CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b)(1)
Application Number(s)	NDA 201-613 (fexofenadine tablets: 30, 60, 180 mg) NDA 201-373 (fexofenadine oral suspension 30 mg/5 mL) NDA 21-909 (fexofenadine orally disintegrating tablets, 30 mg)
Priority or Standard	Standard
Submit Date(s)	March 25, 2010
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Division / Office	DNCE/ODE IV
Reviewer Name(s)	Linda Hu
Review Completion Date	
Established Name	Fexofenadine HCl
(Proposed) Trade Name	ALLEGRA
Therapeutic Class	Antihistamine (selective H1-receptor antagonist)
Applicant	Sanofi-Aventis
Formulation(s)	Tablets (30, 60, 180 mg), orally disintegrating tablets (30 mg), oral suspension (6 mg/ml)
Dosing Regimen	Various, by age and formulation
Indication(s)	For temporary relief of symptoms due to hay fever or other upper respiratory allergies. For the reduction of hives and the relief of itching due to hives (urticaria)
Intended Population(s)	OTC consumers with allergic rhinitis or hives

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The adverse event profile from controlled clinical trials, postmarketing pharmacovigilance, and the literature is supportive of safety. This reviewer recommends approval for OTC marketing with label changes to inform consumers that there are potentially serious cardiac rhythm disturbances rarely associated with fexofenadine, so they should stop use and ask a doctor if symptoms appear. In addition, although a nondrowsy claim is acceptable, the label should also state that a few percent of users become drowsy and care should be taken if driving or operating machinery. It is also recommended that the allergy warning "Stop use and ask a doctor if an allergic reaction to the product develops" be clarified to list specific symptoms to watch for. Labeling to help consumers recognize symptoms of rare adverse events involving liver injury should be considered.

A direction to ask a doctor before use if the consumer has heart disease is motivated by the high proportion of serious and fatal cardiac adverse events in which the subject had a prior cardiac history. Consumers who are over 65 or who have kidney disease should also ask a doctor before use, because of the possibility of elevated drug serum levels.

The following language is recommended for the OTC label:

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)
- you have kidney disease or if you are over 65 years old; your doctor should determine if you need a different dose.

When using this product

- do not take with fruit juice or at the same time as aluminum or magnesium antacids.

The word "NONDROWSY*" can be used on the label with a qualification, that although the medicine is unlikely to affect the ability to drive or operate machinery, a few people may be impaired and care should be taken.

1.2 Risk Benefit Assessment

The antihistamines are among the most widely used medications in the world. All antihistamines exert their action, providing symptomatic relief of allergy, by blocking H1 histamine receptors affecting smooth muscle contraction, vascular permeability and pruritis.The original, first generation antihistamines were effective, although their non-selective antagonism of H1 receptors in the brain and their effects on other receptor types caused sedation, somnolence and impaired cognitive function. These side effects have limited their use in the daytime, while driving and while operating machinery. The first generation antihistamines include diphenhydramine, chlorpheniramine and hydroxyzine. They continue to be widely used. Their side effects also include anticholinergic effects.

The second generation antihistamines are more selective for H1 receptors, relative to cholinergic receptors, and had greatly reduced ability to penetrate the blood-brain barrier, thereby reducing the side effects and drowsiness while retaining the clinical benefit of first generation antihistamines. The second generation antihistamines include terfenadine, astemizole, loratadine and cetirizine. Although these drugs were effective and had reduced CNS side effects, two of them (terfenadine and astemizole) also rarely caused serious cardiac arrhythmias by blocking cardiac potassium ion channels.

Terfenadine was withdrawn from marketing in favor of its active metabolite fexofenadine which is a member of the third generation of antihistamines. Fexofenadine, first approved in 1996, offers efficacy that is similar to that of second generation antihistamines without the risk of blocking cardiac delayed rectifier potassium currents.

A Joint meeting of the Nonprescription Drugs and Pulmonary and Allergy Drugs Advisory Committees on 11 May 2001 concluded that fexofenadine, loratadine, and cetirizine demonstrated a risk/benefit profile suitable for an over-the-counter antihistamine. The present review of safety data from controlled clinical trials, postmarketing safety data, literature, and drug abuse and poison center databases did not reveal new information that would alter the conclusion that fexofenadine is suitable for OTC marketing.

