CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201373Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 22, 2010
From	Andrea Leonard-Segal, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDAs 201-613, 21-909 S-003, and 201-373
Applicant Name	Sanofi-aventis
Date of Submission	March 25, 2010
PDUFA Goal Date	January 25, 2010
Proprietary Name / **Established (USAN) Name**	Allegra® Allergy, Allegra®Hives, Children's Allegra® Allergy, and Children's Allegra® Hives/ fexofenadine hydrochloride
Dosage Forms / Strength	Tablet 30 mg, 60 mg, and 180 mg Orally disintegrating tablet (ODT) 30 mg Oral suspension 30 mg / 5 ml
Proposed Indication(s)	1. Allergy products indication Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: • runny nose • itchy watery eyes • sneezing • itching of the nose or throat 2. Hives products indication Reduces hives and relieves itching due to hives (urticaria)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review DNCE	Linda Hu, M.D.
Medical Office Review for Allegra D (NDA 20-786 S027 and NDA 21-704 S008)	Ryan Raffaelli, M.D.
Medical Officer Reviews DCRP QT Interdisciplinary Review Team (QT consult)	Suchitra Balakrishnan, M.D. / Norman Stockbridge, M.D.
Medical Officer Review DPAP	Anya Harry, M.D., Ph.D./ Theresa Michele, M.D.
Statistical Review	Feng Zhou/Joan Buenconsejo (tablet formulation only)
Pharmacology Toxicology Review	Cindi Li, Ph.D., Paul Brown, Ph.D.
CMC Review/OBP Reviews and Addenda	Caroline Strasinger, Ph.D./Shulin Ding, Ph.D. (tablet formulation); Sharon Kelly, Ph.D./Hasmukh Patel, Ph.D. (ODT); Minerva Hughes, Ph.D./Marie Kowblansky Ph.D. (suspension); Moo Jhong Rhee, Ph.D.
CMC Memo 1/21/2011	Terrance Ocheltree, Ph.D., R.Ph.
Clinical Pharmacology Reviews 11/10 and Addenda 1/7/11	Arun Agrawal, Ph.D./Yun Xu, Ph.D.
CDTL Review	Daiva Shetty, M.D.
OSE/DMEPA Reviews	Janet Anderson/Zachary Oleszczuk, Pharm.D/Yelene Maslov, Pharm.D
OSE/DPV I	Melinda Wilson, Pharm. D/Ann McMahon M.D., M.S.
Environmental Assessments for NDAs 201-613 and 201-373	Raanan Bloom, Ph.D./ Nakissa Sadrieh, Ph.D
DNRD – Labeling Reviews	Ayana Rowley Pharm.D./ Marina Chang R.Ph.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DPVI= Division of Pharmacovigilance I
DCRP = Division of Cardiorenal Products
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DNRD=Division of Nonprescription Regulation Development

Signatory Authority Review Template

1. Introduction

This review will summarize the data for two 505(b)(1) NDAs and one 505(b)(1) NDA supplement submitted to switch single ingredient fexofenadine hydrochloride (FH) from prescription to nonprescription status. There are three formulations of FH that the sponsor seeks switch, a tablet (NDA 201-613), an orally disintegrating tablet (ODT) (NDA 21-909 S003), and a suspension (NDA 201-373). Each of these formulations is currently available by prescription. Some of the FDA discipline-specific reviews for the three applications consider the data for the different formulations en masse; some do not. This review will.

There are two separate indications proposed for the FH products.
1. Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
- runny nose
- itchy watery eyes
- sneezing
- itching of the nose or throat

2. Reduces hives and relieves itching due to hives (urticaria)

Fexofenadine is a selective peripheral H1-receptor antagonist which is a pharmacologically active metabolite of terfenadine. As with the two other second generation antihistamines that are currently OTC after having been switched from their prescription marketing status (loratadine hydrochloride (LH), and cetirizine hydrochloride (CH)), the Applicant will separately package FH for each of the two nonprescription indications.

The Applicant proposed that FH will be available for children and adults for each indication. The tablet and ODT formulations will be labeled for adults and children ≥ 6 years of age for allergies and hives. The oral suspension will be labeled for adults and children ≥ 2 years of age for allergies and for adults and children ≥ 6 years of age for hives. FH oral suspension will remain as a prescription product for children < 6 years of age for chronic idiopathic urticaria (CIU) under NDA 21-963.

2. Background

First generation antihistamines such as diphenhydramine, brompheniramine, chlorpheniramine and doxylamine have been available OTC for decades to treat symptoms of upper respiratory allergies. A troublesome adverse effect when taken for allergic rhinitis is that they are very sedating which makes these products difficult for some allergy sufferers to use, especially during the day. Furthermore, first generation antihistamines with long half lives can leave allergy sufferers feeling drowsy in the morning even if they take a product at night.

