CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-872/S-31

Trade Name:	Allegra
Generic or Proper Name:	Fexofenadine hydrochloride tablet, 180 mg
Sponsor:	Sanofi-aventis U.S. LLC
Approval Date:	May 20, 2016
Indication:	addition of fexofenadine hydrochloride, 180 mg gelcap tablet as product line extension

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 20-872/S-031

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-872/S-31

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020872/S-031

SUPPLEMENT APPROVAL

sanofi-aventis U.S. LLC
Attention: Mridul Shah, MS
Assistant Director, Global Regulatory Affairs
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Ms. Shah:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 20, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ALLEGRA® (fexofenadine hydrochloride) tablet, 180 mg.

We acknowledge receipt of your amendment dated April 10, 2014.

This "Prior Approval" sNDA proposes the addition of fexofenadine hydrochloride 180 mg gelcap tablet as a product line extension. We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

LABELING

Submit final printed labeling (FPL), as soon as they are available, but no more than 30 days after they are printed. The FPL must be identical to the enclosed labeling for the 8-, 24- , and 40-count outer carton 180 mg submitted on April 10, 2014, and to the 8-count 180 mg immediate container (blister card) submitted on December 20, 2013; the FPL must be in the "Drug Facts" format (21 CFR 201.66), where applicable.

The FPL should be submitted electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Labeling for approved NDA 020872/S-031**." Approval of this submission by FDA is not required before the labeling is used.

The "New! Gel Coated Tablets" flag must be removed after 180 days of marketing.

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sherry Stewart, Regulatory Project Manager, at (301) 796-9618.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURES: Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUCIE L YANG
04/16/2014
signing on behalf of Dr. Theresa Michele

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-872/S-31

LABELING

Allegra Allergy 24hr Gelcap CARTON

04.04.14

ALG_Gelcap_40ct_Carton

Reference ID: 3490804

Allegra Allergy 24hr Gelcap CARTON

04.04.14

ALG_Gelcap_24ct_Carton

Reference ID: 3490804

Allegra Allergy 24hr Gelcap CARTON

04.04.14

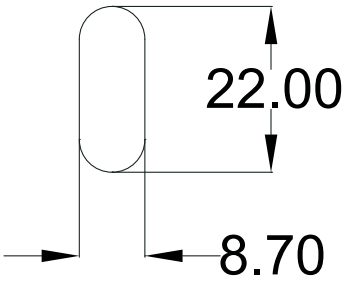
ALG_Gelcap_8ct_Carton

Reference ID: 3490804

Allegra Allergy 24hr Gelcap BLISTER

10.30.13

ALG_Gelcap_8ct_Blister



DIE = FPO

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Reference ID: 3490804

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-872/S-31

CLINICAL REVIEW

MEMORANDUM

Department Of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation (DNCE)

Date: April 5, 2014

Subject: Allegra Allergy Gelcaps (Fexofenadine HCl gelcap tablet, 180 mg)

NDA: NDA 20-872 CMC Prior Approval Supplement
(Sequence No. 0047)

Sponsor: Sanofi-aventis

Background

Sanofi-aventis is submitting a Prior Approval Supplement to NDA 20872 for Allegra (fexofenadine HCl) Gelcap Tablet, 180 mg, containing CMC information and bioequivalence study data. In an Agency-Sponsor meeting held on December 11, 2012, the Sponsor requested if the gelcap tablet could be submitted as a prior approval supplement to NDA 20872 for Allegra Allergy (fexofenadine HCl) tablets. The Agency did not initially agree to the proposal, because the new product was a capsule and therefore a new dosage form that would require an NDA. However, based on additional information provided by the Sponsor, and an opinion from the Office of General Counsel, the Agency subsequently agreed in an advice letter dated March 12, 2013 (IND 043573) that the Gelcap product is a tablet and the Gelcap can be filed in a prior approval supplement to the existing NDA 20872. In addition, because the proposed product is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, PREA is not triggered and a Pediatric Study Plan is not required.

(b)(4) The Sponsor has conducted bioequivalence study BEQ13500 of the new gelcap tablet formulation, which is provided in the present submission .

Product Information

The fexofenadine HCl gelcap tablet, 180 mg was developed as a line extension to the approved nonprescription Allegra Allergy film-coated tablet, 180 mg. The gelcap tablet is not intended to replace the approved tablet formulation. (b)(4) . The finished tablet is coated with two flexible, opaque purple gelatin covers over its ends, leaving a gap in the middle between the two covers (b)(4) (b)(4)

Figure 1 upper pair, approved fexofenadine tablet; lower pair, new Gelcap tablet

The proposed indication for the gelcap tablet is the same as for the currently approved Allegra Allergy Tablets:

Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

- Runny nose
- Sneezing
- Itchy, watery eyes
- Itching of the nose or throat

(b)(4)

A comparison of the composition of the fexofenadine gelcap tablet formula and film-coated tablet formula is provided in Table 1. The compositions are the same aside from the film coating for the current tablet and the gelatin coating for the new gelcap tablet.

More detailed information regarding the formulation can be found in the original NDA review. (extracted from Dr.Cindy Li's review).

Nonclinical Findings

No new nonclinical studies were conducted or submitted in support of this supplement. The proposed fexofenadine HCl gelcap tablet is based on the approved film-coated tablet. (b)(4)

No additional nonclinical safety studies were deemed necessary for the new fexofenadine gelcap tablet, HCl 180 mg.

Table 1 Comparative Table: Composition Of Film-Coated Tablet And Gelcap Tablet Formulations

Components	Composition (per unit) in mg	
	fexofenadine HCl 180 mg tablet	fexofenadine HCl 180 mg Gelcap tablet
Core tablet		
		(b)(4)

Components	Composition (per unit) in mg	
	fexofenadine HCl 180 mg tablet	fexofenadine HCl 180 mg Gelcap tablet
Film coating		
		(b)(4)
		(b)(4)
Application of gelatin cover		
		(b)(4)
Printing		
		(b)(4)
		(b)(4)
Total mass		

a) (b)(4)

(b)(4)

(b)(4)

b (b)(4)

(b)(4)

c) (b)(4)

d) (b)(4)

(b)(4)

f) (b)(4)

g) (b)(4)

Clinical Findings

In support of the line extension product changes, **one bioequivalence study BEQ 13500 was carried** out comparing the proposed fexofenadine HCl gelcap tablet, 180 mg with the currently approved fexofenadine HCl film-coated tablet, 180 mg.

BIOEQUIVALENCE STUDY BEQ13500

This is an open-label, randomized, two-treatment crossover bioavailability study comparing the new fexofenadine hydrochloride gelcap tablet to the marketed Allegra tablet in healthy male and female subjects, aged 18 to 55 years old. It was a single center, open label trial comparing single doses of the fexofenadine 180 mg gelcap versus the reference Allegra fexofenadine 180 mg tablet. The study enrolled 120 subjects (84 males and 36 females) of whom 116 subjects completed both treatment periods. Four subjects withdrew after receiving the reference drug but before receiving the test formulation.

The **primary objective** is to determine the bioavailability of the 180 mg gelcap tablet formulation (Test) versus the 180 mg marketed tablet formulation (Reference) of fexofenadine hydrochloride (HCl).

The **secondary objective** is to assess the safety of both 180 mg formulations of fexofenadine HCl from adverse event monitoring.

GRAPHICAL STUDY DESIGN

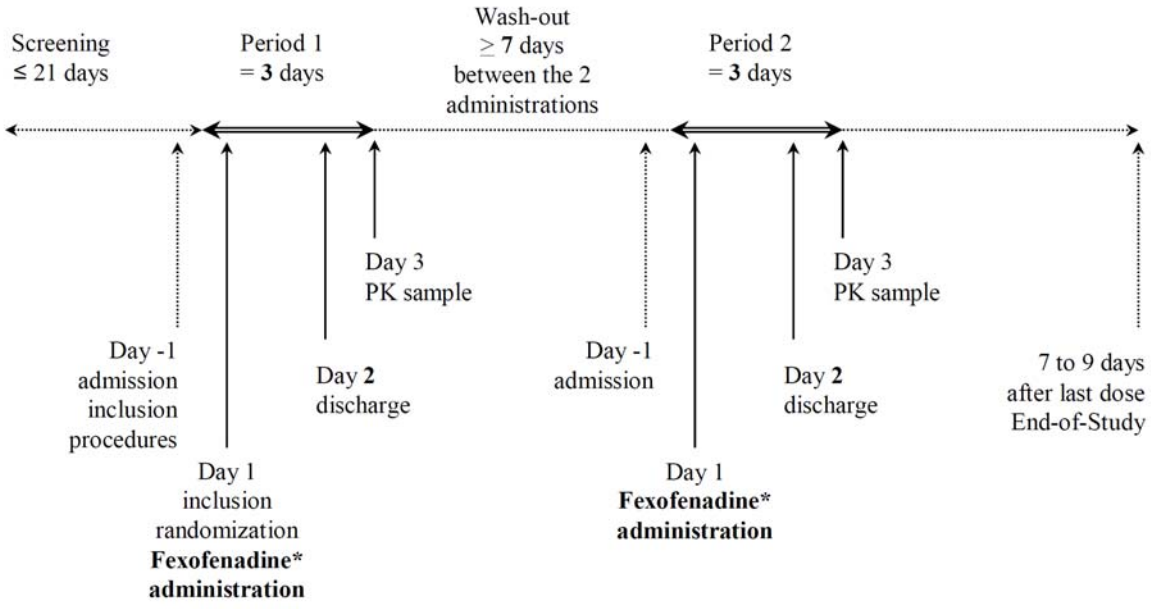

Figure 2 Timeline of Study. *Reference or test formulation depending on randomization

The screening period is for up to 3 weeks. There is a 7 day washout period between the two treatment periods. Each treatment period lasts three days including one treatment day. Follow-up is for 7 to 9 days after the last treatment, up to 6 weeks maximum. The study schedule is summarized in Figure 2 and Figure 3.

The schedule of physical exams and laboratory exams is shown Figure 3.