Clinical Trial Database. The controlled clinical trial dabase submitted in this application comprised 136 unique studies, including 124 studies of fexofenadine mono-product:

- Biopharmaceutical and pharmacokinetic studies in adults and pediatric subjects under 12 years of age;
- Pharmacodynamic studies in adults and pediatric subjects under 12 years of age;
- Controlled efficacy and safety studies in adults and pediatric subjects under 12 years of age
- Long term safety studies in adults up to one year use

A total of 18,361 subjects were exposed to fexofenadine single drug products and 6397 subjects were exposed to placebo. A total of 4640 adults were exposed to doses of fexofenadine between 180 mg QD (which is the dose proposed in the present application) and 180 mg BID. In addition, 438 adults were exposed to doses of fexofenadine ≥180 mg BID. In the pivotal controlled pediatric studies, 646 children under 12 years of age were exposed to fexofenadine with 229 exposed to placebo. In the other controlled pediatric trials, the number of subjects exposed to fexofenadine totaled 989, including 221 children from 2 to 5 years old and 193 children under 2 years old; there were also 901 children exposed to placebo. The long term safety studies in adults exposed 1121 subjects to fexofenadine and 453 subejcts to placebo.

In general, fexofenadine was well tolerated in the controlled clinical trials. The most commonly reported treatment-emergent adverse event (TEAE) was headache. In the biopharmaceutics and PK trials, TEAEs were reported by 19.74% of subjects; and in the pharmacodynamics studies TEAEs were reported by 11.5% of subjects. In the pivotal and the other controlled trials in adults, the incidences of TEAEs were near 35%, similar in the total fexofenadine and the placebo groups. Still higher TEAE incidences were reported in the long term safety studies, but again similar to placebo.

The adverse event (AE) profile from the controlled clinical trial database is supportive of safety at the approved doses of 60 mg BID and 180 mg QD in support of this application. No consistent dose dependence or relationships to gender, race or age were found in TEAE reporting rates from the controlled clinical trials in adult subjects. The adverse event profile in pediatric subjects under 12 years old was also similar to placebo and supportive of safety, although the most frequent TEAEs in subjects under 6 years of age comprised disorders typical of young children (pyrexia, vomiting, cough, headache, and abdominal pain upper).

Somnolence was reported in the controlled clinical trials by 0.79% to 1.49% of adult subjects and was significantly greater for the total fexofenadine group than for placebo.

The rates of TEAEs leading to discontinuation were, for all the types of trials, similar in the total fexofenadine and the placebo groups. In the biopharmaceutics and PK trials, there were two subjects who discontinued after the first day of fexofenadine use because of cardiac AEs, one for ventricular extrasystoles and one for second degree AV block. No further information is available.

From 18361 subjects given fexofenadine and 6397 subjects given placebo in the controlled clinical trial database, there were a total of 117 subjects who reported SAEs, but 50 of the 117 were not given fexofenadine. Of the SAE cases from the clinical trials, there were three cases where a contribution of fexofenadine to the SAE was possible or probable (all were cases also assessed as related to study drug by the investigator):

- Atrial fibrillation on day 7 of fexofenadine (probable)
- Abdominal pain (two events in one subject, possible)
- Chest pain, tachycardia and hypertension, day 45 of fexofenadine (possible)

Among subjects who discontinued the clinical trials with adverse events, there was one case of acute MI which occurred after 18 days of treatment; this case was assessed as not related by the investigator.

There were two pediatric SAE cases in the fexofenadine groups:

- Neutropenia which is assessed as possible but confounded because the child seroconverted for mycoplasma and influenza
- Status asthmaticus (unlikely relation to fexofenadine)

In the pivotal and other controlled clinical trials in adults, the numbers of cases reporting somnolence (nonserious and serious) were higher in the 60 mg BID, 180 mg QD, and total fexofenadine groups than for placebo. In addition, the numbers of cases (nonserious and serious) reporting cardiac terms was higher for the >180 mg QD group (above the proposed dose in the application) than for placebo. The number of cardiac AE terms reported in the clinical trials database was higher in the total fexofenadine group than for placebo. These comparisons were all statistically significant at $p<0.05$.

Postmarketing. The postmarketing data submitted in this application comprised:

- Sanofi-aventis pharmacovigilance database, spontaneous case reports with fexofenadine as a suspect drug received between 25 July 1996 and 30 September 2009;
- Data mining of FDA AERS database, spontaneous reports from 1 February 1969 to 30 June 2009
- Data mining of WHO UMC database, spontaneous reports from 1 January 1967 to 31 September 2009
- Safety update, Sanofi Aventis pharmacovigilance database from 1 October 2009 to 31 March 2010

The first US approval for fexofenadine was obtained on 25 July 1996, and the estimated worldwide exposure to fexofenadine is 32 million pt-yrs. The countries with the greatest cumulative exposure are: the US (17.23 million pt-yrs), Japan (3.78 million pt-yrs), India (1.18 million pt-yrs), the United Kingdom (1.22 million pt-yrs), Australia (1.08 million pt-yrs), and France (1.06 million pt-yrs).

