and the rate of absorption by 43%. This drug interaction is not noted in the proposed labeling. The labeling should be revised to advise the prescriber that co-administration of fexofenadine with aluminum- and magnesium-containing antacids reduces the bioavailability of fexofenadine.

The applicant used a population pharmacokinetics modeling approach to analyze pharmacokinetic data from the three clinical pharmacology studies to estimate the effect of concomitant intake of eight ounces of grapefruit or orange juice with fexofenadine HCl. The relative bioavailability for a juice effect was reduced by a population mean of 36% when eight ounces of grapefruit or orange juice was administered concomitantly with a single 180 mg dose of fexofenadine HCl. The estimated decrease in bioavailability of fexofenadine when taken with grapefruit or orange juices is only slightly less than the decrease in bioavailability noted when fexofenadine is taken with a high-fat meal or with aluminum- and magnesium containing antacids. Proposed labeling should be revised to include this interaction with grapefruit and orange juices.

Safety data in this application support the safety of the proposed combination product. adverse events, vital signs, laboratory studies and ECGs in the pivotal clinical pharmacology studies identified no new safety signal. Safety data from the two controlled clinical studies included in this application were previously submitted to NDA 20-872 and were previously examined in detail. The safety data from these controlled clinical studies revealed no safety signal. Drug abuse and overdose data suggest that there is a low potential for risk to the consumer from abuse or overdose of fexofenadine. Although there is a risk of abuse and overdose for pseudoephedrine, the risk for this combination fexofenadine/pseudoephedrine prescription drug product would be expected to be less

than more easily obtained and widely available OTC drug products. The commonly reported postmarketing spontaneous adverse events were similar to those noted in labeling for the currently approved Allegra-D product. The applicant's review of the medical literature and safety update reveal no new safety concerns and support the safety of the proposed combination product.

10.2. Recommendations

From a clinical perspective, this reviewer recommends an approval action. No Phase 4 studies or specific risk management plans are recommended or are necessary at this time. However, changes in the manufacturing process that affect the dissolution profile of the pseudoephedrine tablet — were instituted late in the review cycle and, from the CMC perspective, may be sufficient to prevent an approval action for this application.

11. REFERENCES

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12. APPENDIX, BRIEF LABEL REVIEW

Proposed package labeling was included in this submission [labeling\proposed.pdf, pages 1-9; labeling\contain\contain.pdf, pages 1-3; summary\summary.pdf, pages 6-18]. Comments on proposed labeling are noted below. Final comments on proposed labeling will be incorporated in the labeling negotiated with the sponsor.

1. The proposed label does not address the decrease in bioavailability of fexofenadine when taken with aluminum- and magnesium-containing antacids. Labeling should be revised to include information on this drug interaction in the CLINCIAL PHARMACOLOGY, Pharmacokinetics section of the label. Such information is included in the PRECAUTIONS section of the Allegra label, but not the currently approved Allegra-D product. This information should be included in the label.

2. The proposed label does not address the decrease in bioavailability of fexofenadine when taken with grapefruit and orange juices. Labeling should be revised to include

information on this drug interaction in the CLINCIAL PHARMACOLOGY, Pharmacokinetics section of the label. Such information is not included in the currently approved Allegra and Allegra-D products. This information should be included in the label.

3. The Pharmacodynamics section of CLINICAL PHARMACOLOGY provides information on human histamine skin wheal and flare studies. The statement "the clinical significance of these observations is unknown" should be added to this section. This statement is included in the same section of the currently approved Allegra-D label, but not the Allegra label. This information should be included in the label.

4. The Drug Interactions section of PRECAUTIONS discusses two studies of the effects of co-administration of fexofenadine with ketoconazole and erythromycin. This discussion is also included in the labels for the currently approved Allegra-D and Allegra products. A table providing data from these studies is included in the currently approved products. This table is not included in the proposed labeling. Proposed labeling should be revised to include this table.