The second generation antihistamines were developed to limit sedation as an adverse effect. The minimal risk of sedation occurs because these products have limited penetration of the central nervous system.

In 1998 a Citizen Petition was submitted to FDA requesting that cetirizine, loratadine and fexofenadine be switched from prescription to nonprescription status. Joint Advisory Committees on Nonprescription Drug Products and Pulmonary and Allergy Drug Products met in 2001 and in 2002 to discuss the concept of switching second generation antihistamines for over-the-counter (OTC) use for symptoms of upper respiratory allergies and hives. The committees recommended that the safety profiles of LH, CH, and FH made them appropriate candidates for nonprescription use for these indications. Subsequently, the innovator sponsors for LH and CH submitted applications to switch their products and both were both approved OTC.

Table 1 lists commonly marketed antihistamines that are available without a prescription in the United States. There are other first generation antihistamines allowed without a prescription under the OTC monograph regulatory process (21 CFR 241) that are not listed in the table.

Table 1: OTC Antihistamines

loratadine	2nd generation antihistamine
cetirizine	2nd generation antihistamine
chlorpheniramine*	1st generation antihistamine
brompheniramine*	1st generation antihistamine
diphenhydramine*	1st generation antihistamine
doxylamine*	1st generation antihistamine
clemastine	1st generation antihistamine

* monograph antihistamines

Fexofenadine was approved as a prescription drug in the United States on July 25, 1996 as a capsule formulation at the 60 mg BID daily dose for seasonal allergic rhinitis (SAR) in adults and children ≥ 12 years of age. (The capsule formulation is no longer marketed.)

Subsequently, tablets 30 mg BID were approved for children ages 6 – 11 years and tablets 60 mg BID and 180 mg Qd were approved for adults for both SAR and CIU. Afterwards, ODT and suspension formulations were approved for adults and children.

Currently, in the prescription setting, FH is used to treat SAR in children down to 2 years of age and CIU in the pediatric population down to age 6 months. The pediatric dosing is 30 mg

BID for SAR and CIU for children ages 2 – 11 years of age and 15 mg BID for children 6 months to < 2 years old for CIU.

FH is also approved as a generic drug in the United States. Additionally, FH has been approved in combination with pseudoephedrine HCl in different strengths under NDAs 20-786 and 21-704. It is approved internationally as a prescription product in approximately 85 countries and has been available without a prescription for over 10 years in 12 countries. The estimated patient exposure with fexofenadine is over 32 million patient-years (17.23 million patient years in the United States).

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug products (tablets, ODT, and oral suspension) and drug substance. Manufacturing site inspections were acceptable. There are no outstanding issues. For the suspension, in accordance with the GMP regulation requirements, the applicant has committed to post-approval stability testing of two new bottle sizes (150 mL and 300 mL bottles).

The partial switch of the oral suspension is expected to increase the use of FH. An environmental assessment was submitted by the Sponsor and a finding of no significant environmental impact was assessed by Dr. Bloom in his November 30, 2010 review. Likewise, Dr. Bloom's November 30, 2010 environmental assessment for the FH tablets shows that no adverse effects are expected from the nonprescription introduction of FH into the environment. No assessment of environmental impact was required for the ODT supplement.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval. Fexofenadine is rated as a Pregnancy Category C drug. In consideration of the pregnancy warning in the Drug Facts label, it is important to note that the animal reproductive and development data showed species-specific findings with unclear clinical relevance at approximately a 3-fold margin when compared to the maximum human exposure. Since there are no adequate and well-controlled studies in pregnant or lactating women, I agree with the reviewers' recommendation that the OTC labeling should state, "If pregnant or breast feeding, ask a health professional before use." FH does not exhibit evidence of carcinogenicity or mutagenicity.

5. Clinical Pharmacology/Biopharmaceutics

No new human pharmacokinetics and bioavailability and clinical pharmacology studies were conducted in support of the switch applications because of the extensive data already available, including postmarketing safety data, on prescription fexofenadine. Per FDA's request for safety updates to support the switch applications, Sanofi-aventis submitted thirteen previously conducted clinical pharmacology related study reports. The clinical pharmacologists reviewed these and determined that the data therein do not suggest a need to modify labeling or clinical pharmacology recommendations regarding fexofenadine. In December 2010, after the November 2010 review was completed, the sponsor submitted eight additional clinical pharmacology related study reports which they had not submitted previously. The clinical pharmacology reviewers wrote addenda to their reviews accounting for these eight reports; there was no additional information to impact their prior review recommendations and/or the label. I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

Substantially reduced bioavailability of fexofenadine occurs in the presence of fruit juice and antacids. Because of this, the clinical pharmacology reviewers recommended that prescription labeling recommendations for fexofenadine not to be taken with fruit juice and/or aluminum and magnesium containing antacids should be carried over to the nonprescription label. Drs. Agrawal and Xu also recommended that the labeling should inform consumers to take the ODT formulation of fexofenadine on an empty stomach because of a food effect, which is present in all three formulations but clinically meaningful for the ODT formulation.