Phase	Screening		Period 1			Period 2				End-of-study
Day	D-21 to D-2	D -1	D1	D2	D3	D -1	D1	D2	D3	D8-D10
Informed consent	X									
Institutionalization		X				X				
Discharge				X				X		
Visit at clinical site	X				X				X	X
Inclusion /exclusion criteria	X	X	X							
Medical / surgical history	X	X								
Prior / concomitant medications	<	-	-	-	-	-	-	-	-	>
Inclusion / Randomization			X							
Investigational medicinal product administration										
Fexofenadine[a]			X				X			
Safety										
Physical examination, oral body temperature	X	X								
Height, body weight	X									
Vital signs, ECG	X									
Hematology, biochemistry, urinalysis	X									
Serology tests	X									
β-HCG blood test (if applicable)		X				X				X
Plasma FSH (if applicable)	X									
Urine drug screen, alcohol test	X	X				X				
Adverse event collection	<	-	-	-	-	-	-	-	-	>
Pharmacokinetics										
Fexofenadine plasma samples			X	X	X		X	X	X	

ECG = electrocardiogram; IMP = investigational medicinal product.

a Tablet reference formulation or gelcap tablet test formulation depending on the randomization sequence

Figure 3 Study Schedule of Activities

The sampling times for blood collection are shown in Figure 4 : pre-dose (0 hours), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36 hours post-dose (Day 2), and finally at 48 hours post-dose (Day 3) in each treatment period.

Day	D1												D2			D3
Time (hour/minute)[a]	0H	0H15	0H30	0H45	1H	1H30	2H	3H	4H	6H	8H	12H	24H	30H	36H	48H
Indicative clock time	8 am	8:15 am	8:30 am	8:45 am	9 am	9:30 am	10 am	11 am	12 pm	2 pm	4 pm	8 pm	8 am	2 pm	8 pm	8 am
Discharge															X	
Visit at clinical site																X
Concomitant medications	<	-	-	-	-	-	-	-	-	-	-	-	-	-	-	>
Inclusion / Randomization	X[b]															
IMP administration																
Fexofenadine	X[c]															
Safety																
Adverse event collection	<	-	-	-	-	-	-	-	-	-	-	-	-	-	-	>
Pharmacokinetics																
Fexofenadine plasma samples	P00	P01	P02	P03	P04	P05	P06	P07	P08	P09	P10	P11	P12	P13	P14	P15

a Time (hour/minute) is expressed in reference to the last administration of fexofenadine (T0H)

b Only on Period 1

c Tablet reference formulation or gelcap tablet test formulation depending on the randomization sequence

Note: when several items take place at the same time, the following order should be respected: blood sampling, drug administration, meal.

In order to respect exact timing of pharmacokinetic samples, the other measures will be done ahead of the scheduled time.

IMP = investigational medicinal product.

Figure 4 Sampling times

Standard 12-lead ECGs are recorded after at least 10 minutes in supine position. The Investigator's medical opinion and automatic values will be recorded in the e-CRF.

Inclusion Criteria

I 01. Male or female subjects, between 18 and 55 years of age, inclusive.

I 02. Body weight between 50.0 and 95.0 kg, inclusive, if male, and between 40.0 and 85.0 kg, inclusive, if female, body mass index between 18.0 and 30.0 kg/m^2, inclusive.

I 03. Certified as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination).

I 04. Normal vital signs after 10 minutes resting in supine position:

95 mmHg < systolic blood pressure (SBP) <140 mmHg

45 mmHg < diastolic blood pressure (DBP) <90 mmHg

50 bpm < heart rate (HR) <100 bpm

I 05. Normal standard 12-lead electrocardiogram (ECG) after 10 minutes resting in supine position; 120 ms<PR<220 ms, QRS<120 ms, QTc≤430 ms if male, ≤450 ms if female.

I 06. Laboratory parameters within the normal range, unless the Investigator considers an abnormality to be clinically irrelevant for healthy subjects.

I 07. If female, subject must use a double contraception method, except if she has undergone sterilization at least 3 months earlier or is postmenopausal. The accepted double contraception methods include use of a highly effective method of birth control (intrauterine device or hormonal contraception) in addition to one of the following contraceptive options: (1) condom; (2) diaphragm or cervical/vault cap; (3) spermicide. Menopause is defined as being between 45 and 60 years of age and being amenorrheic for at least 2 years with plasma FSH level > 30 UI/L.

I 08. Having given written informed consent prior to undertaking any study-related procedure.

I 09. Not under any administrative or legal supervision.

Exclusion Criteria

E 01. Any history or presence of clinically relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynecologic (if female), or infectious disease, or signs of acute illness.

E 02. Frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month).

E 03. Blood donation, any volume, within 1 month before inclusion.

E 04. Symptomatic postural hypotension, irrespective of the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in systolic blood pressure ≥20 mmHg within 3 minutes when changing from supine to standing position.

E 05. Presence or history of drug hypersensitivity, or allergic disease diagnosed and treated by a physician.

E 06. History or presence of drug or alcohol abuse (alcohol consumption more than 40 g per day).

E 07. Smoking more than 5 cigarettes or equivalent per day, unable to stop smoking during the study.

E 08. Excessive consumption of beverages containing xanthine bases (more than 4 cups or glasses per day).

E 09. If female, pregnancy (defined as positive β-HCG blood test), breast-feeding.

E 10. Any medication (including St John's Wort) within 14 days before inclusion or within 5 times the elimination half-life or pharmacodynamic half-life of the medication, with the exception of hormonal contraception or menopausal hormone replacement therapy; any vaccination within the last 28 days.

E 11. Any subject who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.

E 12. Any subject in the exclusion period of a previous study according to applicable regulations.

E 13. Any subject who cannot be contacted in case of emergency.

E 14. Any subject who is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study.

E 15. Positive result on any of the following tests: hepatitis B surface (HBs Ag) antigen, anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti HIV2 Ab).

E 16. Positive result on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).

E 17. Positive alcohol test.

E 18. Any contra-indications to fexofenadine, according to the applicable labeling.

E 19. Any consumption of citrus (grapefruit, orange, etc) or their juices, as well as all fruit juices, within 5 days before inclusion.

E 20. Any intake of aluminum and magnesium containing antacids within 14 days before inclusion.

Comment. The inclusion/exclusion criteria were acceptable. However subjects should not have been included in the trial if they had donated blood within the past 2 months as this is a PK trial and subjects will have many blood draws.

The summary table of PK results according to the Sponsor is summarized in Table 2.

Table 2 Summary of PK Parameters

Mean ± SD (Geometric Mean) [CV%] of pharmacokinetic parameters of fexofenadine in plasma

Parameter	Reference (N = 120)	Test [a] (N = 116)
C_{max} (ng/mL)	546 ± 280 (481) [51.3]	483 ± 216 (434) [44.8]
AUC_{last} (ng·h/mL)	3430 ± 1370 (3170) [39.9]	3220 ± 1350 (2960) [41.9] [b]
AUC (ng·h/mL)	3560 ± 1390 (3300) [39.1] [c]	3370 ± 1370 (3110) [40.6] [d]
t_{max} [e] (h)	1.50 (0.50 - 6.00)	1.50 (0.75 - 6.00)
t_{lag} [e] (h)	0.00 (0.00 - 0.25)	0.00 (0.00 - 0.25)
$t_{1/2z}$ (h)	13.5 ± 7.31 (12.2) [54.0]	14.9 ± 8.93 (13.2) [60.1] [b]

[a] 4 out of 120 enrolled subjects discontinued from the study
[b] N = 115 since one subject had no PK samples after 4 hours post-dose
[c] N = 119 since one subject had area extrapolation > 20%.
[d] N = 114 since one subject had no PK samples after 4 hours post-dose and one subject had area extrapolation > 20%
[e] Median (Min - Max).

Reference = Marketed 180 mg Allegra® film-coated tablet. Test = New 180 mg fexofenadine HCl gelcap tablet

Estimates of formulation ratio with 90% confidence interval for fexofenadine

Comparison	Parameter	Estimate	90% CI
Test vs. Reference	C_{max}	0.900	(0.836 to 0.968)
	AUC_{last}	0.935	(0.883 to 0.990)
	AUC	0.947	(0.899 to 0.996)

PGM=PRODOPS/M016455/BEQ13500/CSR/REPORT/PGM/pk_beq13500.sas.sas
OUT=REPORT/OUTPUT/pk_fr_k_t_2_i.rtf (28JUN2013 - 4:04)

Comment. The 90% CIs for the ratio of geometric means for the two formulations (Test/Reference) for C_{max}, AUC_{last}, and AUC were within the bioequivalence reference interval of 0.80 to 1.25.

Safety Results

Of the 120 subjects (84 males and 36 females) randomized and treated, 116 subjects completed the 2 treatment periods. Four subjects discontinued the study; 3 due to poor compliance to the protocol (after Day 3 of Period 1 for 2 subjects and on Day 1 of Period 2 for 1 subject) and 1 for personal reasons (family emergency, Day 1 of Period 2).

Subjects were monitored for safety via adverse events (AEs) spontaneously reported by the subjects or observed by the Investigator, physical examination, clinical laboratory

tests (hematology, biochemistry, serology, and urinalysis), vital sign assessments, and ECG recordings. For female subjects, beta-human chorionic gonadotropin (HCG) tests were performed at Day -1 of each treatment period and at the end of the study.

Clinical laboratory evaluations, ECGs and vital signs were carried out at screening only.

There were no serious adverse events or AEs leading to discontinuation reported during the study. Treatment-emergent AEs were reported in 5/120 subjects (4.2%) receiving the reference formulation and in 5/116 subjects (5.1%) receiving the test formulation. All TEAEs were of mild intensity and resolved without sequelae. The most frequently reported TEAE was headache, experienced by 1/120 subjects (0.8%) who received the reference formulation and 2/116 subjects (1.7%) who received the test formulation. Other TEAEs which were mentioned once each for the test formulation were ear pain, epistaxis, sore throat and abdominal cramps. The other TEAEs mentioned once each for the reference formulation were sore throat, dyspepsia, nausea, and toothache.

