CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 20, 2010
From	Daiva Shetty, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	201-613 21-909, S-003 201-373
Applicant	Sanofi Aventis
Date of Submission	March 26, 2010
PDUFA Goal Date	January 26, 2010
Proprietary Name / Established (USAN) names	Allegra® Allergy (fexofenadine hydrochloride), Allegra® Hives, Children's Allegra® Allergy, and Children's Allegra® Hives
Dosage forms / Strength	Tablets 30 mg, 60 mg, and 180 mg Orally disintegrating tablets 30 mg Oral suspension 30 mg/5 ml
Proposed Indication(s)	1. temporary relieves these symptoms due to hay fever or other upper respiratory allergies: a. runny nose b. sneezing c. itchy, watery eyes d. itching of the nose and throat 2. reduces hives and relieves itching due to hives (urticaria)
Recommended:	Approval

1. Introduction

The three NDA submissions propose to switch from prescription to over-the counter (Rx-to-OTC) status three different formulations of fexofenadine hydrochloride (hereafter referred as fexofenadine): tablets, orally disintegrating tablets, and oral suspension.

The proposed OTC indications are: 1) the temporary relief of symptoms due to hay fever or other upper respiratory allergies, 2) the reduction of hives and the relief of itching due to hives. The targeted population and dose are dependent on the specific formulation. The tablet and orally disintegrating tablet (ODT) formulations will be labeled for adults and children ≥ 6 years of age. The oral suspension will be labeled for adults and children ≥ 2 however, the indication for treatment of itching due to hives, will be for adults and children ≥ 6 years of age. Fexofenadine oral suspension for pediatric patients younger than 6 years of age with chronic idiopathic uricaria (CIU) will remain as prescription use under NDA 21-963.

2. Background

Fexofenadine was first approved in the United States on 7/25/1996 as a capsule formulation at the dose of 60 mg BID. Subsequently, other formulations and dosing regimens were developed and approved: 30 mg, 120 mg, and 180 mg tablets, 30 mg orally disintegrating tablet (ODT), and 6 mg/ml oral suspension. There are several generic versions of fexofenadine currently available. Fexofenadine is also approved in several foreign countries since 1996. Fexofenadine is indicated for the treatment of seasonal allergic rhinitis (SAR) symptoms and CIU. In addition, fexofenadine has been approved in combination with pseudoephedrine in two different strengths; these combination products are also proposed for OTC marketing and reviewed separately under NDAs 20-786 and 21-704.

Several meetings have been held to discuss the overall suitability of fexofenadine and other 2nd generation antihistamines for OTC use. In May 2001, the Joint Advisory Committees on Nonprescription Drug Products and Pulmonary and Allergy Drug Products concluded that fexofenadine demonstrated a safety profile suitable for use in an OTC setting. In addition, a Joint Advisory Committee Meeting on Nonprescription Drug Products and Pulmonary and Allergy Drug Products was held on April 22, 2002. At this meeting, indications for management of urticaria were considered suitable for OTC.

A pre-IND meeting was held on December 14, 2009 between the sponsor and FDA to discuss the overall submission strategy to support the full Rx-to-OTC switch of the proposed Allegra® and Allegra-D® products.

3. CMC/Device

CMC information for the three NDAs was reviewed by three different CMC reviewers; each of three reviews will be discussed separately.

Dr. Caroline Strasinger has reviewed CMC information for NDA 201-613 which includes 30 mg, 60 mg, and 180 mg tablets (see her review in DARRTS signed on 11/4/2010). All three tablet formulations have been approved and marketed as Rx drugs and no new information pertaining to the drug substance or the drug products has been submitted to this NDA. The following changes for the purposes of OTC marketing have been made: new packaging configuration for the high density polyethylene (HDPE) bottles and the addition of a peel push-through aluminum foil lidding to add the child-resistant functionality to the blister packs. Stability data to assure strength, purity, and quality of the drug products were submitted as well. The reviewer found the data provided sufficient and acceptable. Since manufacturing facility inspection was not completed at the time of her review, she could not recommend approval until an "Acceptable" recommendation is made by the Office of Compliance.

CMC data for NDA 21-909 (b) (4) (30 mg orally disintegrating tablet) have been reviewed by Dr. Sharon Kelly (see her review in DARRTS signed on 11/24/2010). The reviewer states that this submission does not propose any new changes to previously approved CMC information, including drug substance and final drug product manufacturers, container closure system, and expiration dates. The reviewer recommended an Approval action pending acceptable environmental assessment and facility inspection recommendations.

