

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-704

Pharmacology Review(s)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-704
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 12/19/03
PRODUCT: Allegra-D 24 hr (fexofenadine HCl 180 mg
and pseudoephedrine HCl 240 mg)
Extended Release tablet
INTENDED CLINICAL POPULATION: Seasonal allergic rhinitis patients
SPONSOR: Aventis Pharmaceuticals, Inc.

DOCUMENTS REVIEWED: Section 5.
REVIEW DIVISION: Division of Pulmonary and Allergic Drug
Products (HFD-570)
PHARM/TOX REVIEWER: Lawrence F. Sancilio, Ph.D.
PHARM/TOX SUPERVISOR: Ching-long J. Sun, Ph.D.
DIVISION DIRECTOR: Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER: Christine Yu, R.Ph.

Date of review submission to Division File System (DFS): 9/30/04

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability
Recommend approval.
- B. Recommendation for nonclinical studies
None.
- C. Recommendations on labeling
Incorporate the multiples of the preclinical dose to the maximum human dose based on AUCs or mg/m²

II. Summary of nonclinical findings

- A. This NDA is a 505(b)(2) application and is a combination of fexofenadine and pseudoephedrine. The preclinical data for fexofenadine is the sponsor's (NDA 20-265, NDA 20-872 and NDA 18-949). The 24- hr sustained release pseudoephedrine is an OTC product which renders this combination a 505(b)(2) application. Following oral administration, terfenadine is rapidly metabolized to fexofenadine. In the following oral studies, the toxicity profile of fexofenadine was determined from the oral administration of terfenadine. In a 3-month gavage study in rats, the targeted organs were the blood, seminal vesicles, pituitary and adrenal glands. In the 2-year study in dogs, the targeted organs were the central nervous and gastrointestinal systems and the testes. In reproductive toxicity studies in rats, there was no effect on fertility and no teratogenicity although there was decreased body weight and fetus survival. In rabbits, no teratogenicity was seen. Terfenadine was not carcinogenic in rats and mice.

Additional oral toxicity studies were conducted with fexofenadine in mice and dogs. In a 3-month dietary study in mice, no organ was targeted. In a 6-month toxicity in dogs, no organ was targeted. In a reproductive toxicity study in mice, fertility was not affected, and there was no teratogenicity. Combination studies with fexofenadine and pseudoephedrine produced reduced fetal weight and delayed ossification in rats and decreased fetal weight in rabbits.

Fexofenadine was not genotoxic in the Reverse Bacterial Mutation, the CHO Forward Mutation, the Rat Lymphocyte Aberration and Mouse Micronucleus assays.

Pseudoephedrine HCl is considered safe and effective under the Final Tentative monograph for OTC Cough, Cold, Allergy Bronchodilator and Antihistaminic Combination Drug Products and Final Monograph for OTC Nasal Decongestant Products.

B. Pharmacologic activity

Fexofenadine: Non-sedative H₁ receptor antagonist. In in vitro and in vivo studies, the antihistaminic potency of fexofenadine was 0.3– 2.0 times as potent as terfenadine.

Pseudoephedrine: a sympathomimetic that exerts decongestant action on the nasal mucosa.

C. Nonclinical safety issues relevant to clinical use

None.

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-704

Review number: 1

Sequence number/date/type of submission: 0, 12/19/03

Information to sponsor: Yes () No ()

Sponsor and/or agent: Aventis Pharmaceuticals Inc., Kansas City,
Missouri.

Manufacturer for drug substance: Aventis Pharmaceuticals Inc., Kansas City,
Missouri.

[

]

Reviewer name: Lawrence F. Sancilio, Ph.D.

Division name: Division of Pulmonary and Allergy and Drug Products.