5. The OVERDOSAGE section of the label includes the following sentence: "Hemodialysis did not effectively remove fexofenadine from blood (up to 1.7% removed) following terfenadine administration." This sentence should be revised to note that fexofenadine is the major active metabolite of terfenadine:

   "Following administration of terfenadine, hemodialysis did not effectively remove fexofenadine, the major active metabolite of terfenadine, from blood (up to 1.7% removed)."

6. The proposed DOSAGE AND ADMINISTRATION section of the label states that [redacted]. This statement should be revised to state that the product should be taken on an empty stomach with water.

7. The applicant has submitted an NDA labeling supplement for their currently approved Allegra-D product [NDA 20-786, S-017, 6/8/04]. This supplement proposes changing the name of the currently approved Allegra-D product to Allegra-D 12 Hour to minimize the potential for confusion with the proposed Allegra-D 24 Hour product, as the Division recommended at the End-of-Phase 2 meeting [IND 48,486 N030 MR, 11/13/02, Meeting minutes; IND 48,486 N030 MR, 11/13/02, Medical Officer Review, Charles E. Lee, M.D].

Reviewed by:

_____

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

_____

Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/S. Al Habet/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Jao/CMC Reviewer
HFD-570/Sancilio/Pharmacology Reviewer
HFD-570/C. Yu/CSO

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/s/

Charles Lee
10/5/04 08:23:56 AM
MEDICAL OFFICER

Lydia McClain
10/5/04 12:37:03 PM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-704	**TRADE NAME:**	Allegra-D 24 Hour™
APPLICANT/SPONSOR:	Aventis Laboratories, Inc.	**USAN NAME:**	Fexofenadine HCl/pseudoephedrine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	H_1-antihistamine/decongestant
DATE:	1/9/04	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
12/19/03	12/19/03	NDA 21-704	Electronic submission

RELATED APPLICATIONS

Document Date	Application Type	Comments
12/20/96	NDA 20-786	NDA for Allegra-D®, fexofenadine HCl/pseudoephedrine HCl
7/17/98	NDA 20-872	NDA for Allegra® Tablets, fexofenadine HCl
7/31/95	NDA 20-625	NDA for Allegra® Capsules, fexofenadine HCl

REVIEW SUMMARY:

This is a 45-day filing and planning review of an NDA for an extended release formulation of fexofenadine HCl and pseudoephedrine HCl. The sponsor is Aventis Pharmaceuticals, Inc. The sponsor has developed a combination product containing immediate release fexofenadine HCl 180 mg and extended release pseudoephedrine HCl 240 mg for once daily use. The sponsor's proposed formulation is a tablet containing fexofenadine HCl 180 mg and pseudoephedrine 240 mg as active ingredients. The formulation consists of an] pseudoephedrine tablet [to effect the controlled released of the pseudoephedrine over 24 hours. An immediate release outer coating of fexofenadine HCl provides immediate release of fexofenadine. The proposed indication is for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. This application is an electronic submission. There are two pivotal clinical pharmacology studies submitted in support of this application. The sponsor has also provided a report for one clinical efficacy and safety study and a study synopsis for a long term safety study of fexofenadine HCl to support the efficacy and safety of the proposed product. These study reports and study synopses are appropriately indexed and organized to allow review. The sponsor has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, copies of proposed labeling, and appropriate case report forms.

The submission is adequate to allow clinical review. The submission is fileable.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	SAFE TO PROCEED	___	CLINICAL HOLD		
NDA/SUPPLEMENTS:	X	FILEABLE	___	NOT FILEABLE		
	___	APPROVAL	___	APPROVABLE	___	NOT APPROVABLE
OTHER ACTION:						

1. GENERAL INFORMATION AND BACKGROUND

Allegra® (fexofenadine hydrochloride) is an antihistamine with selective H_1-receptor antagonist activity. Allegra is currently approved for the following indications and in the following age groups:

- Allegra 180 mg po QD in seasonal allergic rhinitis (SAR) for adults and children >12 years of age
- Allegra 60 mg po BID in chronic idiopathic urticaria (CIU) and SAR for adults and children >12 years of age
- Allegra 30 mg po BID in SAR and CIU for children 6-11 years of age

Allegra-D® is an antihistamine/decongestant combination tablet product containing immediate release fexofenadine HCl 60 mg and extended release pseudoephedrine HCl 120 mg. The dose is 1 tablet twice daily. The product is approved in adults and children 12 years of age and older.