The third NDA 201-373, for the 6 mg/mL oral suspension of fexoxenadine has been reviewed by Dr. Minerva Hughes (see her review in DARRTS signed on 11/22/2010). This reviewer also found that the sponsor provided sufficient information to assure the identity, strength, purity, and quality of the drug product; however, she did not recommend approval of the NDA until the manufacturing site is evaluated and found to be acceptable by the Office of Compliance.

None of the three CMC reviewers recommended any Phase 4 commitments.

An environmental assessment review has been done by Dr. Raanan Bloom (see review in DARRTS entered 11/30/10). The reviewer assessed that no adverse effects are expected from the introduction of fexofenadine into environment and recommended a Finding of No Significant Impact (FONSI) classification.

Report from the Office of Compliance on the manufacturing site inspection is pending at the time of this review. This is the only outstanding CMC issue for all three NDAs.

4. Nonclinical Pharmacology/Toxicology

All preclinical data were submitted to the original prescription fexofenadine NDAs. No new nonclinical pharmacology and toxicology studies were conducted in support of the switch applications because of the extensive data, including post-marketing safety data already available on prescription fexofenadine. Dr. Li assessed previously reviewed data for the Rx-to-OTC switch of fexofenadine and concluded that there are no outstanding approvability issues from the pharmacology/toxicology perspective. See her review entered in DARRTS on 11/23/10.

5. Clinical Pharmacology/Biopharmaceutics

No specific clinical pharmacology studies have been conducted in support of the Rx-to-OTC switch fexofenadine applications. A total of 36 biopharmaceutics studies were conducted in the adult population. A total of 14 pharmacokinetic studies were conducted. Of these studies, 11 were in the adult population, which consisted of subjects who were 12 years of age and older, and 3 were in the pediatric population, which consisted of subjects who were between 6 months and 11 years of age, inclusive. A total of 34 pharmacodynamic studies were conducted. Of these studies, 31 were in the adult population and 3 were in the pediatric population.

Among the clinical pharmacology studies, there were 13 study reports in the current submission that have not been previously reviewed by FDA. They were submitted mainly for the purpose of the overall safety assessment. Dr. Agrawal have reviewed these studies and concluded that information provided does not warrant new labeling changes (see his review entered in DARRTS on 11/22/10). Following is the summary of the fexofenadine clinical pharmacology data:

- Aluminum and magnesium containing antacids, and fruit juice decrease fexofenadine's AUC as well as Cmax.

- Fexofenadine exposure is much greater in older subjects (> 65 years old) and those with impaired renal function.
- Pharmacokinetics in subjects with hepatic impairment does not differ from that in healthy subjects.
- There are no clinically significant gender differences.
- Co-administration with either ketoconazole or erythromycin increases plasma levels of fexofenadine, however the increase is within the range of plasma levels seen in controlled clinical trials.
- Only the orally disintegrating tablet (ODT) formulation shows a food interaction; i.e., high fat meal decreases the bioavailability of fexofenadine by approximately 50%.

The reviewer recommended the following information from the Rx label to be carried over to the OTC label: consult a doctor before use for patients with kidney disease, those over 65 years of age, not to take the drug at the same time as aluminum or magnesium containing antacids and fruit juice, and to take ODT on an empty stomach. These warnings have been incorporated into the label, and I agree that they need to be listed.

The pharmacology reviewer did not recommend adding a warning about the drug-drug interactions with ketoconazole or erythromycin. Rx label does not recommend dose adjustment in this situation as well. Dr. Hu (medical officer reviewing safety), however, recommended to list on the label that consumers should ask a doctor before use of fexofenadine if they are taking erythromycin, azithromycin, or clarithromycin. The sponsor provided data from specific clinical trials where subjects were given fexofenadine 120 mg bid for 7 days concomitantly with erythromycin or ketoconazole. No serious adverse events (SAEs), laboratory, or ECG changes were observed in these trials. Dr. Hu recommended the above warning based on a total of 17 postmarketing SAE cases where fexofenadine interactions with microlides were suspected as a possible cause for an AE; of those 17 cases, Dr. Hu selected 5 cardiac SAE cases and 2 deaths. I reviewed all five SAE case reports, and found them to be not convincing. The cases did not provide enough details on medical histories, concomitant medications, or physical examinations, and also had other confounding/risk factors. Most reported transient tachycardia and all resolved. The two death cases do not have sufficient details to implicate fexofenadine as a cause for death: one case involved multiple other concomitant medications in addition to possibly undiagnosed congenital long QT, the second case did not provide enough details on the order of events to assess the relationship between the drug intake and the cause of death. Based on my assessment, the drug interaction warning with macrolides or ketoconazole is not warranted.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Refer to the review dated 11/23/10 by Dr. Anya Harry, medical officer in the Division of Pulmonary Allergy and Rheumatology Products and the 10/26/10 statistical review by Dr. Zhou from the Division of Biometrics II.