The Sponsor's pharmacovigilance database comprised a total of 14,572 spontaneous reports involving 24,945 adverse events (AEs) reported to Sanofi-aventis from worldwide sources. More than 90% of the cases were nonserious.

A total of 953 SAE reports were reviewed, including the 946 cases submitted in the Sanofi database plus additional cases from the Sponsor's safety update and from AERS that were retrieved by the reviewer. The Sponsor performed data mining analyses in AERS to determine the Empirical Bayes Geometric Mean (EBGM) values for all AEs and for serious AEs associated with fexofenadine and two comparator drugs, loratadine and cetirizine. The method determines if a given drug is reported more often in association

with a given adverse event than would be expected based on overall association rates in AERS. A similar data mining analysis was performed for the WHO database.

The data mining EBGM analyses of AERS for SAEs identified safety signals for fexofenadine in association with cardiac arrhythmias and hepatic/hepatobiliary disorders. A data mining EBGM safety signal for cardiac terms was also identified in the WHO database.

There were a total of 46 death cases in the postmarketing database, including 44 deaths in Sanofi-aventis database. Most cases were confounded, but in 28 deaths a contribution of fexofenadine to the events is not excluded. Of these, 12 cases (43%) had a positive cardiac history. There were six death cases in subjects under the age of 30. Three death cases were found with a probable contribution of fexofenadine to the event:

- Collapse and sudden death in a healthy 15 year old treated with fexofenadine for a bug bite. Ventricular escape rhythm with ventricular tachycardia, ventricular fibrillation aystole were noted and Torsade de pointes was listed as the probable cause of death
- Arrhythmia and sudden death in an 18 year old female who had long QT syndrome
- Shock and cardiac arrest in a 26 year old male after a single dose of fexofenadine. Also had hypokalemia.

Table 39 summarizes the 46 fatal SAE cases in the postmarketing database.

There were a total of 907 nonfatal SAE cases in the postmarketing database. The review focused on SAE cases with cardiac, hepatic, hypersensitivity, and drug interaction events. Table 40 summarizes 119 SAE cases with cardiac events in which a contribution of fexofenadine to the SAE could not be excluded (possible or probable causality). Table 42 summarizes 59 SAE cases with hepatic events and probable or possible causality for fexofenadine. Table 43 summarizes 56 SAE cases with hypersensitivity events and probable or possible causality for fexofenadine (selected from 144 probable or possible SAE cases). Table 45 shows 20 SAE cases with fexofenadine and a macrolide or an anticonvulsant.

The review of the postmarketing database, the clinical trials database, and literature led to the following findings:

- Although the overall risk/benefit profile of fexofenadine like cetirizine and loratadine remains favorable for OTC marketing, the use of fexofenadine does involve risks about which consumers should be informed. These include the possibility of somnolence when using the drug and the occurrence of rare but potentially serious side effects, principally cardiac.
- Nondrowsy - fexofenadine is relatively nonsedating compared to the first generation antihistamines and compared to cetirizine, but it does cause somnolence or sedation in 0.79% to 1.49% of users according to the controlled clinical trial data. In view of the extensive use of fexofenadine, this incidence of somnolence may affect large

numbers of consumers. There are over 700 postmarketing spontaneous reports of somnolence or sedation reactions, including four serious reports with automobile accidents. 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.

- Cardiac side effects – the clinical trial data and the postmarketing data reveal that fexofenadine is associated with cardiac arrhythmias, most often presenting as tachycardias, palpitations, and arrhythmias. There were 119 serious cardiac adverse events in the postmarketing database associated with fexofenadine. This is a low reporting rate, in view of the extent of product exposure (over 32 million patient-years), but according to the data mining analyses, the reporting rate is disproportionately high compared to the expected rate in AERS.
- Hepatic side effects - the clinical trial data and the postmarketing data also reveal that fexofenadine is rarely associated with liver injury. This liver damage can be serious but is generally reversible with stopping use of the medication and treatment. There were 59 serious hepatic adverse event cases in the postmarketing database associated wih fexofenadine, which is again a low reporting rate but disproportionately high compared to the expected rate in AERS.
- Hypersensitivity – there were 144 cases of serious hypersensitivity reactions in the postmarketing database associated with fexofenadine. There is a hypersensitivity contraindication in the US prescription label. The proposed labeling includes the warning, "Stop use and ask a doctor if an allergic reaction to the product occurs. Seek medical help right away." It would be helpful if the label also listed symptoms to watch for, like "difficulty breathing, swelling of the tongue or throat" as in the Netherlands label.