HFD #: 570

Review completion date: 9/30/04

Drug:

Trade name: Allegra-D 24 hour (180 mg of fexofenadine and 240 mg of
Pseudoephedrine)

Generic name: Fexofenadine HCl
Pseudoephedrine HCl

Code name: Fexofenadine HCl, MDL 16,455A
Pseudoephedrine HCl, unknown

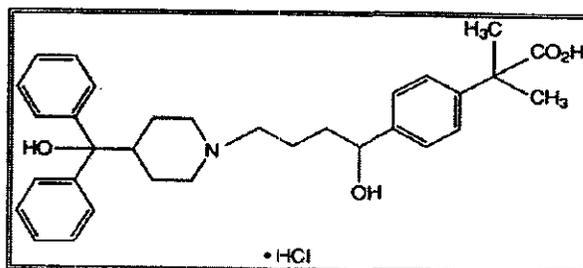
Chemical name: Fexofenadine HCl, Benzeneacetic acid, 4-
[1-(hydroxydiphenylmethyl)-1-piperidinyl]butyl-, - dimethyl-,
hydrochloride salt ±
Pseudoephedrine HCl, [S-(R*.R*)] - - [1-(methylamino)ethyl]-
benzenemethanol hydrochloride

CAS registry number: Fexofenadine HCl, 138452-21-8
Pseudoephedrine HCl, 345-78-8

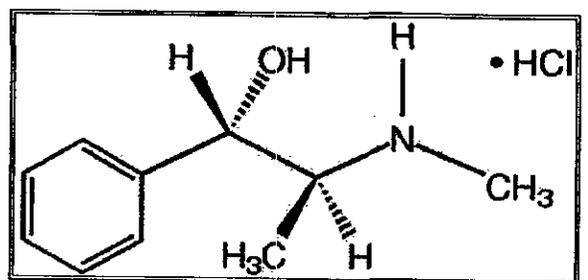
Molecular formula/molecular weight: Fexofenadine HCl, C₃₂H₃₉NO₄.HCl/538.18
Pseudoephedrine HCl, C₁₀H₁₅NO.HCl/201.70

Structure:

Fexofenadine HCl



Pseudoephedrine HCl



Relevant INDs/NDAs/DMFs: IND 43,573 (fexofenadine HCl), NDA 18-949 (terfenadine tablets) NDA 20- 872, (fexofenadine HCl tablets), NDA 20625 (fexofenadine HCl capsules), IND 48,486 (fexofenadine, 60 mg/pseudoephedrine, 120 mg), NDA 20-625 (fexofenadine capsules), NDA 19-664 fexofenadine, 60 mg/pseudoephedrine, 120 mg) and NDA 20-872 (fexofenadine, 60 mg/pseudoephedrine, 120 mg), NDA 20-012 (sustained released pseudoephedrine) and DMF ζ J

Drug class: Fexofenadine HCl: H₁ receptor antagonist.
Pseudoephedrine HCl: sympathomimetic amine.

Intended clinical population: Allergic rhinitis patients,

Ingredient	mg/Tablet
Tablet Core	
Pseudoephedrine HCl	240.00
Microcrystalline Cellulose	
Microcrystalline Cellulose	
Sodium Chloride	
Polyethylene Glycol	
Povidone	
Mg Stearate	
Polyethylene Glycol	
Colloidal Silicone Dioxide	
Cellulose Acetate	
Cellulose Acetate .	
Polyethylene Glycc.	
Talc	
Copovidone	
Titanium Oxide	
Brilliant Blue Aluminum Lake	
Fexofenadine HCl	180.00
Polyethylene Glycol	
Hydroxypropyl Methylcellulose	
Croscarmellose	
Opadry White	
Hydroxypropyl methylcellulose	
Titanium dioxide, USP/NF	
Triacetin (USP/NF)	
Black Ink	
(Opacode	
Total	

Route of administration: Oral.

Daily Dose: 1 tablet daily.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies submitted and reviewed within this submission:

Study to detect toxicity of dietary administration of fexofenadine to reproductive and developmental events in mice, No. B2001TOX109

Plasma concentration of fexofenadine during all reproductive stages of development, Amendment 1 and 2, No. B2001TOX110

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY: See reviews by L. Sancilio, NDA 20-265, 7/31/95; NDA 20-872, 7/17/98.

2.6.2.1 Brief summary: NA.

2.6.2.2 Primary pharmacodynamics: NA.

Mechanism of action: NA.

Drug activity related to proposed indication: NA.