Prescription labeling recommends starting the dosing for renally impaired children and adults at 30 mg and 60 mg once daily, respectively. Because dose reduction of this renally excreted drug is recommended in people with reduced renal function, Drs. Agrawal and Xu recommended that the nonprescription labeling should advise people with known kidney disease to ask a doctor before use. They also recommended that labeling should instruct people $\geq$ 65 years old to ask a doctor before use. This is because of the potential for decreased renal function and documented increased bioavailability of FH in the older population. The pharmacokinetics of FH in patients with hepatic disease does not differ substantially from that observed in healthy patients, so a warning not to use in the presence of liver disease is not needed.

Drs. Hu, and Shetty agreed with the above Drug Facts labeling recommendations and so do I.

<u>Effects on QTc (animal data and clinical trials):</u>
No effect on QTc was seen in dogs or rabbits at very high exposures. No effect was observed on calcium channel current, delayed potassium channel current, or action potential duration in guinea pig monocytes, sodium current in rat neonatal myocytes, or on several delayed rectifier potassium channels cloned from human heart at concentrations up to 1×10^{-5} M of fexofenadine. No statistically significant increase in mean QTc interval compared to placebo was observed in 714 SAR patients given FH in doses of 60 mg to 240 mg twice daily for two weeks. Pediatric patients (n = 855) treated with up to 60 mg FH twice daily demonstrated no QTc changes. In addition, no statistically significant increase in mean QTc interval compared

to placebo was observed in 40 healthy volunteers given FH in doses up to 400 mg BID for six days or in 231 healthy volunteers given 240 mg of FH daily for one year.

Macrolides and Ketoconazole:
Fexofenadine exhibits minimal (~ 5%) metabolism. Fexofenadine is not metabolized significantly by the cytochrome P450 system. Thus, it is not expected to have cytochrome P450 metabolic drug interactions.

Co-administration with either erythromycin 500 mg every eight hours or ketoconazole 400 mg daily lead to increased fexofenadine plasma concentrations in healthy adults in the steady state (Cmax + 82% / AUC + 109% with erythromycin and Cmax + 135% / AUC +164% with ketoconazole). The reviewers note that this is probably because of increased gastrointestinal absorption due to transport-related effects. These higher plasma concentrations were within the range of plasma levels achieved in adequate and well-controlled clinical trials. Three clinical trials testing erythromycin and ketoconazole with concurrent use of FH 120 mg BID for seven days did not result in any significant AEs, changes in QTc intervals or any relevant ECG changes. Fexofenadine has no effect on the pharmacokinetics of erythromycin or ketoconazole. For these reasons, the prescription labeling does not recommend dose adjustment or use with caution when FH is taken with erythromycin or ketoconazole and Drs. Agrawal and Xu did not recommend including such cautionary statements on the OTC label in their review.

By contrast, Dr. Hu recommended including a warning about drug interactions with macrolides on the nonprescription label. Dr. Hu based her recommendation essentially on five postmarketing serious adverse event case reports (page 138 of her review) that she found compelling against the background of 32 million patient years of use of fexofenadine. The patients who were the subjects of these case reports developed tachycardias. Dr. Shetty also reviewed these cases and found them to be confounded and lacking in adequate detail to be able to implicate fexofenadine as a cause for the adverse cardiac events. She disagreed with Dr. Hu and agreed with prior reviewer assessments that the drug interaction warning is not warranted.

I also reviewed the individual MedWatch forms for these cases (199911526HMRI, 199812436HMRI, 200520584GDDC, 199912441HMRI, and 199710046HMRI). I agree with Dr. Shetty's assessment that these cases are confounded and that necessary information is lacking so one cannot say that, in any of them, the association between fexofenadine and macrolides was likely to have caused the event. One patient was taking albuterol concomitantly and another was taking salmeterol concomitantly. These beta agonists are known cardiac stimulants. Other relevant information (such as coffee consumption, presence or absence of structural cardiac disease, etc.) was absent in the reports. One patient reported an irregular pulse that does not appear to have been documented by a healthcare professional and the narrative states that "relevant tests/laboratory data was marked negative." The report is sparse and there is no description of other possible causes such as coffee ingestion, etc. One report is of a 63-year-old man who had also been taking pseudoephedrine and developed atrial fibrillation. His prior medical history is not presented (and, importantly, nor are his risk factors for atrial fibrillation). One case report is on a middle aged female smoker with a family