Conclusion

The proposed fexofenadine gelcap tablet is based on the approved nonprescription Allegra Allergy tablet, 180 mg. (b)(4) There were no serious AEs and only a few mild AEs in the BE study. This review did not find any new safety issues regarding the change in formulation that would preclude approval. The reviewer agrees with the Sponsor's conclusion that both formulations of 180 mg fexofenadine HCl were safe and well tolerated.

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/s/

LINDA S HU
04/09/2014

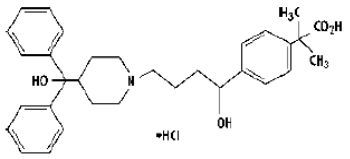
NARAYAN NAIR
04/09/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-872/S-31

CHEMISTRY REVIEW

CHEMIST'S REVIEW	1. ORGANIZATION:	2. NDA Numbers: 20-872
3. Name and Address of Applicant (City & State) sanofi-aventis U.S. LLC 55 Corporate Drive Bridgewater, NJ 08807		**4. Supplement(s)** **Number(s)** **Date(s)** S-031 12/20/13
5. Drug Name Allegra®	**6. Nonproprietary Name** Fexofenadine Hydrochloride	**7. Amendments - Dates**
8. Supplement Provides For: Allegra® (fexofenadine HCl) Gelcap Tablet, 180 mg, containing CMC information and bioequivalence study data.		
9. Pharmacological Category Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: Runny nose, Sneezing, Itchy, watery eyes, Itching of the nose or throat.	**10. How Dispensed** Rx	**11. Related NDAs**
12. Dosage Form(s) Gelcaps	**13. Potency** 180 mg	
14. Chemical Name and Structure: (±)-4-[1 nylmethyl)-1-piperidinyl]-butyl]- α, α-dimethylhydroxy-4-benzeneacetic acid hydrochloride  Molecular Formula: $C_{32}H_{39}NO_4$•HCl Molecular Weight: 538.13		**15. Records/Reports** **Current** **Yes X** **No** **Reviewed** Yes No X
16. Comments: This is a **PA** supplement submitted for Allegra® (fexofenadine HCl) Gelcap Tablet, 180 mg, containing CMC information and bioequivalence study data. The Office of Compliance has given an overall acceptable recommendation for all the proposed drug product manufacturing and the testing site on January, 08, 2014 (see EER Summary Report on page 25 – 27). Pharm/Tox review recommends that the supplement can be approved from the nonclinical perspective (Pharm/Tox Review by **Cindy Xinguang Li, Ph.D.**, DARRTS entry dated, 3/26/2014). ONDQA-Biopharmaceutics recommends (**Assadollah Noory, Ph.D.**) the approval of supplement 31 to NDA 20-872 (see DARRTS entry, dated 4/8/2014).		
17. Conclusions and Recommendations: This supplement is **approved** from CMC perspective, additionally supported by Pharm/Tox and ONDQA-Biopharm recommendations.		
18. Reviewer:		
Name: Kris Raman, Ph.D. Sr. CMC Review Chemist	**Signature:**	**Date Completed:** 3/31/2014, revised 4/9/2014

REVIEW NOTES

Fexofenadine HCl gelcap tablet, 180 mg was developed to provide a new product option for the consumer as a line extension to the approved nonprescription Allegra® Allergy® film-coated tablet, 180 mg. The gelcap tablet is not intended to replace the approved tablet formulation. The gelcap tablet uses (b)(4)

Different dosage strengths of fexofenadine hydrochloride tablets are currently registered and marketed (30 mg, 60 mg and 180 mg). However, no gelatin covered film-coated tablet is yet available, in spite of the fact that patients would appreciate this pharmaceutical form for its facilitation of swallowing.

The formulation approach is consistent with the development of a solid oral dosage form. The aim was to produce a stable immediate-release oral dosage form, which displays satisfactory physical characteristics.

The tablet core formulation used in the fexofenadine HCl gelcap tablet, 180 mg product is identical to the one in the currently approved fexofenadine HCl 180 mg film-coated tablet. (b)(4) (b)(4)

The gelatin covers do not cover the whole tablet. (b)(4)

The proposed gelatin covered film-coated tablet resulting from the application of gelatin covers process is provided in **Figure 1**.

Figure 1: Illustration of a Gelcap Tablet

A comparative table of the Gelcap tablet formula and film-coated tablet formula is provided in **Table 1**.

Table 1: Comparative Composition of Film-Coated Tablet and Gelcap Tablet Formulations

Components	Composition (per unit) in mg	
	fexofenadine HCl 180 mg tablet	fexofenadine HCl 180 mg Gelcap tablet
Core tablet		
		(b)(4)

Table 1: Comparative Composition of Film-Coated Tablet and Gelcap Tablet Formulations (contd.)

Components	Composition (per unit) in mg	
	fexofenadine HCl 180 mg tablet	fexofenadine HCl 180 mg Gelcap tablet
Film coating		
		(b)(4)
		(b)(4)
Application of gelatin cover		
		(b)(4)
Printing		
		(b)(4)
		(b)(4)
Total mass		
		(b)(4)

a) (b)(4)

b) (b)(4)

(b)(4)

c) (b)(4)

d) (b)(4)

e) (b)(4)

f) (b)(4)

g) (b)(4)

It should be noted that the quality of the drug substance used to manufacture both the gelcap tablet and the tablet formulae remains the same.

DRUG PRODUCT

Drug Substance

The product contains fexofenadine hydrochloride as the active ingredient. The drug substance fexofenadine hydrochloride complies with the requirements of the current edition of the USP. The composition of the fexofenadine HCl gelcap tablet, 180 mg drug product is provided in

Composition of the Drug Product

Table 1: Composition of the Drug Product - Fexofenadine HCl Gelcap Tablet, 180 mg

Components	Composition per unit (mg/tablet)	Function	Reference to standards [a]
Fexofenadine Hydrochloride	(b)(4)		
Microcrystalline Cellulose	(b)(4)		
Pregelatinized Starch	(b)(4)		
Croscarmellose Sodium	(b)(4)		
	(b)(4)		
Magnesium Stearate	(b)(4)		
	(b)(4)		
	(b)(4)		
	(b)(4)		

Compatibility with Excipients

The drug product fexofenadine HCl gelcap tablet, 180 mg is based on the currently registered and marketed drug product, fexofenadine HCl 180 mg film-coated tablet. (b)(4)

(b)(4)

Table 18: Commercial Scale Batch Analyses Results

Test	Acceptance criteria	Results

(b)(4) [redacted]

Conclusion

The manufacturing process has been successfully performed on the full scale batch. The in- [redacted] (b)(4) ance criteria. [redacted] (b)(4) The uniformity of dosage of the tablets is compliant with specification. Batch analysis results comply with the acceptance criteria. All results indicate that the manufacturing process of fexofenadine HCl gelcap tablet, 180 mg is capable, within its specified design parameters, of producing a finished product of the required quality.

The process validation would then be validated following validation scheme presented in Section 3.2.P.3.5 (*Process Validation And /Or Evaluatio*n).

Container Closure System

Fexofenadine HCl gelcap tablet, 180 mg has proposed primary packaging for commercial distribution in blister cards consisting of transparent (b)(4) blister packs sealed with child resistant (CR) peel push-through aluminum foil lidding (b)(4). Detailed information on the construction of the blister materials is provided in Table 1.

Table 19: Composition of the Blister Materials

Component Part	Material	Material Type
(b)(4)		

Suppliers

(b)(4)

for Class A Packs.

Container-closure packaging materials of construction comply with all the applicable sections of Code of Federal Regulations 21CFR 170 through 199.

Drug Product Stability

Stability studies have been conducted on two primary stability batches at pilot scale (Batch (b)(4)) and one industrial batch at industrial scale (b)(4)).

The 3.2.P.8.3 - QUA-AB-2013-25941 section presents the 12-month results for the two primary stability pilot batches and the 9-month results for one industrial batch.

The stability study (b)(4)

Summary of Stability Batches

Batch Number	(b)(4)
Manufacturing site for the Fexofenadine HCl gelcap tablet, 180 mg	(b)(4)
Manufacturing date	(b)(4)
Batch size (gel tablets)	

(b)

Stability Protocol

The stability protocol and storages conditions are based on the current ICH guidelines. The stability program is described in **Table 22**.

Table 22: Stability Protocol

	Testing Intervals (months)									
Stability Conditions	**0**	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**
Long Term - 25°C/60%RH	X	X	X	X	X	X	X	X	X	X
Intermediate - 30°C/65%RH	X	X	X	X	X	X	--	--	--	--
Accelerated - 40°C/75%RH	X	X	X	X	--	--	--	--	--	

Analytical Tests

The following tests will be performed initially and periodically according to the stability through the final stability time point: appearance, disintegration, dissolution, degradation products and assay of fexofenadine hydrochloride.

Table 23: Analytical Tests for Stability Studies

Analytical tests	Analytical procedure
(b)(4)	

Evaluation of Analytical Data

The appearance and color (characters) of the gelcap tablets met specifications for all three batches under all storage conditions. (b)(4).

The dissolution profiles are compliant and similar under all storage conditions.

(b)(4)

Assay of the fexofenadine HCl active substance content remains within specification limits.

Microbiological was performed only after 12 months of stability on the two primary stability batches at 25°C/60% RH, the microbiological test is compliant.

All the results comply with the specifications and the following assessments can be made after 12-month storage long term stability study for primary stability batches, 9-month storage long term stability study for industrial batch and 6-month storage accelerated study for primary stability batches and industrial batch.

The supportive stability data on fexofenadine HCl film-coated tablet, 180 mg are presented in section 3.2.P.8.3 referenced QUA-AB-2013-26294.

Conclusion

Review of physical and chemical stability data after 12 months (for the primary stability batches) and 9 months (for the industrial scale batch) of storage under long-term or intermediate conditions and 6 months under accelerated testing conditions confirm that fexofenadine HCl Gelcap tablet, 180 mg is physically and chemically stable.