No new clinical trials were required to support the application due to the extensive preapproval and subsequent post-approval database for fexofenadine. However, the Sponsor submitted the results of four Phase 3 perennial allergic rhinitis (PAR) studies conducted previously but not submitted with the earlier NDAs. These trials were not required for approval of the OTC switch application but were submitted to further support the nonprescription indication of indoor and outdoor allergies to be included on the principal display panel (PDP). These studies include two pivotal trials that studied the approved doses (PJPR0057 & M016455M/3097) and two supportive trials that studied doses higher than the approved ones (M016455M/3001 & M016455M/3002).

The two pivotal studies showed evidence that treatment with Allegra® 60mg BID significantly reduced PM reflective Total Symptoms Score (rTSS) which included runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat compared to placebo in patients 12 years of age and older with PAR after four weeks of treatment. Study M016455M/3097 showed that Allegra® 180mg QD numerically improved the AM instantaneous Total Symptoms Score (iTSS) after eight weeks treatment. There is some evidence that treatment with Allegra® 180mg QD reduced PM reflective Total Symptoms Score (rTSS) compared to placebo after four weeks of treatment. Exploratory analysis on Studies PJPR0057 and M016455M/3097 suggest that Allegra® 60mg BID and 180mg QD improved the 24-hour reflective Total Symptoms Score (24-hrs rTSS) after four weeks of treatment.

The two supportive trials were not reviewed in detail because they studied fexofenadine doses that are not proposed for marketing (240 mg QD and 120 mg BID). They demonstrated that the higher doses improve symptoms of PAR.

Dr. Harry concluded that these trials would be supportive of a PAR indication under a prescription NDA, but since the distinction of SAR and PAR does not translate to the OTC labeling, the use of the terms “Indoor and outdoor” allergies has been permitted. She recommended approval.

There are no unresolved or outstanding efficacy issues.

8. Safety

Dr. Linda Hu has conducted overall safety review for the fexofenadine single ingredient NDAs (see her review entered in DARRTS on 12/2/2010). Dr. Hu concluded that the adverse event profile of fexofenadine from controlled clinical trials, postmarketing pharmacovigilance, and the literature is supportive of safety and recommended an approval for OTC marketing. However, she also recommended several specific safety warnings, i.e. cardiac, liver, drowsiness, severe allergy, and drug interaction. I disagree with these additional warnings. My reasons for disagreement are outlined in the Section 13 of this review.

Fexofenadine’s safety has been established through the extensive clinical trial testing as well as over 10 years of worldwide postmarketing experience. The Integrated Summary of Safety was primarily based on analyses of safety data from 136 clinical studies using various mono-

products and fixed dose combination products. Summary of the exposure data from the clinical studies is presented below.

Type of studies	Population	Number of subjects exposed	Mean duration of exposure (days)
PK	Adults	1174	16.62
PD	Adults	1800	6.63
PK	Pediatrics	214	4.83
Pivotal controlled	Adults	3874	16.62
Other controlled	Adults	8263	28.79
Studies PJPR0066/77	Adults/Pediatrics	646	15.51
Other controlled	Pediatrics	986	15.03
Long-term safety	Adults	1109	259.63

A total of 18361 subjects were exposed to fexofenadine during the drug development. In general, fexofenadine was well tolerated in the clinical trials. The most common treatment emergent adverse events in adult clinical trials were: headache, back pain, dizziness, stomach discomfort, and pain in extremity. The most common adverse reactions reported in pediatric trials were: cough, upper respiratory tract infection, pyrexia, otitis media, vomiting, diarrhea, somnolence/fatigue, and rhinorrhea.