2.6.2.3 Secondary pharmacodynamics: NA.

2.6.2.4 Safety pharmacology: NA.

Neurological effects: NA.

Cardiovascular effects: NA.

Pulmonary effects: NA.

Renal effects: NA.

Gastrointestinal effects: NA.

Abuse liability: NA.

Other: NA.

2.6.2.5 Pharmacodynamic drug interactions: NA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: See reviews by L. Sancilio, NDA 20-265, 7/31/95; NDA 20-872, 7/17/98.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS: See reviews by L. Sancilio, NDA 20-265, 7/31/95; NDA 20-872, 7/17/98.

2.6.4.1 Brief summary: NA.

2.6.4.2 Methods of Analysis: NA.

2.6.4.3 Absorption: NA.

2.6.4.4 Distribution: NA.

2.6.4.5 Metabolism: NA.

2.6.4.6 Excretion: NA.

2.6.4.7 Pharmacokinetic drug interactions: NA.

2.6.4.8 Other Pharmacokinetic Studies: NA.

2.6.4.9 Discussion and Conclusions: NA.

2.6.4.10 Tables and figures to include comparative TK summary: NA.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

For other pharmacokinetics data see review of L. Sancilio, NDA 20-872, 7/17/98

Study/Species/Sex	NOAEL mg/kg	AUC, ug.h/ml
Carcinogenicity		
Rat		
M	150	11.60
F	150	9.10
Mouse		
M	150	5.66
F	150	11.44
Fertility		
Mouse		
M	4,251	48.21
F	4,624	35.98
Teratogenicity		
Mouse	3,730	48.57
Rat	150	11.62
	300	11.93
Rabbit	300	101.63
Lactation		
Mouse, Day 4/5	10,655	243.90
Day 21/22	11,884	56.34

2.6.6 TOXICOLOGY: See reviews by L. Sancilio, NDA 20-265, 7/31/95; NDA 20-872, 7/17/98; C. Oberlander, NDA 18-949, 3/1/83.

2.6.6.1 Overall toxicology summary

General toxicology: The results based on the administration of terfenadine or fexofenadine are summarized in the following table.

Species/Duration	Dose mg/kg	Route	Observations
Terfenadine			
Rat	10	oral	Increased reticulocytes, Increased reticulocytes, and increased seminal vesicle, pituitary (F), thyroid (F) and adrenal (F) weights. Increased reticulocytes and increased pituitary (F), thyroid (F) and adrenal (F) weights.
3 Months	100		
	300		
Dog	30	oral	No effect. After 2-3 weeks convulsions and death (2/8); Central nervous system effects, constipation and testicular tubular atrophy.
2 Years	100/80		
Fexofenadine			
Mouse	848-1080	oral	Body weight gained, M, -9.9%; Hemoglobin, M, + 4.8% Body weight gained, M, -19.8%; Hemoglobin, M, + 5.4% Body weight gained, M, -18.9%; Hemoglobin, M, + 6.8%
3 Months	4367-5154		
Diet	8722-10324		
Dog	90	oral	Emesis, Emesis, green feces Emesis, green feces; accumulation (F)
1 Month	300		
	900		
6 Months	100	oral	Emesis Emesis; discolored feces (poor absorption) Emesis; accumulation (M + F); poor absorption
	300		
	900		

Genetic toxicology: Fexofenadine was not genotoxic in the Reverse Bacterial Mutation, the CHO Forward Mutation, the Rat Lymphocyte Aberration and Mouse Micronucleus assays.

Carcinogenicity: 50 and 150 mg/kg/day of terfenadine were administered in the diet of mice and rats. No clinically relevant neoplasms were seen.

Reproductive toxicology: Exposure to fexofenadine was achieved through the administration of terfenadine. In rats and rabbits at p.o. doses up to 300 mg/kg in both species, no teratogenicity was observed. Fertility in rats was not affected at p.o. doses up to 300 mg/kg. At 150 and 300 mg/kg, toxicity was seen in the dams; in the fetuses, there was decreased body weight and decreased survival. A dietary study with fexofenadine [6250 ppm (LD), 12,500 ppm (MD), 25,000 ppm (HD)] was conducted in mice. The daily doses were determined from the amount of food consumed.