The sponsor has developed a combination product containing immediate release fexofenadine HCl 180 mg and extended release pseudoephedrine HCl 240 mg for once daily use. The proposed indication is for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older [labeling\proposed.pdf, page 004].

The sponsor's proposed formulation is a tablet containing fexofenadine HCl 180 mg and pseudoephedrine 240 mg as active ingredients. The formulation consists of [redacted] pseudoephedrine tablet [redacted] to effect the controlled released of the pseudoephedrine over 24 hours. An immediate release outer coating of fexofenadine HCl provides immediate release of fexofenadine [summary\summary.pdf, page 021].

The text from the proposed INDICATIONS AND USAGE section of the label follows: "Allegra-D 24 Hour™ Extended-Release Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/ and/or throat, itchy/watery/red eyes, and nasal congestion. Allegra-D 24 Hour™ should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired" [labeling\proposed.pdf, page 004].

The application is an electronic submission.

CLINICAL DEVELOPMENT PROGRAM

Fexofenadine HCl 180 mg QD is approved for the SAR indication in adults and children 12 years of age and older (NDA 20-872). The Monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antihistaminic Combination Drug products lists antihistamine/decongestant combinations as Category I, or generally recognized as safe and effective (GRASE). Pseudoephedrine HCl is considered to be GRASE for nasal

congestion in adults and children ≥12 years at the dose of 60 mg Q 4H to 6H, not to exceed (NTE) 240 mg/24 hours, under the Final Monograph for OTC Nasal Decongestant Drug Products [21 CFR 341.80].

The sponsor's application is based on the Agency's previous findings of efficacy and safety of approved and OTC monograph reference products and a comparison of the bioavailability and bioequivalence of the proposed new drug to those reference products. The sponsor's drug development program for Allegra-D 24 Hour™ Tablets is based on establishing that their combination fexofenadine/pseudoephedrine product produces equivalent exposures to that of their approved and marketed 180 mg single ingredient fexofenadine product (Allegra® Tablets) and to a marketed OTC monograph 240 mg extended release pseudoephedrine product (Sudafed® 24 Hour Tablets). The sponsor's drug development program also evaluated the effect of food on bioavailability of the proposed combination product [summary\summary.pdf, pages 107, 114; clinstat\clinsum.pdf, pages 005-007].

There were three pivotal studies in the sponsor's drug development program. These studies are described below and summarized in greater depth later in this document:

1. M106455S/1001, a pivotal, single dose and steady state bioequivalence study of 180 mg fexofenadine HCl/240 mg pseudoephedrine combination tablets in healthy subjects [clinstat\clinsum.pdf, page 013]
2. M106455S/1002, an open label, randomized study to assess the effect of food on the pharmacokinetics of 180 mg fexofenadine HCl/240 mg pseudoephedrine combination tablets in healthy subjects [clinstat\clinsum.pdf, page 013].
3. M106455B/3081, a double blind, randomized, placebo controlled, parallel group study comparing the efficacy and safety of fexofenadine 120 mg and 180 mg QD in the treatment of allergic rhinitis. This study was completed as part of NDA 20-872 and was the pivotal study supporting the approval of fexofenadine 180 mg QD in adults and children 12 years of age and older [clinstat\clinsum.pdf, pages 042, 109; clinstat\other\M016455B 3081.pdf, page 013].

The sponsor also provided a report of a pilot bioavailability study (Study KA467) of the prototype of their proposed product [hpbio\bio\ka467.pdf]. The sponsor also provided additional support of the safety of their product with a synopsis of Study M106455/PJPR0027 [clinstat\clintoc.pdf, page 002; summary\summary.pdf, pages 108, 110]. This study provided long-term safety data in support of the approval of NDA 20-872. These studies are described in greater depth in a later section of this filing and planning review.