history of heart disease who developed a supraventricular tachycardia. She had an elevated white blood cell count, an elevated serum glucose and (in the absence of reference units) what appears to be an elevated TSH at 7.22. No relevant history was reported, so it is unclear as to whether this patient had arrhythmias in the past, consumed coffee, had fever, had underlying structural heart disease, etc. I do not find these cases compelling or informative. Tachycardias are common in the population and could have occurred for many reasons independent of timing of drug use. The clinical trial evidence, known pharmacology of FH in the presence of erythromycin and the millions of patient years of use indicate to me that it is safe to use macrolides with fexofenadine. To label otherwise without appropriate justification would be to inappropriately deny the clinical benefit of this combination to people who may need it.

6. Clinical Microbiology

Not applicable. There were no clinical microbiology data or reviews required for these three applications.

7. Clinical/Statistical-Efficacy

Fexofenadine is currently approved by prescription for SAR and for CIU. Nine adequate and well-controlled clinical trials supported its approval for these indications. (Refer to page 8 of Dr. Harry's review.) No new clinical efficacy trials were required to support the switch of fexofenadine to nonprescription status. Despite this, Sanofi-aventis submitted results of four Phase 3 studies in perennial allergic rhinitis (PAR) that they had previously conducted but had never submitted to the prescription NDAs. Two of the studies were pivotal trials using Allegra® 60 mg BID; two studies assessing doses higher than those currently approved (240 mg QD and 120 Mg BID) were considered supportive.

Dr. Anya Harry and Dr. Zhou reviewed the studies and concluded that they would be supportive of a PAR indication in the prescription setting. However, that is not relevant for the current OTC switch applications. The Sponsor submitted these studies with the switch applications to lend support for the language "indoor and outdoor allergies" to be allowed on the Principal Display Panel of the OTC product labels. However, OTC labeling does not distinguish between the SAR and PAR indications and already allows "indoor and outdoor allergies" on all OTC antihistamines approved for temporary relief of symptoms due to hay fever or other upper respiratory allergies, regardless as to whether they have been specifically approved for both SAR and PAR.

8. Safety

Dr. Hu conducted the safety review for FH. She concluded that the safety profile of fexofenadine is supportive of nonprescription marketing status and she recommended that the

applications could be approved. She noted that the data on FH do not demonstrate the potential for abuse or misuse.

The Integrated Summary of Safety is a review of the safety data from 136 clinical trials and from postmarketing adverse event reporting for FH and the combination FH/pseudoephedrine products. The applicant provided the following postmarketing data:

- Sanofi-aventis pharmacovigilence database (1996 – March 2010)
- Data mining of FDA AERS (1969 – 2009)
- Data mining of WHO UMC database (1967- 2009)
- Medical literature

Clinical Trial Safety Data Summary:
There were 18,361 subjects exposed to fexofenadine mono-product formulations in clinical trials and 6397 to placebo. Over 5000 adults were exposed to > 180 mg of fexofenadine/day in clinical trials.

The most common treatment emergent adverse events in the adult clinical trials were: headache, back pain, dizziness, stomach discomfort, and pain in extremity. The most common pediatric adverse events were: cough, upper respiratory tract infection, pyrexia, otitis media, vomiting, diarrhea, somnolence/fatigue, and rhinorrhea. The percentage of treatment emergent adverse events was similar in the FH and placebo groups. There were four deaths reported in the clinical trials, two in the placebo group and two in the FH group. One patient in the FH group who died did not actually take the fexofenadine and the other died as a result of bacterial pneumonia that was unrelated to the drug. There were 117 subjects with serious adverse events reported in the controlled clinical trials; 50 did not receive FH. There were two serious cardiac cases among the 18,361 patients, neither of which could be clearly attributed to the drug. In the pediatric population 6 months to 11 years of age at doses up to 60 mg BID, there were no particular safety risks identified in clinical trials.

Postmarketing Safety Review:
Dr. Hu concluded that the adverse event profile based upon data from 136 clinical trials in adults and children on fexofenadine (124 with the mono-product without pseudoephedrine), postmarketing data, and medical/scientific literature for FH supports the OTC switch of the three formulations. However, she recommended that several safety warnings be added to the Drug Facts Label (cardiac rhythm disturbance, liver, drowsiness, severe allergy and drug interaction). These warnings were not proposed by the Applicant and are not consistent with the prescription label. They are not included in labeling for the other second generation antihistamines, with the exception that cetirizine has a drowsiness warning. (Loratadine is labeled as being “nondrowsy” but has a warning that taking higher than recommended doses may cause drowsiness.)