Storage Conditions and Shelf-Life

Based on compliance of stability results obtained up to date (i.e. 12 months at 25°C/60%RH, 30°C/65%RH and 6 months at 40°C/75%RH), ICH Q1E guidelines, which allows to have 24-month shelf-life; in addition, comparability of stability data after 12 months between the proposed

Fexofenadine HCl gelcap tablet, 180 mg and the current approved Fexofenadine HCl film-coated tablet, 180 mg with similar formulation, for which a 30-month shelf-life has been approved; the applicant proposes for fexofenadine HCl gelcap tablet, 180 mg **the same shelf-life** (30-month) as the one of Fexofenadine HCl film-coated tablet, 180 mg. The storage statement and the shelf-life are described in Table 24.

Table 24: Storage Conditions and Shelf-Life for Fexofenadine HCl Gelcap Tablet, 180 mg

Packaging	Shelf-life	Storage Conditions
(b)(4)	30 months	20°C to 25°C (excursions 15-30°C)

Expiry Dating

Based on comparability of stability data after 12 months between the proposed Fexofenadine HCl gelcap tablet, 180 mg and the current approved Fexofenadine HCl film-coated tablet, 180 mg with similar formulation, for which a 30-month shelf-life has been approved; the applicant's proposed shelf-life of **30-month** for Fexofenadine HCl film-coated tablet, 180 mg may be granted.

Post-Approval Stability Protocol and Stability Commitment

ICH stability studies presented in this submission that are not yet finished will be carried out and terminated according to the stability protocol.

The applicant commits that the stability studies on the (b)(4)

(b)(4)

The applicant commits to conduct long-term stability studies for (b)(4) (b)(4) Tests performed will be (b)(4) shelf-life at time of testing if supported by product stability.

Pharm/Tox Review and Recommendation

(Pharm/Tox Review by Cindy Xinguang Li, Ph.D., DARRTS entry dated, 3/26/2014)

Based on the previous human use experience for fexofenadine, the agency's review of the approved fexofenadine film-coated tablet, as well as the lack of novel issues identified during the current review, the present NDA supplement can be approved from the nonclinical perspective.

Biopharm Consult

Biopharm consult was submitted on 12/29/2013.

Biopharm Recommendation:

ONDQA-Biopharmaceutics completed their review (Assadollah Noory, Ph.D.) of the Biopharmaceutics (see DARRTS entry, dated 4/8/2014) portion of this PAS and finds that the Sponsor has adequately addressed Biopharmaceutics' requirements for the approval of the new Gelcap tablet. ONDQA-Biopharmaceutics recommends the approval of supplement 31 to NDA 20-872.

LABELING

Module 1.14 contains draft labeling for the proposed Allegra (fexofenadine hydrochloride) gelcap tablet, 180 mg primary and secondary packaging. The proposed fexofenadine hydrochloride gelcap tablet, 180 mg has been developed as a line extension for the Allegra brand. The indication will be the same as for the approved nonprescription Allegra® Allergy film-coated tablet, 180 mg. The Sponsor is proposing to market the gelcap product in cartons containing 8, 24 and 40 count gelcaps in blisters. The currently approved Allegra (fexofenadine hydrochloride) tablet, 180 mg Principal Display Panel and Drug Facts blister carton are modified as follows to reflect the proposed gelcap product:

- "Gelcap" is added to the Principal Display Panel to distinguish the product from the currently approved Allegra tablet. "Gelcap" is not considered part of the proprietary name.
- An illustration of the Gelcap is added to the Principal Display Panel.
- A (b)(4) is added to the Principal Display Panel.
- The design of the Principal Display Panel is modified to distinguish the gelcap tablet from the approved Allegra Allergy tablet.
- The net quantity is updated to reflect the proposed gelcap tablet count, e.g., 40 Gel Coated Tablets. The net quantity is also included on the top panel.
- The Drug Facts are updated to reflect the inactive ingredients for the gelcap tablet. Refer to Module 2.3.P.2.1 Components of the Drug Product, for a list of the inactive ingredients.
- "Indoor and Outdoor Allergies" is added to the top or side panels in addition to the Principal Display Panel.
- "Gelcaps" is added to the top panel and each side panel.

Description

Drug Facts are updated to reflect the **inactive ingredients** for the gelcap tablet as follows:

Croscarmellose sodium, D&C red 28, D&C red 33, FD&C blue 1, gelatin, hydroxypropylcellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, PEG-135, pharmaceutical ink, pregelatinized starch, titanium dioxide

Module 1.14.1.1 provides clean and font annotated versions of the labeling for the unit blister and 8, 24, and 40 count cartons and Module 1.14.1.3 provides the draft labeling in structured product labeling (SPL) files.

How Supplied

Item code	Package Description
NDC: 41167-4122-0	1 in 1 Carton 8 in 1 Blister Pack
(b)(4)	

Two (2) pages removed as (b)(4), draft labeling, immediately following this page.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 20872/031	**Sponsor:**	SANOFI AVENTIS US
Org. Code:	560		55 CORPORATE DR
Priority:	3S		BRIDGEWATER, NJ 08807
Stamp Date:	20-DEC-2013	**Brand Name:**	ALLEGRA
PDUFA Date:	20-APR-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	FEXOFENADINE HYDROCHLORIDE
District Goal:	16-MAR-2014	**Product Number; Dosage Form; Ingredient; Strengths**	

007; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 60MG
001; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 30MG
003; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 120MG
009; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 180MG
005; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 30MG
006; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 30MG
008; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 60MG
002; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 60MG
004; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 180MG
010; TABLET, FILM COATED; FEXOFENADINE HYDROCHLORIDE; 180MG

FDA Contacts:	M. GAUTAM BASAK	Prod Qual Reviewer	(HFD-510)	3017960712
	R. MCKNIGHT	Product Quality PM		3017961765
	J. PHAM	Regulatory Project Mgr		3017967031

Overall Recommendation:	ACCEPTABLE	on 08-JAN-2014	by T. SHARP	()	3017963208
	PENDING	on 31-DEC-2013	by EES_PROD		
	PENDING	on 31-DEC-2013	by EES_PROD		

Establishment: (b)(4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: (b)(4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-JAN-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	(b)(4)		
DMF No:			
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	(b)(4)		
DMF No:			
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9611688 **FEI:** 3003492806 SANOFI WINTHROP INDUSTRIE 56 ROUTE DE CHOISY AU BAC COMPIEGNE, , FRANCE		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	(b)(4)		
DMF No:			
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	(b)(4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	(b)(4)		
DMF No:			
Responsibilities:			
Profile:	(b)(4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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/s/

KRISHNA P RAMAN

04/09/2014

This supplement is approved from CMC perspective, additionally supported by Pharm/Tox and ONDQA-Biopharm recommendations.

RAMESH RAGHAVACHARI

04/09/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-872/S-31

NON-CLINICAL REVIEW

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA20872/S031 (supplement)
Applicant's letter date:	12/20/2013
CDER stamp date:	12/20/2013
Product:	ALLEGRA (Fexofenadine gelcap tablet, 180 mg)
Indication:	For the relief of symptoms associated with seasonal allergic rhinitis
Applicant:	Sanofi-aventis U.S. LLC
Review Division:	Division of Nonprescription Clinical Evaluation, Office of New Drug (OND)
Reviewer:	Cindy Xinguang Li, Ph.D.
Secondary Reviewer:	Paul Brown, Ph.D., ODE Associate Director for Pharmacology/Toxicology, OND
Division Director:	Theresa M. Michele, M.D.
Project Manager:	Sherry Stewart, Pharm.D., Regulatory Health Project Manager

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of the present New Drug Application (NDA) submission (NDA20872/S031) are owned by Sanofi-aventis U.S. LLC or are data for which Sanofi-aventis U.S. LLC has obtained a written right of reference. Any information or data necessary for approval of the present NDA submission that Sanofi-aventis U.S. LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of the present NDA submission.

1 Executive Summary

1.1 Introduction

Fexofenadine HCl 30 mg, 60mg and 180 mg **film-coated tablets** were approved under NDA 20872 for OTC (Over The Counter) use on January 24, 2011. The present submission NDA 20872/S031 is a prior approval supplement for a 180 mg fexofenadine **gelcap tablet**. The applicant, Sanofi-aventis, intends to market the proposed product as a new product option for the consumer and as a line extension to the approved fexofenadine HCl film-coated tablet.

The proposed indication is intended for the treatment of seasonal allergic rhinitis (SAR) in adults and children 12 years of age and older, which is the same as the approved film-coated tablet. (b)(4) .

In support of the line extension product changes, one bioequivalency study BEQ13500 was carried out comparing the proposed fexofenadine HCl gelcap tablet, 180 mg with the currently approved fexofenadine HCl film-coated tablet, 180 mg.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were conducted or submitted in support of this supplement. The proposed fexofenadine HCl gelcap tablet is based on the approved film-coated tablet. (b)(4) No additional nonclinical safety studies were deemed necessary for the new fexofenadine gelcap tablet, HCl 180 mg.

1.3 Recommendations

1.3.1 Approvability

Based on the previous human use experience for fexofenadine, the agency's review of the approved fexofenadine film-coated tablet, as well as the lack of novel issues identified during the current review, the present NDA supplement can be approved from the nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

The OTC labeling for this product is suggested to have the statement: "If pregnant or breast-feeding, ask a health professional before use". This is consistent with existing OTC labeling for fexofenadine.