Additional safety information for fexofenadine HCl at higher doses than 180 mg was previously obtained in acute and sub-chronic dose tolerance studies (PJPR0002, PJPR0003, and PJPR0007. These studies were previously submitted to NDA 20-625. The applicant has provided synopses of these clinical study reports in this submission. [clinstat\clinsum.pdf, page 008]. These studies have previously been reviewed for NDA 20-625 and will not be reviewed again for this submission.

2. FOREIGN MARKETING AND REGULATORY HISTORY

Fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg extended release tablets are not marketed in any country [summary\summary.pdf, page 019]. Fexofenadine HCl 60 mg/pseudoephedrine extended release tablets are approved in 38 countries other than the US, including countries in North, Central, and South America, the Caribbean, Asia, and Australia and New Zealand [clinstat\iss\iss.pdf, pages 159-161].

Fexofenadine HCl 60 mg BID and fexofenadine HCl 180 mg QD were developed for the treatment of symptoms of seasonal allergic rhinitis (SAR) in adults and children 12 years of age and over, and were approved for marketing in the US as Allegra® Capsules (NDA 20-625) on 25 July 1996 and as Allegra® Tablets (NDA 20-872) on 25 February 2000, respectively [summary\summary.pdf, page 019]. Allegra-D® (fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg), NDA 20-786, was approved for marketing in the US on December 24, 1997. Pseudoephedrine HCl is generally recognized as safe and effective for the relief of nasal congestion under the Final Monograph for OTC Nasal Decongestant Drug Products. The recommended maximal dose in adults and children 12 years of age and older is not to exceed 240 mg in 24 hours.

An End of Phase 2 meeting was held with the sponsor on 1/29/02 [Meeting minutes and Medical Officer Review, IND 48,486 N030 MR, 11/13/02]. Clinical comments were provided on proposed protocols for proposed pivotal clinical pharmacology studies. The sponsor opened a new IND in early 2003, and included an updated protocol for a proposed pivotal bioequivalence study [IND 66,289 N000, 11/25/02].

A Pre-NDA meeting was held with the sponsor on August 27, 2003 [Meeting minutes and Medical Officer Review, IND 66,289 N003 GC, 7/25/03]. The user fee, application structure and format, and CMC issues such as dissolution, stability, and measurement of impurities were discussed. The sponsor was advised to provide a review of the medical literature published since February 25, 2000, focusing on the safety of fexofenadine and pseudoephedrine. One clinical comment focused on the content of the Integrated Summary of Safety. The sponsor was also advised to provide a summary, review, and analysis of worldwide postmarketing adverse event reports for fexofenadine and pseudoephedrine [Meeting minutes and Medical Officer Review, IND 66,289 N003 GC, 7/25/03].

3. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [356h.pdf]
- Debarment certification [other\debar.pdf]
- Financial disclosure statement [other\financial.pdf]
- Statements of Good Clinical Practice [hpbio\bio\1001\1001.pdf, pages 001, 021; hpbio\bio\1002\1002.pdf, pages 001, 019; clinstat\other\M016455B 3081.pdf, page 018; hpbio\bio\ka467.pdf, pages 4, 034;]
- Integrated Summary of Efficacy [clinstat\ise\ise.pdf]