Dr. Shetty disagrees with adding these five new warnings proposed by Dr. Hu. Dr. Raffaelli reviewed safety data for NDA 20-786 S-027 (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) and NDA 21-704 S-008 (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg) for the switch of two Allegra D products (with the same January 25, 2011 PDUFA data as the mono-ingredient NDAs). Dr. Raffaelli recommended that these two products be

switched to nonprescription marketing but did not recommend the need for the warnings that Dr. Hu recommended.

Cardiac Warning:
Dr. Hu recommends putting an arrhythmia warning on the Drug Facts Label for FH. This is based upon her assessment of 119 nonfatal cardiac serious adverse events identified in the postmarketing data (against the backdrop of 32 million patient years of use). She also highlights clinical trial cases. In her review, she acknowledges that there were other possible causes or confounding factors in these cases so causality could not be established but she still recommends labeling.

I disagree with how Dr. Hu reviews cases for attribution. She tends to look at numbers of cases and the timing of an adverse event related to drug use; this is fine, but provides a superficial analysis at best. What is missing are a lack of cogent medical discussions about the specific cases, consideration of the importance of background rates of conditions, a discussion of the likelihood of adverse events based upon known pharmacology and physiology of the drug, and the impact of confounding medical histories and drugs (or the lack of data about these things in the case histories).

Here are two examples from the clinical trials:

- Dr. Hu highlights the case of a 58-year-old patient who took FH 120 mg QD in a clinical trial. After 45 days on study medication he was seen in the hospital with chest pain and hypertension and was found to have a tachycardia. The ECGs and enzymes were normal. One month later he was hospitalized with dyspnea and cardiomegaly and the ECG shows sinus rhythm with left anterior "ventricular" block (the reporter probably meant to say "fascicular" block), poor R wave progression and ST-T wave changes. The way I interpret this case is that the patient probably had an undiagnosed myocardial infarction around the time of the first hospitalization. Dr. Hu says that this case is possibly related to FH. There was no additional history provided, for example, about risk factors for coronary artery disease (beyond his hypertension and his age). There was no information about a history of underlying structural heart disease or concurrent medications. Dr. Hu does not mention these things or consider in her text that they are important. Nor does she attempt to provide any potential explanation as to how the pharmacology of FH could lead to these cardiac problems when she links the drug "possibly" to the event.

- As a contrasting example, during one of the clinical trials there was a 73-year-old man cited in Dr. Hu's review who discontinued pharmacodynamic study M016455A/4136 because of an arrhythmia noted in the physician examination (atrial fibrillation). This patient was exposed only to placebo; he did not take FH. In this situation, Dr. Hu appropriately states that this event is not related to FH. However, based upon the way she assesses many of the cases, including the one of the 58-year-old man cited above, if this 73-year-old patient had taken FH rather than placebo, I think Dr. Hu would have said the case was possibly or probably related to FH.

These examples demonstrate the complexity of determining attribution. Consideration of background rate of the event is very important. The first patient appears to have had an MI complicated by congestive heart failure and had at least one risk factor besides his age since we know that he was hypertensive. This is, unfortunately, a common medical occurrence. I see no reasonable way to attribute his medical event to FH. Regarding the second patient, atrial fibrillation is a relatively common arrhythmia. A 2009 article on its incidence indicates that among 15,792 men and women aged 45 – 65 followed from 1987 – 2004, 1085 new cases were identified, with incidence rates of 3 – 6.7% per 1000 persons per year.[1] The rate increases with age.[1]

In her review of postmarketing events, Dr. Hu focuses on three cases in people less than thirty years of age in whom she feels that fexofenadine is a probable cause of death. One patient was a 15-year-old Canadian female who was taking FH 60 mg BID for a fly bite. She collapsed at a bar with friends and was found in a ventricular escape rhythm. Her toxicology screen and alcohol were reported to be negative and the autopsy did not report cardiac malformations. The second patient was an 18-year-old female who was taking depoprovera injections and fexofenadine. She had previously taken FH with no problems. She was diagnosed with Long QT Syndrome (LQTS) and had a family member with this syndrome as well. The third was a confounded case of a 26-year-old male with hypokalemia (2.6 mmol/l) taking prednisolone for allergies who took one dose of fexofenadine and developed a cardiac arrest.

These cases are interesting but not convincing of a relationship with the drug. Hypokalemia alone can be responsible for sudden cardiac death. The other two cases of sudden death may be due to genetic LQTS, but we are lacking pharmacologic plausibility that the FH triggered the deaths. We do not have the data that support that pharmacologically FH is a risk factor for LQTS because of its lack of interference with ionic channels in the heart. Furthermore, as is seen in the articles described in the next paragraph, the incidence of LQTS is large enough that one would expect to see a few instances of sudden death in young people across 32 million patient-years solely from the genetic variants causing LQTS. That is consistent with what the fexofenadine safety database shows.