Fexofenadine was administered to M 28 days prior to and throughout the mating period until termination; F received the fexofenadine 14 days prior to and throughout mating, gestation and lactation periods until termination. There was no effect on the various stages of reproduction. Combination studies with fexofenadine and pseudoephedrine produced reduced fetal weight and delayed ossification in rats and decreased fetal weight in rabbits.

2.6.6.2 Single-dose toxicity: NA.

2.6.6.3 Repeat-dose toxicity: NA.

2.6.6.4 Genetic toxicology: NA.

2.6.6.5 Carcinogenicity: NA.

2.6.6.6 Reproductive and developmental toxicology See reviews by C. Oberlander, NDA 18-949, 3/1/83 and L. Sancilio, NDA 18-949, 3/1/83.

Fertility and early embryonic development
Embryofetal development
Prenatal and postnatal development

Study titles: Study to detect toxicity of dietary administration of fexofenadine to reproductive and developmental events in mice, and to determine the plasma concentrations of fexofenadine during all reproductive stages of development

Key study findings: No effect on the reproductive and developmental events; during early lactation, the AUCs increased markedly.

Study no.: B2001TOX0109 and B2001TOX0110

Section #: 5.C.3.A

Conducting laboratory and location: ☐

Dates of study initiation: 7/15/99; 7/2/99

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, Component Batch No. and % purity: 1008768, 1012555 and ☐

Methods

Doses: 6250 ppm (LD), 12,500 ppm (MD), 25,000 ppm (HD)

These doses represent 0.625, 1.25 and 2.5% of the diet. The highest concentration was selected from a 3 month dietary study in which the plateau of systemic exposure observed for 50,000 ppm was similar to slightly lower than those seen with 25,000 ppm. The sponsor indicated that concentrations greater than 25,000 ppm would not result in greater plasma concentration.

Species/strain: — CD-1 (ICR)BR albino mice. The average body weight/group was 28 g for M and 24 g for F.

Number/sex/group: M, 25/group; F, 50/group, 25/group will be used in the Caesarian portion of the study and 25/group will be used in the delivery portion of the study.

Route: Diet.

Study design: F₀ M received the drug 28 days prior to and throughout the mating period until termination; F₀ F received the drug 14 days prior to and throughout mating, gestation and lactation periods until termination. F₀ F in the Caesarian delivery group was terminated on day 17 of gestation. During the mating period one M was paired with one F from the same dosed group. Mating was successful by the presence of a copulatory plug. The day when the copulatory plug was seen, that day was considered gestation day 0.

Satellite groups used for toxicokinetics: A similar study was conducted in another group of mice. The average body weight/group was 26 g for M and 24 g for F. Blood was taken from M at week 4 and from F at week 2 of pre-mating, and at gestation days 17/18, lactation days 4/5 and days 21/22. Collections were taken from 3 mice/group/time point at 1, 5, 9, 13 and 24 hours after the dark cycle. The plasma was analyzed for fexofenadine using a [

] method developed by the sponsor and modified and validated by []

Parameters and endpoints evaluated:

Clinical Signs: Daily

Body Weights: M, twice weekly; F on Days, 2, 6, 8, 10, 14 and 17 of gestation and on lactation days 0, 4, 7, 10, 14, 17 and 21.

Food Consumption: Twice weekly for M and F during the pre-mating period.

Measurement was made of F during gestation and lactation periods when body weight was determined.

F₀ M Necropsy

At termination, the surviving M were sacrificed, and examined for cervical, thoracic or abdominal viscera abnormalities. The following organs were weighed: right epididymidis, right testes, left epididymidis (M not selected for reproductive assessment), left testes, seminal vesicles with coagulating gland and prostate. With the exception of the right epididymidis and right testes, the tissues were preserved.

F₀ M Reproductive Assessment

After at least 10 weeks of dosing, the first 10 surviving M were evaluated for reproductive capacity by using the left epididymidis for sperm motility assessment and total count. The right testes was stored for future spermatogenic staging.