  - This application relies on the support of clinical pharmacology studies to demonstrate bioequivalence of the new drug to the test product. No clinical studies of the efficacy of the product or integrated summary of efficacy were required
- Integrated Summary of Safety (ISS) [clinstat\ise\ise.pdf] included the following:
  - Summary of safety information from clinical pharmacology studies in this application, M106455B/1001 and M106455B/1002 [clinstat\iss\iss.pdf, pages 008-063]
  - Summary of safety information from clinical studies in this application, M106455B/3081 and PJPR0027 [clinstat\iss\iss.pdf, pages 021-024]
  - Adverse events in subgroups in clinical studies M106455B/3081 and PJPR0027 [clinstat\iss\iss.pdf, pages 031-038; clinstat\iss\iss.pdf, pages 095-099]
  - Postmarketing and spontaneous adverse event reports for fexofenadine 60 mg/pseudoephedrine 120 mg [clinstat\iss\iss.pdf, pages 064-087]
  - Drug-drug, drug-demographic, and drug-disease interactions [clinstat\iss\iss.pdf, pages 090-094].
  - Drug abuse information [clinstat\iss\iss.pdf, page 099]
  - Review of the literature for safety information relevant to fexofenadine and pseudoephedrine [clinstat\clinsum.pdf, pages 044-047]
- Proposed labeling and annotated labeling [labeling\proposed.pdf; labeling\contain\contain.pdf; summary\summary.pdf, pages 006-018].
- Case report forms for patients with serious adverse events or discontinuing studies [crf\1001\0001\1060.pdf; crf\1002\0001\1018.pdf]
- List of referenced DMFs [cmc\loa\dmfaccessletters.pdf]
- Environmental assessment [cmc\environ.pdf]
  - The sponsor has requested a categorical exclusion from this requirement [cmc\environ.pdf, pages 002-003].
- Request for waiver of pediatric studies
  - The dose of active drugs in the product and its formulation are not appropriate for use in children less than 12 years of age. A suitable pediatric dosage form currently exists. The sponsor did not, however, provide a request for waiver of pediatric studies. However, such a waiver is not required given that the court has struck down the Pediatric Rule and ruled that it may not be enforced.

4. CLINICAL STUDIES

This submission refers to three clinical pharmacology studies. One study, KA467, was a pilot bioavailability study of the prototype of their proposed product. There are two pivotal bioequivalence and bioavailability studies in this application, M106455S/1001 and M106455S/1002. The application also refers to one efficacy and safety study, M106455B/3081, and one long-term safety study, PJPR0027. Both of these studies have supported the approval of NDA 20-872, and have been previously reviewed [A. Worobec, M.D., Medical Officer Review, NDA 20-872, N000, 7/17/88].

The clinical review of safety information in clinical studies in this application will focus on the two pivotal bioavailability and bioequivalence studies, M106455S/1001 and

M106455S/1002, and the clinical studies M106455B/3081 and PJPR0027. The study reports and synopses are appropriately indexed to allow review. These four studies are summarized in Table 1. More detailed descriptions of these studies follow below.

4.1. Study M106455S/1001

Study M106455S/1001 was a pivotal clinical pharmacology study that compared the bioavailability of the combination formulation of fexofenadine 180 mg/pseudoephedrine 240 mg extended-release tablets (Allegra-D 24 Hour™) to the marketed fexofenadine 180 mg immediate release (Allegra-D®) and pseudoephedrine 240 mg extended release (Sudafed® 24 Hour) tablets after single and multiple doses. The study was an open-label, randomized, two treatment, two period, two-way crossover bioavailability study conducted in 70 healthy male and female subjects from 18-44 years of age [hpbio\bio\1001\1001.pdf, pages 002-005]. Subjects received their first and last doses after a 10-hour fast. The remaining doses were administered with a one hour fast before and after the dose [hpbio\bio\1001\1001.pdf, page 030]. Samples were taken immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours for plasma fexofenadine and pseudoephedrine levels on Days 1 and 9. Trough samples were also drawn prior to dosing on Days 2 through 8. Subjects were housed at the study site from check-in on Day -1 until Day 3, and again from Day 9 until Day 10. Subjects returned to the clinic daily every morning from Day 4 until Day 9. A minimum washout period of eight days separated the treatment periods. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs. There were no withdrawals from the study. There were no serious adverse events [hpbio\bio\1001\1001.pdf, pages 002-005, 026, 066].

4.2. Study M106455S/1002

Study M106455S/1001 was a pivotal clinical pharmacology study that compared the effect of food on the bioavailability of the combination formulation of fexofenadine 180 mg/pseudoephedrine 240 mg extended-release tablets (Allegra-D 24 Hour™). The study was an open-label, randomized, single dose, three period, three treatment, three way crossover bioavailability and food effect study conducted in 24 healthy male and female subjects. Bioavailability was evaluated in the fasting state, 30 minutes after ingestion of a high fat breakfast, and 1.5 hours after a high fat breakfast. Samples were taken immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours for plasma fexofenadine and pseudoephedrine levels [hpbio\bio\1002\1002.pdf, page 058]. Patients were housed at the study site from check-in on Day -1 until after samples were drawn and procedures were completed on Day 3. A minimum washout period of six days separated each treatment period. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs. There was one patient who withdrew from the study because of adverse events of sore throat, URI, and fever. There were no serious adverse events [hpbio\bio\1002\1002.pdf, pages 002-006, 023].