The following published articles create a snapshot view of the incidence of LQTS and what happens in the youthful population. A study published last month assessing sudden cardiac death (SCD) in persons aged 1 – 35 years of age in Denmark (median age ~27 years) found that the incidence is 2.8 per 100,000 person-years. Excluding non-autopsied cases, the incidence was 1.9 per 100,000 person-years. The incidence was 0.8 per 100,000 for those who had an unexplained etiology of SCD after autopsy, which was 29% of autopsied sudden unexpected deaths. In this population, a primary arrhythmogenic cause of death was suspected due to conditions like LQTS and also the Brugada syndrome.[2] The disease prevalence of LQTS as a hereditary cardiac disease is estimated at close to 1 in 2,500 live births and the risk of sudden death as a first manifestation of LQTS is approximately 12%.[3] In another study the prevalence is suggested to be closer to 1 in 2,000. The most prevalent forms of LQTS are LQT1 and LQT2, which are due to mutations in potassium channels and LQT3 which is due to a sodium channel mutation. The clinical manifestations involve syncopal episodes which often result in cardiac arrest and sudden death and usually occur in conditions of either physical (LTQ1) or emotional stress (such as auditory stimuli in LTQ2) or at rest (in LQT3) in

otherwise healthy young individuals, mostly children and teenagers.[3] Of the patients who die with LQTS approximately 70% do so during their first arrhythmic episode.[4]

Terfenadine, the parent drug of FH, was withdrawn from the market because at high serum levels it prolonged the QTc interval and was associated with torsades de pointes (TdP) and the consequent fatal ventricular arrhythmias. This drug caused these cardiac problems by blocking cardiac potassium ion current I_{Kr} (hERG). QT prolongation with terfenadine occurred especially in the clinical setting of metabolic inhibition which led to accumulation of the terfenadine, the parent compound, not of fexofenadine, the metabolite. The cardiac issue with terfenadine (and a similar one with astimazole) has generated a heightened awareness of the potential for these adverse events in other second generation antihistamines and, consequently, they have been evaluated in detail for this concern.

The second generation antihistamines currently available, either by prescription or OTC do not appear to cause QT prolongation and have not been associated with similar cardiac concerns as terfenadine. As already discussed in Section 5 of this review, fexofenadine does not block potassium channels and is not metabolized significantly by the cytochrome P450 system. Thus, it is not expected to have cytochrome P450 metabolic drug interactions or QT prolongation-associated cardiac arrhythmias. It did not cause QT prolongation when given in doses up to 800 mg/day, 690 mg BID alone or when administered with known hepatic microenzyme inhibitors such as ketoconazole and erythromycin. The Division of Drug Risk Evaluation (DDRE) performed three reviews of adverse reactions associated with FH in post-marketing data in 2000, 2001, and 2006. The first of these reviews was to help determine whether FH would be an appropriate drug for OTC use. Although arrhythmias were seen in some postmarketing cases, the reviewers were unable to conclude that there was evidence of a direct association between this drug and those arrhythmias. This is because of pre-existing cardiac disease, thyroid disease and/or concomitant medications that could have been responsible.

For these three fexofenadine switch applications, DNCE sent a consult to the QT group in DCRP to again review the potential for any cardiac concerns. DCRP evaluated data on possible QTc prolongation in all controlled clinical studies, drug interaction studies, and postmarketing databases. Initially, DCRP recommended that a thorough QT (TQT) study be performed to rule out small changes (< 10 msecs) in QT because this could not be excluded in the absence of a TQT assessment as defined by ICH E14. DCRP concluded, though, that the clinical trials data appears sufficient to exclude large effects on the QT interval, that no large effects on QTc and other ECG intervals have been identified in the drug-drug interaction studies, and that most of the postmarketing cases were confounded. Even though there was a temporal association of drug use in some of them, insufficient information was available to make an assessment.

This DCRP recommendation and the clinical rationale for it was discussed at a meeting on October 25, 2010 with the Office of Center Director (Dr. Robert Temple), DNCE, DPARP, ODE IV (Dr. Ganley), and ODE II (Dr. Rosebraugh). After consideration of the data and the discussion at that meeting, the Office of the Center Director asked the QT group in DCRP to reassess their recommendations. DCRP considered all data available (including data in

animals, literature, clinical trials and the postmarketing experience) and wrote an addendum to their review. In the addendum they concluded that "the non-clinical data and clinical information from the literature, the clinical trial data and the postmarketing experience when considered in total provides reasonable reassurance that proarrhythmic liability for fexofenadine is negligible and a TQT assessment is not required for fexofenadine." The review also comments that although TdP is a rare event and hard to document, it was clearly detected with drugs like terfenadine and cisapride. This is not the case with fexofenadine. DCRP did not recommend that the OTC label for FH include a cardiac warning.