The sponsor submitted postmarketing spontaneous adverse event information for fexofenadine and the combination products of fexofenadine and pseudoephedrine from the following sources: the sponsor's Global Pharmacovigilance and Epidemiology department up to 30 September 2009; the FDA AERS database through the Freedom of Information Act entered by the FDA from 1 February 1969 (the beginning of the FDA AERS database) to 30 June 2009; the WHO UMC database from 01 January 1967 (the beginning of the WHO UMC database) to 31 September 2009; and medical literature.

Fexofenadine is currently marketed in more than 100 countries worldwide and has not been withdrawn from any foreign market for safety or other reasons. Based upon available worldwide sales data for fexofenadine from the third quarter of 1997 through the second quarter of 2009, inclusive, approximately 32.05 million patient-years of exposure have occurred in the postmarketing period. Since initial approval, a total of 14,572 spontaneous reports involving 24,945 adverse events have been reported to the Sponsor from worldwide sources. These reports were most commonly received from the US, Japan, and Canada. More than 90% of the received cases were non-serious. Most common postmarketing AE reports (i.e., lack of efficacy, headache, backache, dizziness) are consistent with those reported in clinical trials.

Fexofenadine is a histamine H1-receptor antagonist and like any other antihistamines is not a scheduled drug under the U.S. Drug Enforcement Administration. In pre-clinical studies, it did not exhibit analgesic activity or effects on behavior. During clinical development program there were no drug abuse, dependency, withdrawal, or overdose observed. The analysis of

several postmarketing databases did not suggest any potential for drug abuse or dependence associated with fexofenadine.

Overall, fexofenadine has a favorable safety profile for over-the-counter marketing.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held to discuss a fexofenadine Rx-to-OTC switch during the current review cycle. However, the Joint Advisory Committees on Nonprescription and Pulmonary and Allergy Drug Products in 2001 concluded that the second generation antihistamines, which include fexofenadine, demonstrate a risk/benefit profile suitable for an OTC antihistamine. In addition, a Joint Advisory Committee Meeting on Nonprescription Drug Products and Pulmonary and Allergy Drug Products held on April 22, 2002, discussed and found suitable for OTC urticaria indication.

10. Pediatrics

Fexofenadine has been extensively studied in pediatrics during the Rx drug development stage. The sponsor has conducted pharmacokinetic, safety, and/or efficacy studies in pediatric patients 6 months to less than 6 years of age as part of written Requests for Pediatric Exclusivity. FDA granted a waiver under the Pediatric Research Equity Act (PREA) for studies in patients younger than 6 months of age since the diseases for which fexofenadine is indicated do not exist in patients 0-6 months of age. Since the current applications do not seek an approval for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, the PREA is not triggered. During the Type B pre-IND meeting held on December 14, 2009 between DNCE and the sponsor, FDA stated that the fexofenadine switches will be exempt from any required studies in pediatrics under the PREA. Therefore, the sponsor did not request a waiver for pediatric studies for these applications.

The sponsor proposes to label OTC products for hives in children 6 years of age and older, and for hay fever and other respiratory allergies in children 2 years of age and older. Directions for the treatment of CIU for younger ages will remain under the Rx labeling. OTC label will direct consumers to ask a doctor for dosing directions in those populations. This is consistent with the labeling for other OTC antihistamines and it is acceptable.

11. Other Relevant Regulatory Issues

There were no specific studies required to support these fexofenadine Rx-to-OTC switch applications. Therefore, no DSI inspections were initiated.

12. Labeling

The sponsor intends to market several different configurations of packages for each dosage form (tablet, ODT, suspension) and each indication (allergies vs. hives). Dr. Ayana Rowley reviewer from the Division of Nonprescription Regulation Development conducted a labeling review (entered in DARRTS on 12/3/10). Several changes to the initially proposed OTC labels for fexofenadine have been negotiated with the sponsor during the NDA review cycle to reduce the potential for medication errors. Final labeling is pending at the time of this review.

Proprietary names for the proposed products have been reviewed by the Division of Medication Errors Prevention and Analysis and were found to be acceptable.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend an Approval regulatory action.

- Risk Benefit Assessment

Based on the data submitted, fexofenadine HCl has a favorable safety profile.