2 Drug Information

2.1 Drug

CAS Registry Numbers:
138452-21-8

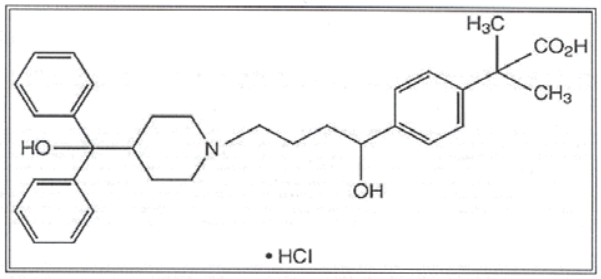
Generic Names:
Fexofenadine HCl

Code Names:
MDL 16,455A

Chemical Names:
(±)-4-[1-hydroxy-4-[4(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride

Molecular Formulae/Molecular Weights:
$C_{32}H_{39}NO_4$ .HCl/538.18

Structure or Biochemical Description



Pharmacologic Class
Histamine H1 receptor antagonist

2.2 Relevant INDs, NDAs, and DMFs

NDA20872, Fexofenadine HCl tablets, Sanofi-aventis

(b)(4)

2.3 Drug Formulation

A comparative table of the fexofenadine **gelcap** tablet formula and **film-coated** tablet formula is provided in following table. More detailed information regarding the formulation can be found in the original NDA review (NDA20872).

Components	Composition (per unit) in mg	
	fexofenadine HCl 180 mg tablet	fexofenadine HCl 180 mg Gelcap tablet
Core tablet		
(b)(4)		

Components	Composition (per unit) in mg	
	fexofenadine HCl 180 mg tablet	fexofenadine HCl 180 mg Gelcap tablet
Film coating		
(b)(4)		
Application of gelatin cover		
(b)(4)		
Printing		
(b)(4)		
Total mass	(b)(4)	

a) (b)(4)

b) (b)(4)

c) (b)(4)

d) (b)(4)

f) (b)(4)

g) (b)(4)

The proposed drug product fexofenadine HCl gelcap tablet, 180 mg is based on the currently approved fexofenadine HCl 180 mg film-coated tablet. The quality of the drug substance used to manufacture both the gelcap tablet and the tablet formulae remains the same. (b)(4)

(1) (b)(4)

(2 (b)(4)

(3) (b)(4)

No additional nonclinical safety studies were deemed necessary for the new fexofenadine gelcap tablet, HCl 180 mg.

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

None. In the new fexofenadine HCl gelcap tablet, 180 mg, as compared to the approved Allegra (fexofenadine HCl) film-coated tablet, 180 mg, no changes have been made to drug product specifications, and the acceptance criterion for impurities are unchanged.

2.6 Proposed Clinical Population and Dosing Regimen

Clinical indication: The gelcap tablet is intended for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and older. It is the same as for the approved nonprescription Allegra® Allergy film-coated tablet, 180 mg:

• Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

- Runny nose
- Sneezing
- Itchy, watery eyes
- Itching of the nose or throat.

(b)(4)

Dosing regimen: The recommended dose is one 180 gelcap tablet per day.

2.7 Regulatory Background

Fexofenadine was first approved in the US in July 1996 for seasonal allergic rhinitis or hay fever as a 60 mg capsule formulation under NDA20625. This specific dosage formulation is not currently marketed in the US. In subsequent submissions, a tablet formulation of 3 different dose strengths (30 mg, 60 mg, and 180 mg) was approved in 2000 and 2005 for seasonal allergic rhinitis and chronic idiopathic urticaria (CIU) or hives under NDA20872. In 2011, fexofenadine HCl 30, 60, and 180 mg tablets were approved for nonprescription use for both seasonal allergic rhinitis and CIU.

In preparation of this prior approval supplement for the fexofenadine HCl gelcap tablet, the applicant met with the Agency on 11 December 2012 to seek guidance regarding the submission strategy. The Agency did not agree with the applicant's proposed filing strategy to submit to the tablet NDA as the Agency considered the drug product a new dosage form (ie, a capsule). The applicant provided additional information to further support that the gelcap dosage form is a tablet. The applicant's proposal for stability of packaged product was considered acceptable. (b)(4)

(b)(4)

applicant conducted one bioequivalency study BEQ13500 comparing the proposed fexofenadine HCl gelcap tablet, 180 mg with the currently approved fexofenadine HCl film-coated tablet, 180 mg.

At the 11 December 2012 meeting, the Agency informed the applicant in an advice letter dated 12 March 2013 that the gelcap product would be considered as a tablet. The Agency also communicated that the gelcap product can be filed in a prior approval supplement to the existing NDA 20872. Further, because the proposed product is not for a new active ingredient, new indication, dosage form, new dosing regimen or new route of administration, the Pediatric Research Equity Act is not triggered, and therefore a Pediatric Study Plan is not required.

3 Studies Submitted

3.1 Studies Reviewed

None. No new nonclinical studies were conducted or submitted for the current sNDA. The nonclinical information has been reviewed for the approval of fexofenadine HCl and can be found in the following table:

Table 1 - Location of nonclinical pharmacology, toxicology, and metabolism information previously submitted in related fexofenadine HCl new drug applications

	NDA 20-625	NDA 20-872
	Fexofenadine HCl 60 mg capsule	Fexofenadine HCl 30, 60, and 180 mg tablet
Submission date	July 31, 1995	July 17, 1998
Approval date	July 25, 1996	February 27, 2000
Overall summary	S5-V1.15-P5	S5-V1.14-P6
Pharmacology	S5-V1.15-P9	S5-V1.14-P10
Toxicology	S5-V1.17-P1	S5-V1.14-P24
	NDA 20-625 annual update, 2002	
Metabolism	S5-V1.19-P1	S5-V1.14-P43
	NDA 20-625 annual update, 2002	

Note: Serial/Volume/Page Number refers to the Original NDA unless otherwise specified.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

See reviews by C. Oberlander, [redacted]; NDA20786, [redacted] NDA 20872, [redacted] NDA21704, [redacted].

4 Integrated Summary and Safety Evaluation

Fexofenadine HCl is an antihistamine with selective peripheral H1-receptor antagonist activity. Fexofenadine HCl drug product was first approved in the US in July 1996 for seasonal allergic rhinitis or hay fever under NDA20625. The tablet formulation of 3 different dose strengths (30 mg, 60 mg, and 180 mg) was approved in 2000 and 2005 for seasonal allergic rhinitis and CIU or hives under NDA20872. The present supplemental NDA submission is for a 180 mg gelcap tablet which serves as a new product option for the consumer and as a line extension.

No new nonclinical studies were conducted or submitted in this sNDA. The nonclinical information on Fexofenadine HCl film-coated ablets has been reviewed and found to be adequate if used within the dosage limits and in the dosage forms established under NDA 20872.

The propose fexofenadine HCl gelcap tablet is based on the approved fexofenadine film-coated tablet. (b)(4) . No additional nonclinical safety studies were therefore deemed necessary to support the new fexofenadine gelcap tablet, HCl 180 mg.

No changes have been made to drug product specifications, and the acceptance criterion for known and unspecified impurities are unchanged, as compared to approved fexofenadine HCl film-coated tablet, 180 mg.

Several reproductive and developmental findings were noted on the labeling information for the prescription Allegra products, e.g. reduced implants, post implantation loss, and decreases in pup weight gain and survival. The overall clinical relevance of these findings is not clear since the findings were observed in rats or rabbits but not in mice, and thus may be considered as a species-specific observation. These findings were seen at a ~3 fold margin when compared to the maximum human exposure. None of the above stated findings are considered to have a significant impact for the Rx to OTC switch and for the line extension change from film-coated tablet to gelcap. The labeling for the proposed gelcap product is suggested to have a statement such as “If pregnant or breast-feeding, ask a health professional before use”. This will limit the use of this product during pregnancy and will be consistent with the current OTC labeling and the prescription labeling which states: “There are no adequate and well-controlled studies in pregnant women. The product should be used only if the potential benefit justifies the potential risk to the fetus".

Based on the previous human use experience for fexofenadine, the agency’s review of the approved fexofenadine film-coated tablet, as well as the lack of novel issues identified during the current review, the present NDA supplement can be approved from the nonclinical perspective.

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/s/

XINGUANG LI
03/25/2014

PAUL C BROWN
03/26/2014
I concur that this NDA supplement can be approved from the pharmacology/toxicology perspective.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-872/S-31

BIOPHARMACEUTICS REVIEW

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

NDA	20-872 (Supplement 31)
Submission Date	December 20, 2013
Brand Name	Allegra®
Generic Name	Fexofenadine HCl
Dosage Form & Strength	180 mg Gelcap Tablet
Indication	Temporarily relive of the symptoms due to hay fever or other upper respiratory allergies
Applicant	Sanofi
Reviewer	Assadollah Noory, Ph.D.
Team Leader	Tapash Ghosh, Ph.D.
Acting Supervisor	Richard Lostritto, PH.D.
OPQ Division	ONDQA/ Biopharmaceutics
OND Division	DNCE
Stamp Date	December 20, 2013

1. SUMMARY

Under the provisions of 505(b)(2), Sanofi-aventis submitted this prior approval supplement (PAS) to NDA 020872 seeking approval for their new fexofenadine gelcap tablet (180 mg), for the temporarily relieve of symptoms due to hay fever or other upper respiratory allergies, runny nose, sneezing, itchy watery eyes, and itching of the nose or throat. In support of approval of the new product, the sponsor has submitted one bioequivalence (BE) study under fasting conditions comparing the bioavailability of the new gelcap tablet to the marketed Allegra® film-coated tablet (180 mg). The dose administration of the new fexofenadine HCl gelcap tablet would be same as for the current marketed 180 mg Allegra® film-coated tablet.

In this submission, the Sponsor also requested the Agency's approval (b)(4) .

1.1. Recommendation:

ONDQA-Biopharmaceutics completed the review of the Biopharmaceutics portion of this PAS and finds that the Sponsor has adequately addressed biopharmaceutics' requirements for the approval of the new Gelcap tablet and (b)(4)

ONDQA-Biopharmaceutics recommends the approval of supplement 31 for NDA 20-872.

1.2. Review Summaries:

Bioequivalence Study: The study was a randomized, open-label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study under fasting conditions assessing the bioequivalence of the new gelcap tablet to the marketed Allegra® film-coated tablet in healthy subjects. A summary result of the study is shown in the following table.