At the request of DNCE, the Office of Surveillance and Epidemiology (OSE) Division of Pharmacovigilance (DPV) reviewed serious events reported with FH (QT prolongation, Torsade de Pointes (TdP), liver failure, and deaths). DNCE also requested a data mining analysis of the FDA Adverse Event Reporting System (AERS) database to confirm the Sponsor's analysis of potential postmarketing safety signals. The new postmarketing reports received by the FDA since the last OSE review on FH are consistent with all postmarketing reports for fexofenadine in AERS, which did not reveal new safety issues. No pattern of causal events attributable to FH or new safety issues with FH were identified with the outcome of death.

OSE found that there were 49 cases of serious QT prolongation and TdP reported. OSE concluded that some cases are suggestive, but not conclusive of a direct association with FH and serious QT prolongation or TdP because cases were confounded by concomitant medications, significant cardiac disease, or were uninformative because of incomplete information.

Dr. Hu noted that the Netherlands had a cardiac arrhythmia warning on their labeling for FH. Further inquiry into this established that the Netherlands and some other European countries have a "tachycardia" and "palpitations" warning as class labeling on all antihistamines as rarely reported events. The Netherlands, as it turns out, reconsidered all available nonclinical and clinical data in 2004 and removed these warnings from FH. Considering the totality of the data and the different reviews, I agree with Dr. Shetty that the cardiac warning suggested by Dr. Hu is not supportable and should not appear on the FH Drug Facts labeling.

Liver Warning:
In the clinical trials in 18,361 patients, no drug-related liver toxicity occurred. Also in PK study PJPR0021, FH 80 mg was given to 17 patients with various degrees of liver failure and it was found that liver impairment did not impact the PK of FH.

Cases of liver failure attributable to FH were not identified in the postmarketing databases; the OSE reviewers concluded that no causal association with FH was established in cases suggestive of liver toxicity. Most cases of liver toxicity contained additional risk factors or concomitant potential medications, originated outside of the US, and described varied patterns of liver injury (ranging from cholestatic (1 case), hepatocellular (1), eosinophilic hepatitis (2), or not assessable (2). Data mining did not elucidate new signals.

Dr. Hu identified 59 postmarketing cases of nonfatal serious liver AEs. All events were reversed. The vast majority were confounded by medical conditions, other medications and/or alcohol so attribution was not clear for FH. Of the 59 cases, she identified 6 that involved FH and no other drugs in which she thought FH was probably the cause.

Other postmarketing safety reviews on FH performed in 2004, and 2005 did not suggest a hepatotoxicity signal. The prescription label does not list liver AEs in the postmarketing section.

After considering all of this information, I find that I disagree with Dr. Hu that a liver warning is needed and agree with Dr. Shetty that a liver warning should not appear on the Drug Facts Label. Considering the vast patient experience with FH any association with liver AEs appears to be nil or at most extremely rare and non-serious.

Drowsiness Warning:
Dr. Hu thinks that this product could carry a "nondrowsy" statement like loratadine, but that consumers should also be informed that some people may be sleepy when using the drug and should use it with caution if driving or operating with machinery. Dr. Shetty disagrees with this recommendation and so do I. My reasoning follows.

Of any of the OTC antihistamines both first and second generation), it appears that FH may be the safest regarding drowsiness and somnolence (< 2% incidence in pivotal clinical trials with no dose response). Loratadine at the approved OTC dose of 10 mg per day was associated with drowsiness in up to 8% of clinical trial subjects; the incidence increased with escalating dosing. Cetirizine at approved OTC dosing caused drowiness in a larger percentage of people (14% compared to 6% placebo) than loratadine and does not carry the "nondrowsy" statement in OTC labeling.

Published literature suggests that FH is no different than placebo in terms of somnolence and is better than several other antihistamines with regard to cognitive and psychomotor function. In her review of the medical literature (see page 145 of the review), Dr. Hu describes a safety study (Tashiro et al. 2004) that noted that the change in reaction time from baseline with fexofenadine was not significantly different from placebo, but was significant for cetirizine ($P = 0.017$). Dr. Hu also describes an earlier Positron Emission Tomography study by the same author in 2002 showing that, during psychomotor testing, almost no H1 receptors in the cerebral cortex were occupied by FH while approximately 20% - 50% of H1 receptors were occupied by cetirizine ($P < 0.01$). The remainder of her literature review is consistent with the lack of impact of FH on cognitive function. She even describes one article (Vermeeren et al, 2005, page 145 of the review) that found that FH did not impair driving performance.