4.3. Study M106455B/3081

Study M106455B/3081 was a pivotal efficacy and safety study of fexofenadine 120 mg and 180 mg once daily in the treatment of autumn seasonal allergic rhinitis. The study originally was submitted to provide support for the efficacy and safety of these products for NDA 20-872. The study was a double blind, randomized, parallel group, multiple center, efficacy and safety study conducted in 864 male and female patients with fall seasonal allergic rhinitis, 12 to 65 years of age. There was a five to seven day, single blind, placebo run-in period. The primary efficacy endpoint was change from baseline in average 8 AM instantaneous Total Symptom Score over the two week double blind treatment period. Secondary efficacy endpoints included change from baseline in average 8 AM reflective Total Symptom Score over the two week double blind treatment period, change from baseline in average 8 AM 12-hour reflective Total Symptom Score over the two week double blind treatment period, change from baseline in average 8 PM 12-hour reflective Total Symptom Score over the two week double blind treatment period, and change from baseline in average individual 8 AM instantaneous symptom score over the two week double blind treatment period, among others. Safety endpoints included adverse events, vital signs, physical examinations, and clinical laboratory studies. Seven of the 570 patients who were exposed to fexofenadine withdrew from the study because of adverse events. There were four of 293 placebo-treated patients who withdrew from the study because of adverse events. There were no deaths in the study [clinstat\other\M016455B 3081.pdf, pages 013-017, 023, 027, 062].

4.4. Study PJPR0027

Study PJPR0027 was a long term safety and tolerance study of fexofenadine 240 mg once daily in normal healthy subjects. The study was originally submitted to provide support for the safety of fexofenadine 120 mg and 180 mg once daily for NDA 20-872. The study was a double blind, randomized, parallel group, multiple center, safety study conducted in 469 healthy male and female subjects. The study treatment period was one year. The primary safety parameter was QTc. Other safety endpoints included adverse events, vital signs, clinical laboratory studies, and other ECG parameters. There were 15 of 234 fexofenadine-treated subjects (6.4%) and 16 of 234 placebo-treated subjects (6.8%) who withdrew from the study because of adverse events. Serious adverse events were reported with similar incidences in the two treatment groups. There was one death in the study in a placebo-treated subject due to a self-inflicted gunshot wound [clinstat\other\PJPR0027 synopsis.pdf, pages 001-004].

Table 1. Summary of studies to receive clinical review, NDA 21-704 [clinstat\clinsum.pdf, page 013; clinstat\other\M016455B 3081, pages 013-017, 062; clinstat\other\PJPR0027 synopsis.pdf, pages 001-004].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted in this application
M106455S/1001	Pivotal bioavailability and bioequivalence study	F 180 mg plus PSE 240 mg BID F 180 mg/PSE 240 mg combination BID	8 days, single and multiple dose	Single center, randomized, open label, two period, two-way crossover	70	Healthy men and women, 18-44 years	Protocol Study report Tabulations Case report forms
M106455S/1002	Pivotal food effect study	F 180 mg/PSE 240 mg combination BID fasting F 180 mg/PSE 240 mg combination BID 30 min after high fat breakfast F 180 mg/PSE 240 mg combination BID 1.5 hr after high fat breakfast	Single dose	Single center, randomized, open label, two period, two-way crossover	70	Healthy men and women, 18-44 years	Protocol Study report Tabulations Case report forms
M106455B/3081	Pivotal efficacy and safety study	F 120 mg QD F 180 mg QD Placebo QD	2 weeks	Multiple center, randomized, double blind, placebo controlled, parallel group	864	Men and women with fall SAR, 12-65 years	Protocol Study report
PJPR0027	Long-term safety study	F 240 mg QD Placebo QD	1 year	Multiple center, randomized, double blind, placebo controlled, parallel group	469	Healthy men and women, 12-65 years	Study synopsis

F = fexofenadine, PSE = pseudoephedrine

5. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [labeling\proposed.pdf, pages 1-9; labeling\contain\contain.pdf, pages 1-3; summary\summary.pdf, pages 6-18]. A brief review of proposed labeling was performed. The proposed label is similar to that of Allegra-D® 12 Hour Tablets. Labeling comments are noted below.