Table 1: Summary Statistics

Parameter	Test (mean +/- SD), Geo. Mean		Reference (mean +/- SD), Geo. Mean		Point Estimate (%) & 90% C. I.	
Cmax (ng/mL)	483 ± 216	434	546 ± 280	481	90.0	83.6 - 96.8
AUC_{0-t} (ng•h/mL)	3220 ± 1350	2960	3430 ± 1370	3170	93.5	88.3 - 99.0
$AUC_{0-\infty}$ (ng•h/mL)	3370 ± 1370	3110	3560 ± 1390	3300	94.7	89.9 - 99.6
Test	180 mg fexofenadine HCl gelcap tablet					
Reference	180 mg Allegra® film-coated tablet					

The 90% confidence intervals for fexofenadine are within 80% to 125% for both AUC and C_{max} indicating that the new 180 mg fexofenadine gelcap tablet is bioequivalent to 180 mg Allegra® film-coated tablet under fasting conditions.

Modification of the Dissolution Method: The dissolution method and specification criteria will remain the same as the previously approved, shown in the table below.

Table 1: Dissolution Methodology And Specification

Apparatus	USP Apparatus II, Paddle Method
Rotation Speed	50 rpm
Medium	0.001N HCl pH 3
Volume	900 mL
Temperature	37°C ±0.5°C
Sampling Time	10 and 30 minutes
Filtration	(b)(4)
Specifications	10 minutes: Q (b)(4)
	30 minutes: Q (b)(4)

The drug substance information and the manufacturing process (b)(4) is the same as approved for the Allegra film coated 180 mg tablet. The Sponsor proposed (b)(4).

Drug product stability available for the three gelcap tablet batches, one commercial scale and two pilot scale registration batches, demonstrate that the method and specification are acceptable

Dissolution results for the Gelcap tablet batch (test product) and the Allegra® film coated tablet batch (reference product) used in the bioequivalence study demonstrate that the products have comparable dissolution profiles.

Approval of a (b)(4) (b)(4)

(b)(4)

(b)(4)

Signature 04/08/2014
Assadollah Noory, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature 04/08/2014
John Duan, Ph.D.
Acting Team Leader
Office of New Drug Quality Assessment

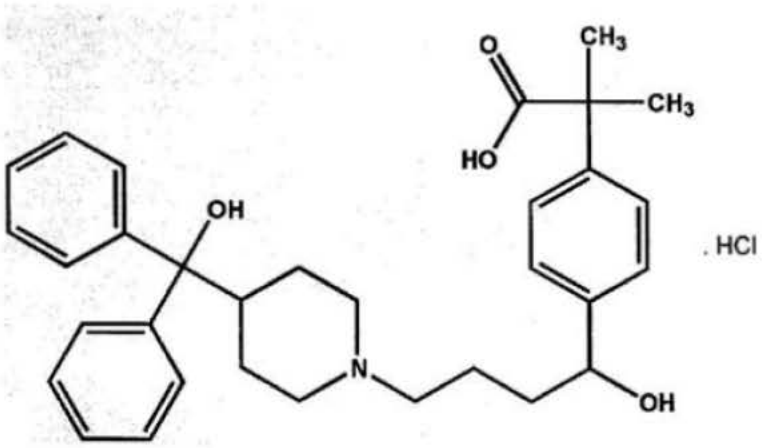
2. BACKGROUND

Fexofenadine HCl gelcap tablet 180 mg was developed to provide a new product option for the consumer as a line extension to the approved nonprescription 180 mg Allegra® film-coated tablet. The gelcap tablet (b)(4)

(b)(4)

On December 11, 2012 the Agency agreed that the gelcap product is a tablet and can be filed as a prior approval supplement (PAS).

The empirical formula of fexofenadine is $C_{32}H_{39}NO_4$. HCl with a molecular weight of 538.12.



Structural Formula

3. FORMULATION COMPOSITION

There are no changes in the manufacturing process, (b)(4)

The following table shows the formulation composition of the new gelcap tablet and the marketed film coated tablet.

Table 3: Formulation Composition

Components	Composition (per unit) in mg	
	fexofenadine HCl 180 mg tablet	fexofenadine HCl 180 mg Gelcap tablet
Core tablet		
[redacted] (b)(4)		
Film coating		
[redacted] (b)(4)		
[redacted] (b)(4)		
Application of gelatin cover		
[redacted] (b)(4)		
Printing		
[redacted] (b)(4)		
Total mass		[redacted] (b)(4)

4. BIOANALYTICAL

The concentrations of fexofenadine in human plasma were determined by HPLC/MS/MS methods. Validation of the bioanalytical method's performance is presented in the following table.

Table 4: Bioanalytical Method Validation

Analytical Parameters	Fexofenadine
Analytical Range, ng/mL	1.00 to 1000.80
Between-Run Precision (%)	4.03 to 12.92%
Between- Run Accuracy (%)	-4.51 to 4.37%
Within-Run Precision (%)	2.52 to 7.30%
Within-Run Accuracy (%)	-5.73 to 3.24%
Recovery (%)	80.01
Freeze-thaw Stability (four cycles) (%)	-10.52 to -3.17
Freezer Stability (261 days, -20°C) (%)	-3.59% to -2.06

The bioanalytical method is acceptable for the analysis of fexofenadine from the plasma samples.

5. LABELING RECOMMENDATIONS

ONDQA-Biopharmaceutics recommends that there should be no changes in the "DOSAGE AND ADMINISTRATION" section for the Gelcap tablet compared to the approved Allrgra® film coated tablet.

6. INDIVIDUAL STUDY REVIEWS

6.1. Study BEQ13500

Title:
An open-label, randomized, 2-treatment crossover bioavailability study comparing fexofenadine hydrochloride gelcap tablet to the marketed Allegra® film coated tablet in healthy male and female

Principal Investigator:
(b)(4)

Study Start Date: 12 February 2013 **Study End Date:** 09 May 2013

Treatments:

Test: 180 mg fexofenadine HCl gelcap tablet, batch number C1027681, (new)

References: 180 mg Allegra® film-coated tablet, batch number C1030722, (Marketed)

Objective:
To determine the bioavailability of the 180 mg gelcap tablet formulation (test) versus the 180 mg marketed tablet formulation (reference) of fexofenadine HCl in healthy male and female volunteers under fasting conditions and to monitor the safety and tolerability of test and reference products following a single dose administration.

Study Design:
The study was an open-label, randomized, 2-sequence, 2-period, 2-treatment crossover bioequivalence study under fasting conditions. The study medications were administered with 240 mL of noncarbonated water. The wash-out period was 7 days.

Study Population:
The sample size calculations for the bioequivalence study was based on the pooled within-subject standard deviation (SDw) for fexofenadine log C_{max} (0.289), log AUC_{last} (0.214), and log AUC (0.212) from several internal historical studies taken under consideration. Therefore, assuming a true SDw of 0.300 and allowing for a 10% true difference between formulation means, the number of subjects required to conclude bioequivalence between the two fexofenadine HCl formulations with 90% power was 114. Therefore, 120 subjects were planned to be included in the study to get at least 114 evaluable subjects. 109 of 120 subjects enrolled in this study completed the study. 4 subjects did not complete the study treatment periods, 3 subjects were discontinued due to poor compliance to

study protocol, and 4 subjects discontinued due to personal reasons. The following table contains subjects' demographics.

Table 5: Study Subjects

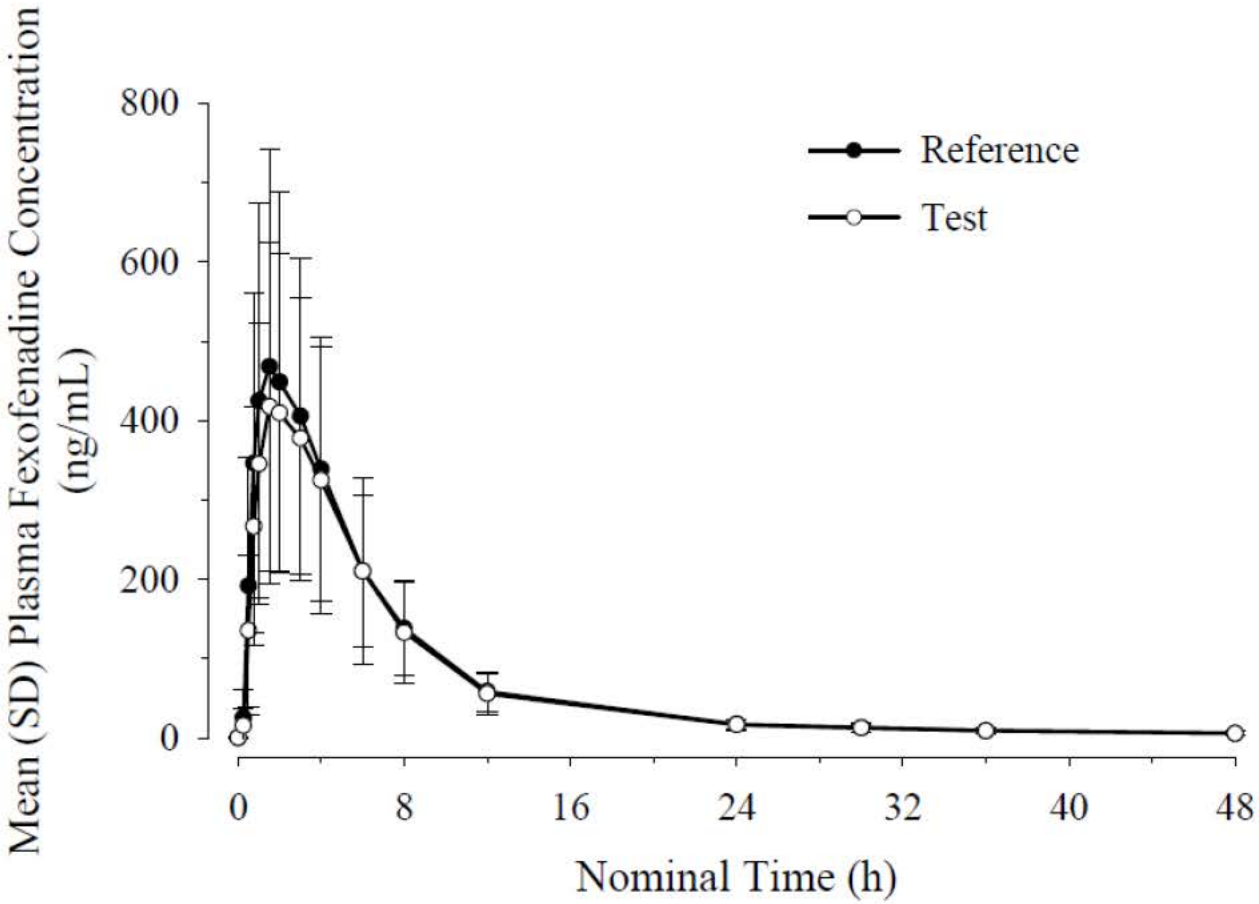
Subjects Demographics	
Gender	84 Male; 36 Female
Age (yr)	36.4 ± 9.4 (19.0 - 54.0)
Weight (kg)	75.0 ± 11.2 (50.2 - 95.0)
BMI (kg/m^2)	Less than 30
Race	50 white, 67 Black, 2 Asian/Oriental, 1 Other
Note: Data presented as mean ± SD (Range)	