My interpretation of the data is that the weight of evidence suggests that fexofenadine, unlike many antihistamines, does not cause drowsiness. Further, if it does in some rare instance, the data indicate that it is not of clinical significance.

Hypersensitivity:
Dr. Hu recommends putting an expanded allergy warning on this product. The label would otherwise have the standard OTC drug allergy warning. The standard warning states, "Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away." Dr. Shetty does not think the data support an expanded allergy warning.

Based upon 144 cases of possible or probable serious postmarketing hypersensitivity reactions to FH, Dr. Hu selected 56 to present in the review. I agree with Dr. Shetty that the reported cases lacked adequate detail to assess causality in these already allergic people who are taking FH for their allergic conditions. Additionally, many cases were confounded by other medications. To be sure, people can develop allergies to any medication, even those indicated to treat allergies. The incidence of substantial allergic reactions is extremely low considering the widespread use of FH. Actually, considering the small number of reported cases among the 32 million patient-years of use, it seems that significant allergic reactions with FH may be rarer than for many commonly used medications. This is comforting to me considering that the population using the product is an allergic population from the "get go."

As Dr. Shetty discusses in her review, it is important to select the most important information to write into the Drug Facts label. OTC labels do not have the "real estate" to list every conceivable rare adverse event that may possibly (or possibly not) occur with a drug. I agree with Dr. Shetty. We try to put the most important information on the label, information that will lead to proper and safe use. We cannot overwhelm the consumer with extraneous information because, it has been shown, that the more writing that is on the label, the less it is apt to be read. FH is a drug with an excellent safety profile demonstrated over substantial time and extent of use and I think Dr. Hu's suggested warnings would make it appear much less safe than it is and are unjustified. I agree with Dr. Shetty's and Dr. Raffaelli's interpretation of the safety data and with what would constitute appropriate labeling for OTC fexofenadine.

9. Advisory Committee Meeting

No advisory committee meeting was convened for this switch application. FH is the third of the 2nd generation antihistamines to be presented in application to switch OTC and the applications did not raise new controversial issues. The two previous products (loratadine and cetirizine) are approved for nonprescription marketing and have been available without a prescription for several years. In 2001, a Joint Advisory Committee on Nonprescription and Pulmonary and Allergy Drug Products concluded that the second generation antihistamines (including loratadine, cetirizine and fexofenadine) had a risk/benefit profile favorable for OTC marketing. In 2002, another joint advisory committee found that second generation antihistamines could be approved nonprescription for hives.

10. Pediatrics

Fexofenadine has been extensively studied (PK, safety, efficacy) and used in the pediatric population down to the age of six months. FDA previously granted a waiver for studies in infants < 6 months of age because the conditions for which the product is indicated do not

exist in this age population. The clinical trial and postmarketing data in the pediatric population support that FH is safe and effective for OTC use for allergic rhinitis down to the age of 2 years and for hives down to the age of 6 years.

These switch applications do not trigger the need to address the Pediatric Research Equity Act. (Refer to the e-mail from Donna Katz from the Office of the Chief Counsel dated 01/13/2011.)

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The sponsor will be marketing several different packages for each dosage form and for each indication. The Division of Medication Errors Prevention and Analysis conducted several reviews for these applications. In their final review, dated 12/13/2010, they concluded that the four proprietary names proposed by the applicant for the OTC fexofenadine products are acceptable and that the labeling does not need improvement from their perspective. The four approved names follow: Allegra® Allergy, Children's Allegra® Allergy, Allegra® Hives, Children's Allegra® Hives.

Dr. Ayana Rowley and Marina Chang reviewed the labeling and negotiated several changes to the labels with the sponsor. The sponsor complied with the recommendations and provided labeling that is acceptable for approval as stated in Dr. Rowley's final labeling review dated January 13, 2011.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA 201-613, NDA 21-909 S003, and NDA 201-373 switch applications should be approved.

- Risk Benefit Assessment

All reviewers for this application recommended approval of the prescription to nonprescription switch. Fexofenadine has been demonstrated to be safe and effective for the treatment of symptoms of allergic rhinitis and hives in well over a hundred clinical trials. As detailed in Section 8 above, no new safety signals were noted during the review of the switch applications. The extensive worldwide postmarketing experience with fexofenadine (as a prescription and also as a nonprescription product) and the medical literature support the safety of this second generation antihistamine for nonprescription availability.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

References:

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3. Crotti L, Celano G, Dagradi F Schwartz P: Congenital Long QT Syndrome. Orphanet J Rare Dis 2008 Jul 7;3:18.
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/s/

ANDREA LEONARD SEGAL
01/22/2011