F₀ Delivery by Caesarian Section on Day 17 of Gestation

Necropsy

After sacrificing, gross examination was made of the thoracic, visceral and pelvic viscera. The uterus from each gravid F was excised and weighed and examined for placement of implantations sites, live and dead fetuses, early and late resorptions, and any abnormalities of the placenta or amniotic sac. The ovaries were examined for the number of corpora lutea.

Fetal Examination

Each fetus was sexed weighed and examined for external abnormalities. Approximately one-half of the fetuses from each litter were processed for assessing soft tissue development. The remaining fetuses were processed for skeletal examination. The results were judged to be malformations or variations. Malformations were gross changes, incompatible with life or may affect the quality of life. Variations are structural deviations that have no effect on body conformity or the well being of the animal.

F₀ Normal Delivery and Raised Litters to Day 21 Postpartum

The animals that either failed to produce a viable litter by gestation day 23, or died or were sacrificed following weaning or total litter death, were examined grossly for abnormalities of the cervical, thoracic or abdominal viscera. For those animals that were sacrificed, their uteri, ovaries and abnormal tissues were preserved and implantation sites determined.

Examination of F₁ Pups

After birth, each live and dead pup was sexed. The live pups were weighed and examined for external abnormalities. On days 4 (before culling), 7, 14 and 21, the number of live pups, their individual weight and clinical signs were recorded. On day 4, litters with more than 8 pups were culled randomly to produce litters, as nearly as possible, to contain 4 pups of each sex. The culled animals were killed and examined for cervical, thoracic or abdominal viscera abnormalities.

Developmental landmarks of pinna unfolding (beginning on day 1), surface righting reflex (beginning on day 4), hair growth (beginning on day 7), incisor eruption (beginning on day 7), eye opening (beginning on day 11) and auditory startle (beginning on day 21) were evaluated until all pups were positive for the landmark.

The litters were observed daily for behavior changes. Pups that died during lactation were examined, if possible, for cervical, thoracic or abdominal viscera abnormalities and preserved.

Weaning

On day 21 of lactation, the pups were weaned and one pup/sex/litter were randomized and maintained until they entered the maturation phase of 7 weeks. They were mated for up to 14 days during which mating was confirmed by daily vaginal lavage and examined for a retained copulatory plug. The F were returned to individual cages for the gestation period and examined for clinical signs and mortality. Body weights were determined on gestation day 0, 7 and 13 at which time they were given a physical exam. After the last physical exam, they were sacrificed and examined for cervical, thoracic or abdominal viscera abnormalities. The uteri were excised and weighed and examined for placement of implantation sites, live and dead fetuses, early and late resorptions, and any abnormalities of the placenta or amniotic sac. The ovaries were examined for the number of corpora lutea.

The M that died or were sacrificed were examined for cervical, thoracic or abdominal viscera abnormalities.

F₁ Animals Evaluated for Maturation

The following evaluations for maturation were made:

Vaginal openings for F and balanopreputial gland for M; beginning on days 30 and 35 post partum, respectively, they were examined daily until all the pups matured. The body weight was determined on the day the event occurred.

Locomotor (open field) activity: Determined on day 22 post partum and during 5-week post weaning.

Pupillary reflex: Determined initially on day 22 post partum.

Water Maze test for memory: Initially determined on week 3 post weaning and again 7 days later.

During the 7-week maturation phase, all mice were weighed and observed for clinical signs.

Results

Formulation Analyses: From weeks 1, 4 and 8, the percents of target concentrations were conducted on the LD and HD. The ranges were 97.4% to 104% for the LD and 94.2% to 102% for the HD.

Doses:

Stage/Sex	Dietary Doses, mg/kg/Day (Range)		
	LD	MD	HD
Premating			
M	993-1180	1064-2287	4101-4842
F	1109-1308	2164-2744	4283-5463
Gestation			
F	872- 1385	1719-3026	3594-5393
Lactation			
F	1857-3052	4041-5878	8079-11587

F₀ Mice

Mortality: MD, 1 F on pre mating day 27; enlarged liver.

HD, 1 F on pre mating day 5; thin and hunched with pale liver and kidneys.

Deaths were not considered treatment related.