The Netherlands nonprescription label (see Appendix 9.2) describes drowsiness, cardiac, and hypersensitivity adverse effects, and similar language should be considered for the US OTC label.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Usual post marketing monitoring.

1.4 Recommendations for Postmarket Requirements and Commitments

NA

2 Introduction and Regulatory Background

Fexofenadine hydrochloride (henceforth referred to as fexofenadine) is a selective H1-receptor antagonist. This non-sedating oral antihistamine was first approved in the United States under NDA 20-625 on 25 July 1996 as a 60 mg capsule, administered twice daily (BID) for the relief of symptoms associated with seasonal allergic rhinitis (SAR). Subsequently, 30 mg, 60 mg and 180 mg tablet formulations were approved for the SAR indication, and later was approved for relief of symptoms of chronic idiopathic urticaria (CIU). In addition, pediatric formulations (an oral suspension and an orally disintegrating tablet) have been approved for SAR and CIU.

Under the trade name Allegra®, mono-product (single ingredient) fexofenadine is approved in capsule [60 mg], tablet [30, 60, and 180 mg], oral suspension [6 mg/mL], and oral disintegrating tablet [ODT], [30 mg] formulations. Under the trade names Allegra-D® 12 Hour and Allegra-D® 24 Hour, it is available in fixed-dose combinations with pseudoephedrine (fexofenadine 60 mg / pseudoephedrine 120 mg, and fexofenadine 180 mg / pseudoephedrine 240 mg). The 60 mg capsule formulation (NDA 20-625) is not currently marketed in the US. Fexofenadine is marketed in more than 100 countries.

All together, fexofenadine mono-products are approved and have been available with a prescription in approximately 85 countries for over 10 years. They have been approved and available without a prescription in approximately 13 countries for over 10 years.

United States

Table 1 shows approved NDAs for mono-product fexofenadine which are the subject of the present review. The fixed combination products which are also included in the OTC switch application are reviewed by Dr. Rafaelli.

Sanofi-Aventis is proposing the switch of fexofenadine tablets, fexofenadine orally disintegrating tablets, and the fixed-dose combination products of fexofenadine and pseudoephedrine from prescription to nonprescription use. For the fexofenadine HCl oral suspension, the sponsor proposes to maintain NDA 21-963 for the prescription use of fexofenadine HCl oral suspension for CIU in pediatric patients 6 months to less than 6 years of age (partial switch). All other approved indications are requested to be switched from prescription to nonprescription use.

Table 1 Fexofenadine New Drug Applications relevant to tablet doses

Product	Formulation	IND	NDA
ALLEGRA capsules	Capsules, 60 mg	IND 43,573	NDA 20-625 *
ALLEGRA tablets	Tablet, 30 mg, 60 mg, 180 mg	IND 43,573	NDA 20-872
ALLEGRA oral suspension,	Suspension, oral 6 mg/mL	IND 51,709	NDA 21-963

(6 mg/mL)			
ALLEGRA ODT (orally disintegrating tablets)	Orally disintegrating tablet, 30 mg	IND 62,912	NDA 21-909

* Formulation currently not marketed. Discontinued in 2002 and was not due to safety and efficacy concerns.

Under NDA 20-625, fexofenadine was approved on 25 July 1996 as a capsule formulation at the dose of 60 mg BID for the treatment of SAR in adults and adolescents 12 years and older. Subsequently, under NDA 20-872, fexofenadine was approved on 27 February 2000 as a tablet formulation for doses of 30 mg BID, 60 mg BID, and 180 mg QD. Fexofenadine 60-mg BID and 180-mg QD tablets were approved for the relief of symptoms associated with SAR in adults and children 12 years of age and older. The fexofenadine 60-mg BID formulation was approved for the relief of symptoms of chronic idiopathic urticaria (CIU) in adults and children 12 years of age and older. The mono-product 30-mg BID formulation was approved for the treatment of SAR and CIU in children 6 to 11 years of age, inclusive. On 13 October 2005, under NDA 20-872 S-015, the mono-product 180 mg QD formulation was approved for the treatment of CIU in adults and children 12 years of age and older.

On 16 October 2006, under NDA 21-963, an oral suspension of fexofenadine 6 mg/mL was approved for the treatment of SAR and CIU in children 2 to 11 years of age inclusive at a dose of 30 mg BID, and for the treatment of CIU in children ≥6 months to <2 years of age at a dose of 15 mg BID. On 26 July 2007, under NDA 21-909, an orally disintegrating tablet of fexofenadine 30 mg was approved for the relief of symptoms associated with SAR and CIU in children 6 to 11 years of age, inclusive.