1. Both the proposed label and the current label for the approved Allegra-D product do not address the decrease in bioavailability of fexofenadine when taken with aluminum and magnesium-containing antacids. Consideration should be given to noting this drug interaction in the label of both products.

2. Both the proposed label and the current label for the approved Allegra-D® and Allegra® products do not address the decrease in bioavailability of fexofenadine when taken with food. Consideration should be given to noting this drug interaction in the labels of these products.

3. The proposed label does not include the following sentence, which is currently found in the PRECAUTIONS, General section of the Allegra-D® label:

   "Due to its pseudoephedrine component, Allegra-D should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see WARNINGS and CONTRAINDICATIONS."

   The proposed label does, however, contain a warning about use of pseudoephedrine with these conditions in the WARNINGS and CONTRAINDICATIONS sections of the label. The text for these sections of WARNINGS and CONTRAINDICATIONS are the same as that in the currently approved Allegra-D® product.

4. The current Allegra-D label includes a table describing the effects of erythromycin and ketoconazole on fexofenadine pharmacokinetics. This table is not in the proposed label. Text describing this interaction is included in the proposed label, however.

Detailed label review will be performed later in the course of review of this NDA.

6. DSI REVIEW/AUDIT

DSI clinical audit will not be requested because no efficacy or safety studies were included in the development program for this drug product.

7. SUMMARY

This NDA is an application for an extended release formulation of fexofenadine HCl and pseudoephedrine HCl. The sponsor is Aventis Pharmaceuticals, Inc. The sponsor has developed a combination product containing immediate release fexofenadine HCl 180 mg and extended release pseudoephedrine HCl 240 mg for once daily use. The sponsor's proposed formulation is a tablet containing fexofenadine HCl 180 mg and pseudoephedrine 240 mg as active ingredients. The formulation consists of [

] pseudoephedrine tablet [
] to effect the controlled released of the pseudoephedrine over 24 hours. An immediate release outer coating of fexofenadine HCl provides immediate release of fexofenadine. The proposed indication is for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older [labeling\proposed.pdf, page 004]. This application is an electronic submission. There are two pivotal clinical pharmacology studies submitted in support of this application. The sponsor has also provided a report for one clinical efficacy and safety study and a study synopsis for a long term safety study of fexofenadine HCl to support the efficacy and safety of the proposed product. These study reports and study synopses are appropriately indexed and organized to allow review. The sponsor has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, copies of proposed labeling, and appropriate case report forms.

The submission is adequate to allow clinical review. The submission is fileable.

8. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The schedule for review is displayed in Table 2. Clinical review will focus primarily on safety and will be performed for each study before moving to the next study. Review of clinical pharmacology studies will be completed by June 18, 2004. Review of clinical studies will be complete by August 13, 2004. The review of the safety review and ISS will take place next and will be complete by August 27, 2004. Label review will be complete by September 3, 2004. Draft review will be complete by September 17, 2004, approximately four weeks before the action date.

Table 2. Proposed schedule for review of NDA 21-704.

Clinical pharmacology studies M106455S/1001 and M106455S/1001	6/18/04
Clinical study M106455B/3081	7/29/04
Clinical study PJPR0027	8/13/04
ISS	8/27/04
Label Review	9/3/04
Draft Review Complete	9/17/04
Division Due Date	10/5/04
Action Date, 10 months	10/19/04

9. COMMENTS FOR THE SPONSOR

There are no comments for the sponsor.

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Jao/CMC Reviewer
HFD-570/Sancilio/Pharmacology Reviewer
HFD-570/C. Yu/CSO