Special safety concerns and disagreements with a primary reviewer of safety

Dr. Hu raised several safety concerns and recommended several specific warnings which I disagree with:
Stop use and ask a doctor if
- you develop fast or irregular heart beat or if you feel faint. This drug may rarely cause serious heart rhythm disturbances
- an allergic reaction to the product occurs (for example, swelling of the tongue or throat, or trouble breathing). Seek medical help right away.
- skin or eyes turn yellow or if you have dark urine

Ask a doctor before use if
- you have or ever had heart disease, since this kind of medicine may lead to a fast or irregular heart beat
- you are taking certain antibiotics (erythromycin, azithromycin, or clarithromycin)

In addition, Dr. Hu disagrees with the proposed "Nondrowsy" statement on the PDP.

My evaluation and recommendations on no need for the above proposed warnings are discussed below.

1. Cardiac warning.

Dr. Hu recommended a warning "Stop use and ask a doctor if you develop fast or irregular heart beat or if you feel faint. This drug may rarely cause serious heart rhythm disturbances. Ask a doctor before use if you have or ever had heart disease, since this kind of medicine may lead to a fast or irregular heart beat." Her recommendation is based on the119 non-fatal cardiac serious AEs identified in the postmarketing safety databases. She also acknowledges that there were other possible causes or confounding factors present so a definite causal relationship cannot be established.

Dr. Hu identified a cardiac warning (…this medicine may lead to a fast or irregular heart beat) in the Netherlands and harmonized European Union Patient Leaflet and requested the sponsor

to submit data that was used to support this warning. The sponsor explained that the warning is not specific to fexofenadine, rather it is a class labeling contained in all antihistamine labels. Two adverse events related to cardiovascular events — "tachycardia" and "palpitations" — are listed in some of the European labels as rarely reported events. However, the Dutch Medicine Evaluation Board reconsidered all available preclinical and clinical data in 2004 and no longer required these two warnings.

Since fexofenadine is an active metabolite of terfenadine, a high index of suspicion for cardiac events has been raised in the past. Reviews of postmarketing databases focusing on cardiovascular disorders and deaths, supraventricular arrhythmias, and ventricular arrythmias have been conducted in 2000, 2001, and 2006. The evidence was inconclusive to establish a direct association with cardiac adverse events. In addition, data in the past have shown that fexofenadine does not inhibit the main subunit of the HERG K+ channel, which is responsible for cardiac arrythmias with terfenadine.

To conduct more in depth analysis of the relationship between fexofenadine and cardiac event, DNCE requested consults from the Office of Surveillance and Epidemiology (OSE) and the Division of Cardiovascular and Renal Products (DCRP).

OSE reviewed all postmarketing reports of adverse events associated with fexofenadine submitted to AERS as of 7/20/2010. OSE concluded that AEs reported are suggestive, but not conclusive, of a direct association with fexofenadine and serious QT prolongation or Torsade de Pointes.

DCRP QT Interdisciplinary Review Team (IRT) generated three reviews during this NDA review cycle (see reviews by Dr. Suchitra Balakrisnan entered in DARRTS on 8/9/10, 11/3/10, and 11/17/10). DCRP evaluated data on possible QTc prolongation effects in all controlled clinical studies, drug interaction studies, and postmarketing databases and concluded: 1) small effects (<10 ms) on the QT interval cannot be excluded in the absence of a TQT assessment, 2) the clinical trials data appears sufficient to exclude large effects on the QT interval, 3) no large effects on QTc and other ECG intervals have been identified in the drug-drug interaction studies, 4) most of the postmarketing cases were assessed as confounded, even though there was a temporal association in some of them, insufficient information was available to make an assessment. Based on the available data, in their initial 8/9/10 review DCRP recommended that the sponsor conduct a TQT study as defined by ICH E14 to rule out small effects on QTc interval (<10 ms). To discuss the potential implications of the QT-IRTs recommendation, a joint meeting was held between the QT-IRT, DNCE, DPARP, ODE II, ODE IV, and the Office of the Center Director on October 25, 2010. DNCE has expressed concerns that the recommendations affect the OTC switch NDAs for Allegra-D -12 hour and -24 hour products, both currently under review, it also impacts the other second generation antihistamines that are OTC (loratadine and cetirizine) as well as the second generation antihistamines that are prescription. After consideration of the data, the Office of the center Director asked the QT-IRT to re-assess their recommendations. DCRP reassessed all available non-clinical data and clinical information from the literature, the clinical trial data, and the post-marketing experience and concluded that data when considered in total provides reasonable re-assurance that pro-arrhythmic liability for fexofenadine is negligible and a TQT assessment is not

required for fexofenadine. DCRP did not recommend any additional cardiac warnings for fexofenadine. I agree with their conclusion and do not recommend a cardiac warning.