Table 2 shows the available mono-product fexofenadine formulations and dosing regimens for the SAR and CIU indications, in four age groups (adult and pediatric populations). All the listed mono-product fexofenadine formulations, all four age groups for the SAR indication, and the 6 years and older age groups for CIU, are proposed for OTC switch. As shown by shading in Table 2, the Sponsor proposes that CIU in children under 6 years of age will remain a prescription indication.

Table 2 Dosing regimen and administration

Mono-product fexofenadine Tablets: 30 mg, 60 mg, 180 mg Oral disintegrating tabs: 30 mg Oral suspension: 6 mg/mL; 5 mL (30 mg) or 2.5 mL (15 mg)	**≥12 years**	**6 to 11 years**	**2 to 5 years**	**6 months to <2 years**
SAR	60 mg BID 180 mg QD	30 mg BID	30 mg BID	Not indicated
CIU	60 mg BID 180 mg QD	30 mg BID	30 mg BID*	15 mg BID*
The remaining prescription indications and dosing are shown in the shaded areas.				

Europe
In addition to the approvals in the US described above, fexofenadine tablets have been approved in Europe in adults and adolescents 12 years of age and older for SAR at a dose of 120 mg QD and for CIU at a dose of 180 mg QD. Fexofenadine 30 mg tablets BID are also approved in pediatric patients 6 to 11 years of age for SAR. Fexofenadine is marketed in Europe under the trade name of Telfast. Fexofenadine 120 mg is also currently marketed OTC in several European countries.

Japan
Fexofenadine is currently approved in Japan for the treatment of allergic rhinitis, CIU, and skin diseases at the dose of 60 mg BID in adults and at the dose of 30 mg BID in pediatric patients 7 to 11 years of age.

2.1 Product Information

Fexofenadine is an antihistamine with selective H_1-receptor antagonist activity. Following the oral administration of fexofenadine, there is minimal systemic metabolism (about 5%), while 80% is recovered from the feces and 12% from urine. Fexofenadine does not cross the blood-brain barrier and is poorly lipid-soluble. It is a third generation antihistamine which is less sedating than the first generation antihistamines, many of which are available OTC.

Fexofenadine (all forms) is currently marketed in more than 100 countries worldwide including the US, European nations, Canada, Australia, and Japan, as well as Middle Eastern, Central and South American, and African nations. Based upon Intercontinental Marketing Services sales estimates from July 1997 (first available data in Intercontinental Marketing Services) through June 2009, approximately (b) (4) kg of fexofenadine have been sold, for an estimated patient exposure of 32.05 million patient-years.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are several nonprescription antihistamines available in the United States for the allergic rhinitis indication including chlorpheniramine, brompheniramine, clemastine, loratadine, and cetirizine. Loratadine and cetirizine are also available OTC for the relief of itching due to hives.

Multiple antihistamines are available OTC, as specified by the OTC Monograph for Antihistamine Drug Products [21 CFR 341.72] which includes brompheniramine, chlorcyclizine, chlorpheniramine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine (2 salts), doxylamine, phenindamine, pheniramine, pyrilamine, thonzylamine and triprolidine. Also available OTC under NDAs for the treatment of allergic rhinitis are: intranasal sodium cromolyn, the first generation antihistamine clemastine, and the second generation antihistamines loratadine and cetirizine. Additional classes of medications are available by prescription for the treatment of allergic rhinitis,

including intranasal ipratropium Br for the treatment of rhinorrhea associated with SAR, intranasal azelastine HCl for the treatment of SAR, and intranasal corticosteroids for the treatment of perennial allergic rhinitis (PAR) and SAR.

Various antihistamines are also first-line drugs for the treatment of CIU. The antihistamines, Claritin (loratadine) and Zyrtec (cetirizine) have been approved OTC for the relief of itching due to hives.

2.3 Availability of Proposed Active Ingredient in the United States

Fexofenadine has been available as a prescription product in the United States since 1996.

2.4 Important Safety Issues With Consideration to Related Drugs

Oral antihistamines have been available as prescription and nonprescription drugs for the treatment of allergic rhinitis and CIU for many years. The antihistamines loratadine, cetirizine, and fexofenadine have generally been considered to be safe and efficacious drugs devoid of the side effects of older antihistamines, like drowsiness and cognitive impairment (Ten Eick et al. 2001). The 3 antihistamines, and then loratadine alone, were discussed during joint meetings of the Nonprescription Drugs Advisory Committee and Pulmonary – Allergy Drugs Advisory Committee on 11 May 2001 and on 22 April 2002, respectively. During the first meeting, the change of status from prescription to nonprescription was supported for these antihistamines. Loratadine has been approved for nonprescription use since 27 November 2002 and cetirizine since 16 November 2007.