Clinical Signs: None, treatment related.

Estrus Cycle (F₀ Caesarian section): No treatment related effect.

Body Weight Gained:

 M, 0-42 days, no treatment related effect.

 0-84 days, no treatment related effect.

 F, Caesarian Delivery,

 Mating, 0-14 days; Gestation, 0-17 days: No treatment related effect.

 Normal delivery,

 Mating, 0-14 days; Gestation, 0-17 days; Lactation, 0-21 days: No treatment related effect.

Food Consumption: M, no treatment related effect.

 F, Caesarian or Normal Delivery: No treatment related effect.

F₀ M and F Necropsy: No treatment related gross pathology.

Relative Organ Weights: M and F (Caesarian Delivery), no treatment related effect.

F₀ M

No treatment related effect on sperm motility and sperm count determined from the caudal section of the left epididymidis.

F₀ F (Caesarian Delivery)

The following observations were made:

 No effect on the % of animals pregnant;

No abortions in the C and treated groups;
No groups showed early deliveries;
Deaths were not treatment related;
The % of dams with viable fetuses was 100% in all groups;
No treatment related effects on the number of corpora lutea, implantation sites and preimplantation sites;
The total, early and late resorptions in the treated groups were similar to those in the C;
No treatment related effect on the number of live fetuses and sex ratios;
No treatment related effect on postimplantation loss.

F₁ (Delivered by Cesarean Section)

No treatment related effect on fetal weights of the M and F;
No treatment related effect on the number of live fetuses/litter;
No external malformations in the C and treated groups;
No treatment related increase in the incidence of visceral malformations;
Skeletal Variations of Unossified Vertebral Centrum based on
Fetal Incidence: C, 6%; LD, 15%; MD, 19%; HD, 16%;
Litter Incidence: No treatment related effect;

F₀ Natural Delivery

No treatment related effect on the number of pregnancies, deliveries, gestation index, number of pups delivered, the number of stillborn and the number of implantation sites;
No treatment related effect on the Survival, Viability and Weaning Indexes;
No treatment related effect on the number of pups surviving on day 21 postpartum and the percent of live M and F pups/litter on days 0, 4 (preculling and post culling), 7, 14 and 21;

F₁ Natural Delivery

No treatment related effect on the days of preputial separation, vaginal and eye opening, hair growth, incisor eruption and pinna unfolding and the percents of pups that were positive for the landmark;
No treatment related effect on the auditory and surface righting reflex and the percent of pups that were positive for the landmark;
No treatment related effect on activity counts in both sexes on day 22 postpartum and day 5 post weaning;
No treatment related effect on learning and learning reversal studies;
No clinical signs or body weight changes were seen during the postpartum, weaning and maturation phases;

F₁ Natural Delivery- Reproductive Activity

No treatment related effect on changes in body weight during gestation day 0-13;
At necropsy, there was no gross pathology in both sexes.

No treatment related effect on the weights of gravid uteri and the corrected uterine weight (the terminal body weight minus the gravid uterine weight);

No treatment related effect of the percent of animals pregnant, the number of abortions and the percent of early deliveries;

No treatment related effect on the percent of dams with viable fetuses and the number of corpora lutea, implantation sites and post implantation loss;

No treatment related effect on the total number of resorptions including early and late resorptions;

No treatment related effect on the number of live fetuses.