2. Liver warning.

Dr. Hu recommended including signs and symptoms of liver toxicity.

There were no drug-related liver toxicity events reported in over 18 thousand subjects enrolled in clinical trials. Several clinical trials monitored liver function tests (LFTs) and did not find any meaningful differences between the baseline and end of treatment LFTs in any of the treatment regiments. One PK study (PJPR0021) specifically evaluated PK of fexofenadine 80 mg in 17 subjects with various degrees of liver failure and found that liver impairment had little effect on the PK of fexofenadine.

Dr. Hu identified 59 cases of nonfatal hepatic serious AEs with probable or possible causality in the post marketing database. Many of those cases did not have enough information to assess causality, were confounded by underlying medical conditions and/or the use of concomitant medications, alcohol abuse, or intentional overdose. All of these factors could have contributed to the events. There were no re-challenge cases reported. All events were reversible. The mechanism of liver toxicity is not clear. Out of the 59 hepatic events, I found only a few that could have been possible hypersensitivity reactions.

Rx label does not contain warnings for patients with liver disease, nor does it list liver AEs in a postmarketing section of the label. Several postmarketing safety reviews were performed to assess hepatoxocity (by Dr. Joyce Weaver in 2004, Dr. Renan Bonnel in 2005, Melinda Wilson, PharmD in 2010, and Dr. Ryan Raffaelli in 2010); none of them found an increased signal for hepatotoxicity-related events. OTC labels are directed to consumers to inform them about the safe and effective way to use a product. In my opinion, there is no place on OTC labels to list every possible extremely rare adverse event. Unless the policy on OTC labeling change so that other drugs have to include rare postmarketing events with no clear relationship to the drug, liver or cardiac warnings should not be listed on fexofenadine OTC labels.

Based on my assessment of the data from clinical trials and extensive marketing history, liver toxicity warning for fexofenadine is not warranted.

3. Drowsiness warning.

Dr. Hu disagrees with the "Nondrowsy" statement on the proposed OTC PDP. She states that it is acceptable for a "Nondrowsy" claim to be made on the label, but consumers should also be informed that sleepiness can occur when using the drug, so they should use with caution if driving or operating machinery. I disagree with this recommendation.

Fexofenadine is a second generation antihistamine. It is considered the least drowsy antihistamine, and sometimes is classified as a third generation antihistamine. In laboratory animals, no anticholinergic or α1-adrenergic blocking efforts were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

In the pivotal controlled clinical trial database, somnolence was reported in less than 2% of subjects, there was no dose response observed. In fact, incidence of somnolence in the two highest dose categories (>180-360 mg and ≥360 mg) was two times lower than that in the lowest dose categories. In addition, several published studies (see p. 145 of Dr. Hu's review) found that fexofenadine is no different than placebo, and much better than several other antihistamines in its effects on cognitive and psychomotor functions.

Loratadine, another second generation antihistamine already available OTC, is allowed to carry "nondrowsy" claim with a qualifier, that a higher dose may cause drowsiness. Incidence of somnolence for loratadine in clinical trials was upto 8% with a clear dose response, which is not the case for fexofenadine.

For all of these reasons, I recommend that the "Nondrowsy" statement stay on the PDP as proposed by the sponsor.

4. Drug-drug interaction with macrolide antibiotics.

This issue was discussed in section 5 of this review.

5. Hypersensitivity.

Dr. Hu recommended expanding the proposed standard allergy warning to include signs and symptoms of anaphylactic shock. Her recommendation is based on the 144 of serious hypersensitivity reactions in the postmarketing database. Again, the reported cases did not have sufficient details to assess causality and many were confounded by the use of concomitant medications.

As with any other medication, it is always possible that some people may develop allergy to fexofenadine. These allergic events are rare and do not seem to occur at a higher rate than with any other drug. In addition, fexofenadine is indicated for the treatment of allergies. If the label provides more elaborate warning, it may unnecessarily discourage consumers from taking an effective and safe medication for their allergies. Therefore, in my opinion, a general allergy warning as proposed by the sponsor is sufficient.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

None.

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/s/

DAIVA SHETTY
12/21/2010