Certain of the second generation antihistamines, like terfenadine and astemizole, have been linked with cardiac arrhythmias. Terfenadine is associated with QT prolongation, due to blockage of cardiac muscle potassium channels and impaired repolarization of heart muscle. This results in an increased risk of ventricular tachyarrhythmias, notably torsade de pointes (Lindquist and Edwards 1997).

Most cases of terfenadine cardiac toxicity involved subjects with predisposing cardiac disease or interactions with drugs (e.g., macrolide antibiotics, ketoconazole) that increased serum levels by inhibiting the hepatic CYP3A4-mediated metabolism of terfenadine (Taglialatela et al. 1999; Paakari 2002). Fexofenadine is the major active metabolite of terfenadine and is responsible for its therapeutic effect. Terfenadine was withdrawn from marketing in 1997 (in the US).

The Division of Drug Risk Evaluation (DDRE) has previously performed three reviews of adverse reactions associated with fexofenadine in post-marketing data, in 2000, 2001 and 2006. The first of these reviews was performed to determine if there were safety issues that would preclude an OTC switch. The second review analyzed cardiac arrhythmias associated with fexofenadine. The first review concluded that fexofenadine may have

contributed to many of the events reviewed involving ventricular arrhythmias, although information was sometimes limited. The 2000 DDRE review recommended label warnings as follows:

- fexofenadine should not be used by individuals with heart disease
- individuals should consult with their physician before using if taking antibiotics or drugs to treat fungal disease.

The second DDRE review concluded that the cases of supraventricular and ventricular arrhythmias were suggestive but inconclusive of a direct association to fexofenadine. Of all the cases reviewed, many patients had pre-existing cardiac disease, thyroid disease, or concomitant medications that made association of these cardiac events with fexofenadine uncertain. It was unknown whether cardiac disease alone or in combination with fexofenadine may predispose the individuals to cardiac arrhythmias. However, DDRE also noted that cardiac arrhythmias were reported in patients with no apparent risk factors. See Section 8, Postmarketing-Experience.

The third DDRE review dated March 14, 2006 provided an update of fexofenadine-associated cardiovascular deaths, ventricular arrhythmias, and drug-drug interactions (of fexofenadine with antifungals, macrolides, and warfarin), covering the time period from May 17, 2001 to January 30, 2006. A total of 17 cases of reported ventricular arrhythmias were discussed, of which 7 were reports of death/sudden death. Of these 7 deaths, the cause of death was attributed to acute dysrhythmia with mild cardiomyopathy (1), myocardial infarction (3), Torsade de Pointes (1) and undetermined cause (2). Five fatalities reported relevant medical history (underlying cardiac disease and/or history of cardiovascular disease) and concomitant medications. Two patients had pre-existing cardiac disease or diabetes mellitus.

For the 2006 review, DDRE concluded that the 17 cases in their analysis are suggestive but inconclusive of association to fexofenadine and ventricular arrhythmias. Many cases had preexisting cardiovascular disease, or concomitant medications that make the association of the cardiac events with fexofenadine uncertain. Additionally, given the metabolism of fexofenadine via the CYP3A4 pathway, an exact causal role of fexofenadine in drug interaction cases involving clarithromycin, fluconazole, itraconazole, and warfarin that utilize this pathway cannot be excluded.

DDRE also evaluated AERS reports of hepatotoxicity with fexofenadine through October 25, 2004. DDRE assessed 60 cases, including one case of life-threatening liver failure, 12 cases of moderately severe and definitely threatening liver injury, seven cases of moderately severe and possibly threatening injury, and 40 cases of less severe liver injury. In 39 of the 60 cases, hepatic transaminases exceeded three times the upper limit of normal (ULN). The highest hepatic transaminases in the case series exceeded 25 times the ULN. Only 20 cases (33.3%) reported liver injury sufficient to interfere with ability to clear bilirubin. In most of the AERS reports there were contributing factors in addition to fexofenadine, such as concomitant medications or prior liver disease. In the 29 cases

where the pattern of liver injury was apparent, cholestatic liver injury occurred in 17 cases, hepatocellular injury occurred in six cases, and a mixed injury pattern occurred in six cases. DDRE recommended adding a statement in the prescription labeling that increased hepatic transaminases, hyperbilirubinemia, cholestasis, and clinically significant liver injury have been reported in postmarketing surveillance for fexofenadine.