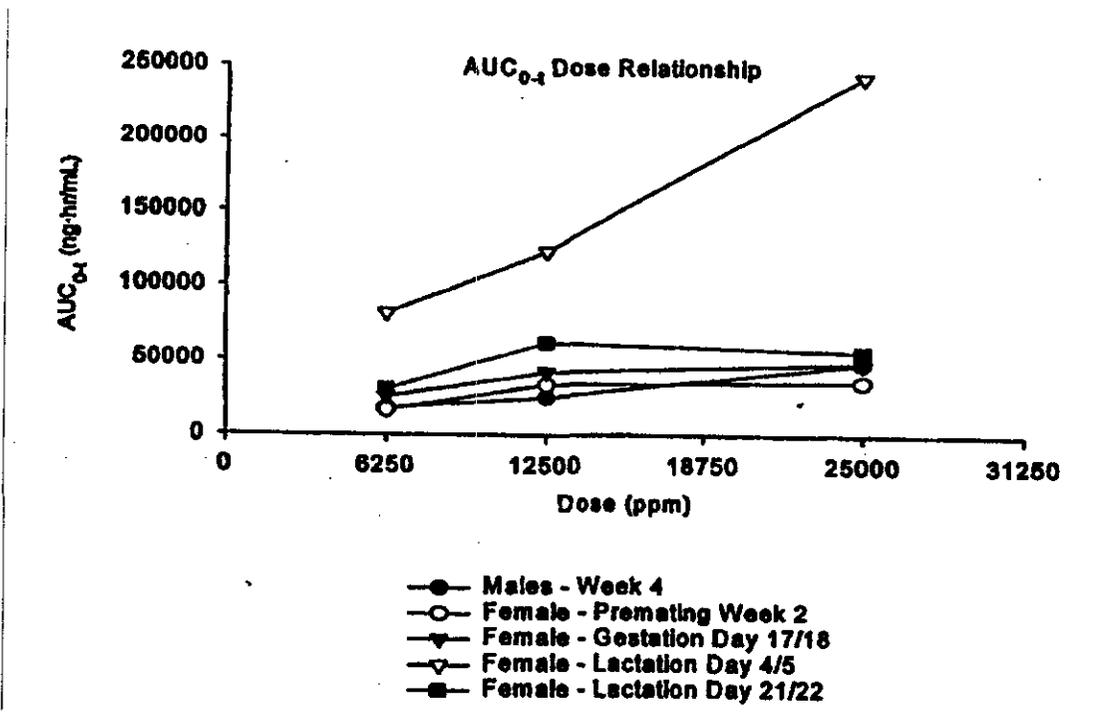
Toxicokinetics

The results are presented in the following table and figure. The figure was copied from the submission.

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Sex, Dose, ppm	Food Consumption g/day	Dose Based on Food Consumption, mg/kg	Time of Sampling	C _{max} ng/ml	T _{max} hr	AUC _{0-t} ng.hr/ml
M	6,250	1,025	Week 4	1,191	9.0	18,054
	12,500	2,056		1,896	9.0	25,239
	25,000	4,251		3,239	13.0	48,205
F	6,250	1,099	Week 2 (prematuring)	1,192	9.0	16,829
	12,500	2,258		1,951	24.0	33,797
	25,000	4,624		2,087	9.0	35,984
	6,250	925	Day 17/18 (gestation)	1,428	13.0	25,801
	12,500	1,889		3,337	5.0	42,221
	25,000	3,730		4,254	9.0	48,566
	6,250	2,676	Day 4/5 (lactation)	3,876	13.0	81,502
	12,500	5,312		7,169	1.0	123,552
	25,000	10,655		14,169	24.0	243,901
	6,250	3,111 ^a	Day 21/22 (lactation)	1,575	13.0	30,694
	12,500	6,091 ^a		4,803	5.0	62,036
	25,000	11,884 ^a		2,892	9.0	56,338

^a These doses are based on the food consumption of the dams and pups



2.6.6.7 Local tolerance: NA.

2.6.6.8 Special toxicology studies: See reviews by L. Sancilio, NDA 20-872, 7/17/98.

2.6.6.9 Discussion and Conclusions: NA.

2.6.6.10 Tables and Figures: NA.

2.6.7 TOXICOLOGY TABULATED SUMMARY: NA.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This NDA is supported by the preclinical data for fexofenadine and terfenadine and the OTC marketed daily dose of pseudoephedrine. The label is modified to conform to the Agency's standards.

Unresolved toxicology issues (if any): None.

Recommendations: Approval of NDA 21-704.

The ratios (AUCs of the oral NOAELs in various assays to the AUC of the maximum human daily dose) in the following table and in the tables following the attachment section were used as reference for the data referred to in the labeling.

In the carcinogenicity and reproductive studies (rats and rabbits), the AUCs were for fexofenadine following the oral administration of the prodrug, terfenadine. In reproductive studies involving mice, AUC data was determined when fexofenadine was administered and not in studies where terfenadine was administered.