Sample Collection for Pharmacokinetic Measurements:
Blood samples were collected at the following specified times during each period for the determination of concentrations of fexofenadine in plasma: prior to dosing (zero hour) and at , 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours post dosing.

Pharmacokinetic and Statistical Analysis:
The pharmacokinetic parameters were determined by the Sponsor using WinNonLin® Professional, Version 5.2.1. The results are shown in the table and figure below.

Table 6: Summary of Plasma Pharmacokinetic Parameters, Mean ± SD

PK-Parameter	Test, N=116	Reference, N=120
C_{max} (ng/mL)	483 ± 216	546 ± 280
T_{max} (hr)*	1.50 (0.75 - 6.00)	1.50 (0.50 - 6.00)
AUC_{0-t} (ng•h/mL)	3220 ± 1350	3430 ± 1370
AUC_{inf} (ng•h/mL)	3370 ± 1370	3560 ± 1390
$T_{1/2}$ (hr)	14.9 ± 8.93	13.5 ± 7.31
* - Mean (Range)		



Reference = Marketed 180 mg Allegra® film-coated tablet (N = 120)
Test = New 180 mg fexofenadine HCl gelcap tablet (N = 116)

SAS® software version 9.2 was used for the statistical analysis of this bioequivalence study by the Sponsor. The statistical results for bioequivalence i.e. geometric mean, the point estimate (ratio of test product divided by the reference product expressed as percent), and 90% confidence intervals are shown in the following table.

Table 7: Summary Statistics

Parameter	Test, Geo. Mean	Reference, Geo. Mean	Point Estimate (%)	90% Confidence Interval
Cmax (ng/mL)	434	481	90.0	83.6 - 96.8
AUC_{0-t} (ng•h/mL)	2960	3170	93.5	88.3 - 99.0
$AUC_{0-\infty}$ (ng•h/mL)	3110	3300	94.7	89.9 - 99.6
Test	180 mg fexofenadine HCl gelcap tablet			
Reference	180 mg Allegra® film-coated tablet			

A comparative presentation of point estimates and 90% confidence intervals reported by the Sponsor and analyzed by this reviewer is shown in the table below.

Table 8: Comparative Results

Parameter	Sponsor Reported		Reviewer Analyzed	
	Point Estimate (%)	90% Confidence Interval	Point Estimate (%)	90% Confidence Interval
Cmax (ng/mL)	90.0	83.6 - 96.8	90.11	83.61 – 96.95
AUC_{0-t} (ng•h/mL)	93.5	88.3 - 99.0	62.58	87.20 – 98.31
$AUC_{0-\infty}$ (ng•h/mL)	94.7	89.9 - 99.6	94.16	89.67 – 99.50

The 90% confidence intervals for fexofenadine are within 80% to 125% for both AUC and C_{max} indicating that 180 mg fexofenadine gelcap tablet is bioequivalent to 180 mg Allegra® film-coated tablet under fasting conditions.

Safety and Tolerability:
The treatment related adverse events were gastrointestinal disorder experienced by 3 subjects, headache by 2 subjects, oropharyngeal pain by 2 subjects, ear pain by 1 subject. There were no serious adverse events reported during this study. All adverse events were mild. No subject dropped out due to an adverse event. Study medications were tolerated by the study subjects.

Protocol Deviations:
There was no protocol deviation reported in this study.

Conclusion:
The 90% confidence limits for fexofenadine are within 80% - 125% for AUC and C_{max} indicating that 180 mg fexofenadine gelcap tablet is bioequivalent to 180 mg Allegra® film-coated tablet. There were no dropouts due to adverse events, and the study medications were tolerated by the study subjects.

Appears this way

6.2. Dissolution

The current approved dissolution methodology for fexofenadine tablets shown in the following table will be used for the new fexofenadine gelcap tablet.

Apparatus	USP Apparatus II, Paddle Method
Rotation Speed	50 rpm
Medium	0.001N HCl pH 3
Volume	900 mL
Temperature	37°C ±0.5°C
Sampling Time	10 and 30 minutes
Filtration	(b)(4) (b)(4)
Specifications	10 minutes: Q
	30 minutes: Q

Analytical Method: The parameters of the analytical procedure are shown in the following table.

Assay	HPLC with UV detection (b)(4)
Mobile Phase	(b)(4)
Aqueous Phase	(b)(4)
Organic Phase	(b)(4)
Retention Times	
Reproducibility (%RSD)	<2.0
Accuracy at 100% (%RSD)	0.6
Precision (%RSD)	0.6
Repeatability (%RSD)	0.7
Reproducibility (%RSD)	1.1

Reviewer's comments: The dissolution methodology and the analytical procedures were approved by the Agency for the currently approved formulation. As the proposed gelcap core formulation is same as the Allegra® film coated formulation the above dissolution methodology is accep0table.

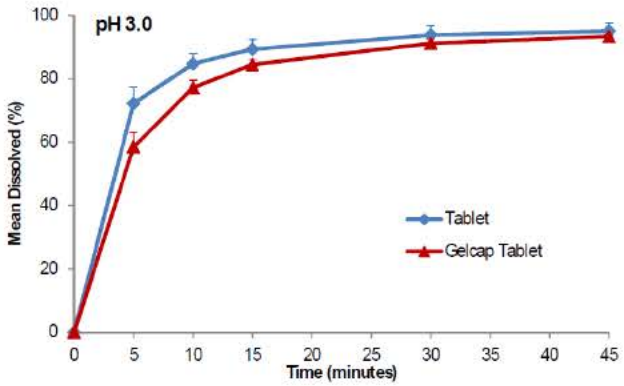
Appears this way

Dissolution Similarity: Information on the two lots used in the bioequivalence study (BEQ13500) and the dissolution result are shown in the following table and figure.

Table 5 - Manufacturing details and comparative dissolution profiles of fexofenadine HCl at pH 3.0 for test and reference products used in BEQ13500

Product	Manufacturing site	Manufacturing Date	Bulk Lot No. (Industrial Batch No.)	Batch Size	No. of Units for dissolution	Collection times Mean % Dissolved (% RSD)					
						0 min	5 min	10 min	15 min	30 min	45 min
Test[a]	Sanofi Winthrop Industrie, Compiegne, France (b)(4)	(b)(4)			(b)(4)	0	58.5 (4.6)	77.2 (2.3)	84.5 (1.5)	91.2 (1.3)	93.4 (1.3)
Reference[b]	Sanofi Winthrop Industrie, Tours, France					0	72.2 (5.2)	84.7 (3.2)	89.3 (3.1)	93.8 (2.9)	95.0 (2.6)

Figure 1 - Comparative dissolution profiles (mean + RSD) of fexofenadine HCl at pH 3.0 for the test and reference products used in BEQ13500



The similarity factor for the batches used in the study is shown in the table below.

Table 20 - Similarity factor (f_2) results for Gelcap tablet and film-coated formulae - pH 3.0 - Bioequivalency batches

Number of points	Time (min)	f_2 result
3	5, 10,15	51.2

This similarity factor f2 calculated by this reviewer was 51.13, which is similar to the result reported by the Sponsor.

Reviewer Comment: The dissolution profiles of the test and reference product used in the above bioequivalence study are similar.

Batch to Batch Consistency: Three pilot scale batches manufactured in France were used to determine the batch to batch consistency of fexofenadine gelcap tablets. The information about these batches is shown in the following table.

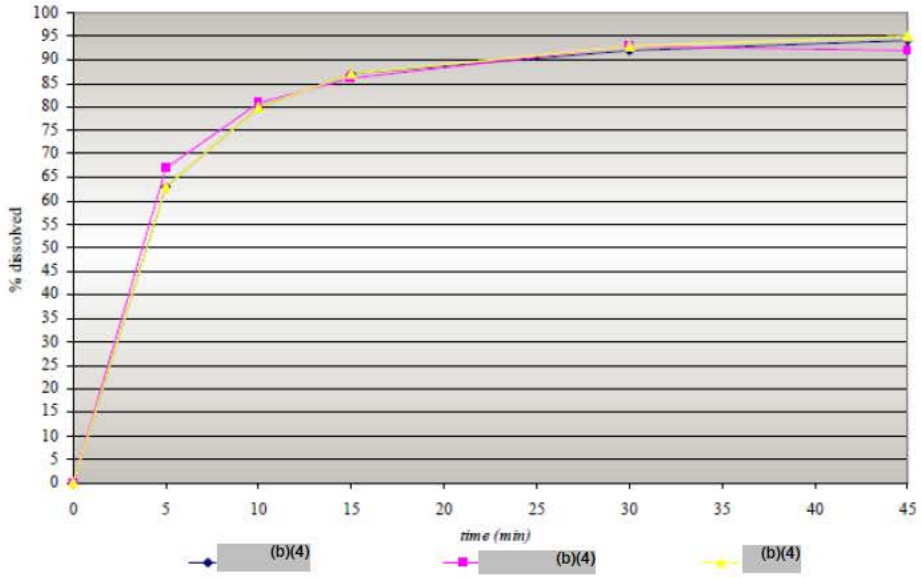
Table 1 – Information on Pilot scale batches

Batch information	(b)(4)		
Batch no. drug substance (fexofenadine HCl)			
Batch size, finished product			
Site of manufacture, finished product	SWI Compiègne, France	SWI Compiègne, France	SWI Compiègne, France (b)(4)
Manufacturing process scale	Pilot Scale	Pilot Scale	Pilot Scale

The results of the dissolution tests are shown in the following table and figure.