The Canadian Adverse Reaction Newsletter of January, 2003; 13 (1) noted that seizures and convulsions accounted for 2.5%, 3.1%, and 2.1% of the total adverse event reports from AERS (July 1999) with cetirizine, fexofenadine and loratadine, respectively. Health Canada had received, from the date of marketing of fexofenadine in Canada (1997) to September, 2002, a total of 465 fexofenadine reports of which 4 involved convulsions or seizures. In all of these cases, there was a prior history of seizure. Health Canada stated that it was unclear whether second generation antihistamines aggravate a pre-existing seizure condition or interact with anticonvulsants.

The WHO Drug Information 2003 publication stated that convulsions have been reported in the literature with first-generation antihistamines (chlorpheniramine, diphenhydramine, pheniramine, and pyribenzamine) as well as with some newer-generation antihistamines (astemizole, cetirizine, fexofenadine, loratadine and terfenadine).

A updated review of post-marketing reports is included below in Section 8.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Two public hearings have been held on suitability of second generation antihistamines for over-the-counter switches:

- Joint meeting of the Nonprescription Drugs and Pulmonary and Allergy Drugs Advisory Committees (11 May 2001): The Advisory Committee concluded that the second generation antihistamines subject of a citizen's petition (fexofenadine, loratadine, and cetirizine) demonstrated a risk/benefit profile suitable for an over-the-counter antihistamine.
- Joint meeting of the Nonprescription Drugs Advisory Committee with consultants from Pulmonary and Allergy Drugs and Dermatological Drugs Advisory Committees (22 April 2002): The Advisory Committee concluded that urticaria was a disease process suitable for an over-the-counter indication.

A Type B meeting was held on 14 December 2009 between FDA's Office of Nonprescription Products and representatives from the Sponsor to discuss the Sponsor's proposed submission strategy to support the switch of all approved and currently marketed formulations and indications as age-appropriate for fexofenadine, including all mono-products (tablets, ODT, and oral suspension) and the fixed-dose combination products fexofenadine and pseudoephedrine from prescription to nonprescription use.

The FDA advised the sponsor to check for inconsistencies between the prescription label and proposed drug facts for all product presentations. The Agency also noted that as long as the label for the proposed products is not significantly different from the currently marketed nonprescription antihistamines, a label comprehension study will not be necessary.

The FDA expressed concern that some consumers may mistakenly take 180 mg of fexofenadine BID. Based on this concern, the Sponsor was requested to evaluate safety data greater than 360 mg fexofenadine and compare safety profiles for greater than or equal to 360 mg and 180 mg. If there are safety concerns, a consumer study may be needed to demonstrate safe use of the QD over-the-counter fexofenadine product.

The FDA agreed to review 4 PAR studies in support of the sell copy claim (ie, "indoor and outdoor allergies") on the principal display panel of the nonprescription retail presentations.

The FDA requested separate analyses of the electrocardiogram (ECG) and QT data from all the clinical studies, including data from pharmacokinetic and pharmacodynamic studies.

One Integrated Summary of Safety/Integrated Summary of Efficacy for mono-products and one Integrated Summary of Safety/Integrated Summary of Efficacy for fixed-dose combination products were requested to be submitted to one master with cross-references for the individual applications.

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Adequate.

3.2 Compliance with Good Clinical Practices

Adequate.

3.3 Financial Disclosures

NDA 201-613

The sponsor stated that 4 studies are trials requiring financial disclosure --PJPR0057, M3001, M3002, and M3097. The Sponsor listed 14 Clinical investigators for those trials with disclosable financial interests, including equity interests in the sponsor as defined by 21 CFR 54.2(b) and significant payments of other sorts as defined by 21 CFR 54.2(f). Sanofi-aventis does not believe any bias, intentional or unintentional, was introduced by these significant payments of other sorts or equity ownership in company stock. As the sponsor of the submitted covered studies, Sanofi-aventis certifies that it did not enter into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Sanofi-aventis also certifies that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in the tested product (property or other financial interest including, but not limited to a patent, trademark, copyright or licensing agreement) as defined in 21 CFR 54.2(c), did not disclose any such interests.

(b) (6) (b) (6), has received payments totaling $26,000. (b) (6), (b) (6), has received payments totaling $52,833. (b) (6), has received payments totaling $105,981.

MO Comment *These 4 PAR studies are being reviewed within the Division of Pulmonary Allergy and Rheumatology Products. The DPARP reviewer is aware of this information and will take this into consideration while conducting the review.*

Sanofi-aventis, U.S. has provided the financial disclosure information for the PAR studies (PJPR0057, M016455M/M3001, M016455M/M3002, and M016455M/M3097) in this NDA as this information has not been previously submitted to the Agency. Financial disclosure information for the SAR and CIU clinical studies, identified as pivotal and summarized in this NDA, was previously submitted in accordance with the regulations in the Allegra prescription NDA submissions to support their respective approvals.