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Study/Species/Sex	NOAEL mg/kg	AUC, ug.h/ml A	Animal AUC/Human AUC	
			A/B	Mean
Carcinogenicity				
Rat				
M	150	11.60	2.8	2.5
F	150	9.10	2.3	
Mouse				
M	150	5.66	1.4	2.1
F	150	11.44	2.8	
Fertility				
Mouse ^b				
M	4,251	48.21	12.0	10.5
F	4,624	35.98	8.9	
Teratogenicity				
Mouse ^b				
	3,730	48.57	12.1	
Rat				
	150	11.62	2.9	
	300	11.93	3.0	
Rabbit				
	300	101.63	25.3	
F				
Human				
	3.6 mg/kg	4.02 (B) ^a		

^a Steady state

^b Study was conducted with fexofenadine; the others were conducted with the parent compound, terfenadine.

Suggested labeling: Additions are in **bold** and deletions are ~~strikeouts~~.

1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

[

]

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Drug: N21-704 Allegra D Pseudoephedrine								
	age	Mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
Pediatric	6			0	20	0	25	0
Adult	>12	240	1	240	50	4.8	37	177.6
	route	Mg/kg/d	conv. Factor	mg/m ²	Dose Ratio Adults Children		Rounded Dose Ratio Adults Children	
Carcinogenicity:								
rat	oral	10	6	60	0.34	---	<1	---
dog			20	0	---	---	---	---
mouse	oral	27	3	81	0.46	---	<1	---
dog			20	0	---	---	---	---
mouse			3	0	---	---	---	---
Repro/Fertility:								
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
Teratogenicity:								
rabbit	oral	200	12	2400	13.5-	N/A	15	N/A
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
Overdosage:								
mouse			3	0	---	---	---	---
rat			6	0	---	---	---	---
rat			6	0	---	---	---	---
rat			6	0	---	---	---	---
Other: (Describe studies here)								
rat	oral	300	6	1800	10.1351	---	10	---
rat	oral	200	6	1200	8	---	8	---
dog			20	0	---	---	---	---
rabbit	oral	200	12	2400	13.5135	---	15	---
rat	oral	1674	6	10044	56.5541	---	55	---

Drug:		N21-704 Allegra D Fexofenadine						
	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
Pediatric	6		2	0	20	0	25	0
Adult	>12	180	1	180	50	3.6	37	133.2
	route	mg/kg/d	conv. factor	mg/m ²	Dose Ratio		Rounded Dose Ratio	
					Adults	Children	Adults	Children
<u>Carcinogenicity:</u>								
	rat		6	0	---	---	---	---
	dog		20	0	---	---	---	---
	mouse		3	0	---	---	---	---
	dog		20	0	---	---	---	---
	mouse		3	0	---	---	---	---
<u>Repro/Fertility:</u>								
	rat		6	0	---	N/A	---	N/A
	rat		6	0	---	N/A	---	N/A
	extra		---	---	---	N/A	---	N/A
	extra		---	---	---	N/A	---	N/A
<u>Teratogenicity:</u>								
	rabbit		12	0	---	N/A	---	N/A
	rat		6	0	---	N/A	---	N/A
	rat		6	0	---	N/A	---	N/A
	rabbit		12	0	---	N/A	---	N/A
	extra		---	---	---	N/A	---	N/A
<u>Overdosage:</u>								
	mouse		3	0	---	---	---	---
	rat		6	0	---	---	---	---
	rat		6	0	---	---	---	---
	rat		6	0	---	---	---	---
<u>Other:</u> (Describe studies here)								
	rat	oral	5000	6	30000	225.225	230	---
	mouse	oral	5000	3	15000	112.613	110	---
	dog	oral	2000	20	40000	300.3	300	---
	rat	oral	438	6	2628	19.7297	20	---
	extra		---	---	---	---	---	---

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/s/

Lawrence Sancilio
9/30/04 03:48:49 PM
PHARMACOLOGIST

Joseph Sun
9/30/04 04:10:43 PM
PHARMACOLOGIST
I concur.