Pilot Batches Manufactured in France: Paddle 50 rpm; 0.001N HCl pH 3.0						
Batch Number		**Time (min)**				
		5	**10**	**15**	**30**	**45**
(b)(4)	Mean (N=6)	63 ± 4.4	80 ± 1.8	87 ± 1.5	92 ± 0.4	94 ± 0.7
	(b)(4)					
	Mean (N=12)	67 + 3.4	81 + 1.4	86 + 1.2	90 + 1.2	92 + 1.4 (b)(4)
	Mean (N=6)	63 ± 3.3	80 ± 1.5	87 ± 1.3	93 ± 0.9	95 ± 1.1
	(b)(4)					

Figure 1 – fexofenadine HCl gelcap tablet, 180 mg - Comparative dissolution profiles at pH 3.0 / 50 rpm



Reviewer Comment: The batch to batch consistency is demonstrated for the pilot scale batches of fexofenadine film gelcap tablets manufactured in France.

Proposed Additional Manufacturing Site: (b)(4) It is noteworthy to point out that the Sponsor did provide a rational for not using the new Gelcap tablet in the dissolution studies (b)(4) of 60 mg tablets. The batches were tested in water and buffer at pH 4.5, 6.8 and 7.5 and 0.001N HCl pH 3.0. The batch information and the results of dissolution test up to 30 minutes are shown in the following two table.

Table 1 - Description of batches

Batch number	Manufacturing date	Batch size (kg)	Manufacturing site
1130886	Mar-2010	(b)(4)	sanofi aventis U.S. LLC (Kansas City, USA)
1T002	Jan-2011		Sanofi Winthrop Industrie (Tours, FR)

Dissolution of Two 60 mg film coated tablet Batches in Different Media (N=12)						
Lot	Medium	5 min	10 min	15 min	30 min	F2 Results
1130886	pH 1.2				(b)(4)	43.6 (5 points)
1T002						
1130886	pH 3.0					Over (b)(4)% dissolved in 15 minutes
1T002						
1130886	pH 4.5					Insufficient time points with less than (b)(4)% dissolved
1T002						
1130886	pH 6.8					Over (b)(4)% dissolved in 15 minutes
1T002						
1130886	Water					Over (b)(4)% dissolved in 15 minutes
1T002						
1130886	pH 7.5					Over (b)(4)% dissolved in 15 minutes
1T002						
1130886: Current manufacturing site batch (USA)					(b)(4)	site batch (France)

Reviewer Comment: according to the SUPAC-IR, the Sponsor needed to only provide multi-point dissolution profile using the compendia medium i.e. 0.001N HCl pH3.0. Based on the above dissolution profile at pH3.0, the batch manufactured in Tours France provided similar dissolution profile as the batch manufactured in Kansas City USA (b)(4) (b)(4)

Proposed Fully (b)(4) (b)(4)

Three lots of each strength of film coated tablets (n=12 units/lot) were tested using the (b)(4) (b)(4) (b)(4) the Approved Method (HPLC) and the F1 (Difference) and F2 (Similarity) factors are Shown in the following table.

Batch #	Strength	HPLC*	%RSD	(b)(4)	%RSD	f2	f1
1076192	30 mg	98.1	1.6		1.2	82.9	2.1
1105833	30 mg	96.9	1.2		2.8	88.6	1.4
1105834	30 mg	97.7	1.6		1.6	92.1	0.9
1105836	60 mg	97.5	2.0		1.5	88.7	1.3
1105838	60 mg	97.2	1.5		1.0	89.4	1.4
1107315	60 mg	99.1	2.4		1.6	91.8	0.9
1107313	120 mg	97.9	1.3		0.8	84.3	1.6
1108153	120 mg	97.7	2.5		1,2	94.9	0.7
1108158	120 mg	97.7	1.1		0.8	84.2	1.8
1088320	180 mg	96.0	1.6		5.1	83.5	1.8
1105504	180 mg	95.1	2.0		1.1	93.9	0.8
1105748	180 mg	92.3	1.3		1.1	96.1	0.6
*- Approved dissolution methodology with HPLC assay							

To determine the differences in the assay methods, additional dissolution tests were performed using one lot from each dosage strength. (b)(4) HPLC. The results are shown in the following table.

Comparison of the Same Solution Using the HPLC Method (b)(4)				
Batch	Strength	HPLC		Difference
1076192	30 mg	98.52		-0.55
1105836	60 mg	98.87		0.05
1107313	120 mg	96.76		-1.76
1088320	180 mg	96.36		1.42

Reviewer Comment: the results support the (b)(4) for dissolution testing, therefore the (b)(4).

Final reviewer's Evaluation:

In summary, the drug substance information and the manufacturing process (b)(4) (b)(4) as approved for the Allegra film coated 180 mg tablet. The Sponsor (b)(4) new Gelcap tablet.

Drug product stability available for the three gelcap tablet batches, one commercial scale and two pilot scale registration batches, demonstrate that the method and specification are acceptable

Dissolution results for the Gelcap tablet batch (test product) and the Allegra® film coated tablet batch (reference product) used in the bioequivalence study demonstrate that the products have comparable dissolution profiles.

(b)(4)

The comparison of the dissolution profiles using the compendia dissolution methodology between the (b)(4) is acceptable.

The Sponsor did not conduct a fed bioequivalence study because the (b)(4) identical in the two products. Therefore, it is expected that the effect of food would be similar to the currently marketed Allegra® film-coated tablet.

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/s/

ASSADOLLAH NOORY
04/08/2014

JOHN Z DUAN
04/08/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-872/S-31

OTHER REVIEW

Labeling Review for
Allegra Allergy
180 mg tablet
Draft Labeling

SUBMISSION DATES:	December 20, 2013 and April 10, 2014
NDA/SUBMISSION TYPE:	020872/S-031 (CMC with Labeling)
ACTIVE INGREDIENTS:	180 mg fexofenadine
DOSAGE FORMS:	Tablet
SPONSOR:	Sanofi-aventis Nancy Dougherty 908-981-4818
REVIEWER:	Ayana K. Rowley, Pharm.D.
TEAM LEADER:	Steven Adah, Ph.D.

I. BACKGROUND

The sponsor has submitted revised carton and immediate container labels to introduce a new product line called a "gel coated tablet" using (b)(4)„ does not replace the currently approved tablet, the submission is only for the 180mg dosage strength and Allergy indication. This submission and "gel coated tablet" has a new set of count sizes (SKUs) with (b)(4) (b)(4).

Submitted Labeling	Representative of Following SKUs
180 mg outer carton -8 count	N/A
180 mg outer carton -24 count	N/A
180 mg outer carton - 40 count	N/A
180 mg immediate container (blister) 8 count	N/A

The proposed labeling was compared to the currently approved outer carton labeling (dated January 23 2012) that was approved as part of NDA 020872/S-29.

REVIEWER'S COMMENTS

A. 8-, 24-, 40- count outer carton 180 mg

i. Outer Carton Label Outside Drug Facts

The sponsor has made the following graphic layout revisions to the carton label as stated in the cover letter. **These are acceptable**.

Principal Display Panel

a. Product Description
   (a) "Gelcap" has been added to the principal display panel along with a graphic depiction of the "gel coated tablet"
b. Non-Drowsy and Original Prescription Strength promotional statements
   (a) The background color of "Non-Drowsy" and "Original Prescription Strength" promotional statements have been revised (b)(4) blue.
c. (b)(4)

(b)(4)

d. "Indoor and Outdoor Allergies"
   (a) The "Indoor and Outdoor Allergies" promotional statement has been relocated to the lower left side of the principal display panel.
e. Net Quantity
   (a) The net quantity of contents has been updated to reflect the proposed gelcap tablet count.

Side Panels

a. "Gelcaps" has been added to the top panel and each side panel
b. "Indoor and Outdoor Allergies" is added to the top (40-count) and side (8-and 24-count) panels.
c. The net quantity of contents has been included on the top panel

ii. Outer Carton Drug Facts Label

a. Inactive Ingredients:
   (a) The drug facts panel has been revised to reflect the inactive ingredients for the gelcap tablet as follows: Croscarmellose sodium, D&C red 28, D&C red 33, FD&C blue 1, gelatin, hydroxypropylcellulose, hydroxypropyl

methylcellulose, magnesium stearate, microcrystalline cellulose, PEG-135, pharmaceutical ink, pregelatinized starch, titanium dioxide

(b) The ONDQA/CMC reviewer has found these ingredients to be acceptable as stated in their review.

b. Font Specifications:

(a) The sponsors draft labeling meets format specifications as in accordance with 21 CFR 201.66. **This is acceptable**.

iii. Immediate Container Label (8 – count blister): The sponsor has introduced a new 8-count blister package. The blister package is acceptable with the required listing of the active ingredient, lot/control numbers and expiration date

II. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Allegra Allergy labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: the 8-, 24-, 40- count outer carton 180 mg submitted on April 10, 2014, and the 8-count 180 mg immediate container submitted on December 20, 2013.

Inform the sponsor that the "(b)(4) (b)(4)".

III. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

Eight (8) pages have been removed as (b)(4), draft labeling, immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANA K ROWLEY
04/14/2014

STEVEN A ADAH
04/14/2014