NDA 201-373, NDA 21-909

No new studies were conducted with the fexofenadine HCl oral suspension formulation or ODT formulation in support of this NDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Sponsor has agreed to submit standard stability data post-approval for the change in blister package configurations to 5 count from 6-count.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No new animal safety information were submitted for the present OTC switch application. Please refer to Dr. Li's review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective H1-receptor antagonist activity. Both enantiomers of fexofenadine hydrochloride display approximately equipotent antihistaminic effects.

4.4.2 Pharmacodynamics

Following single oral dose administration of fexofenadine, peak inhibition of skin wheal and flare responses occurred from 3 to 6 hours post-dose for most doses, followed by a steady decline of drug effect.

4.4.3 Pharmacokinetics

The pharmacokinetics of fexofenadine in subjects with SAR and CIU were similar to those in healthy subjects. Fexofenadine was rapidly absorbed with tmax of 1 to 3 hours (Cmax for the oral suspension occurs at approximately 1 hour) and mean terminal elimination half-life of about 14 hours. After administration of a single 60-mg capsule to healthy adults, the mean C_{max} was 131 ng/mL. After single dose oral administration of the 60 mg tablet or the 180 mg tablet to healthy adult male subjects, the mean C_{max} values were 142 and 494 ng/mL, respectively. Fexofenadine was 60% to 70% bound to plasma

proteins, primarily albumin and α1-acid glycoprotein. Fexofenadine underwent minimal biotransformation where biliary and renal excretion were the principal routes of elimination. Approximately 80% and 11% of the ingested dose was excreted in feces and urine, respectively.

Fexofenadine exhibited linear pharmacokinetics up to the dose of 120 mg BID.

Special Populations
No clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine. In older patients (65 years of age and older), peak plasma levels of fexofenadine were 99% greater than in younger subjects under 65 years of age. The individual oral clearance estimates of fexofenadine averaged 44% and 36% lower in pediatric subjects 6 to 12 years (n=14) and 2 to 5 years of age (n=21), respectively, compared to adult subjects. Administration of a 15 mg dose of fexofenadine to pediatric subjects 6 months to less than 2 years of age and a 30 mg dose to pediatric subjects 2 to 11 years of age produced exposures comparable to those seen with a dose of 60 mg administered to adults.

In subjects with mild to moderate renal impairment, Cmax of fexofenadine was 87% greater, and the mean elimination half-lives were 59% longer, than in healthy subjects. In severe renal impairment, Cmax and mean elimination half-lives were 111% and 72% greater, respectively.

In subjects on dialysis, Cmax was 82% greater and half-life was 31% longer than observed in healthy subjects. A dose of 60 mg once daily is recommended as the starting dose in adult patients with decreased renal function (mild, moderate or severe renal impairment). For pediatric patients with decreased renal function (mild, moderate or severe renal impairment), the recommended starting dose of fexofenadine is 30 mg once daily for patients 2 to 11 years of age and 15 mg once daily for patients 6 months to less than 2 years of age.

The pharmacokinetics of fexofenadine in subjects with hepatic impairment did not differ substantially from that observed in healthy subjects.

Interactions
Coadministration of fexofenadine with a high fat meal decreased bioavailability of fexofenadine (AUC) by 20% to 40% depending on the dosage form (tablet< suspension< oral disintegrating tablet). In healthy subjects, administration of 120 mg of fexofenadine within 15 minutes of an aluminum- or magnesium-containing antacid decreased fexofenadine AUC by 41% and C_{max} by 43%. Fruit juices such as grapefruit and orange decreased the bioavailability of fexofenadine by 36%.

Co-administration of fexofenadine with either ketoconazole (400 mg per day) or erythromycin (500 mg every 8 hours) led to increased plasma concentration of fexofenadine, with 135% and 82% increase in the steady state maximum concentration.

Table 3 Effects on steady-state fexofenadine pharmacokinetics after 7 days of co-administration with fexofenadine 120 mg every 12 hours in healthy adult subjects (n=24)

Concomitant drug	$C_{max,ss}$ (Peak plasma concentration)	$AUC_{(0-12h)ss}$ (Extent of systemic exposure)
Erythromycin (500 mg every 8 hours)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

MO Comment *The Sponsor proposed labeling that directs consumers with kidney disease to ask a doctor before use. Proposed labeling also includes directions not to take with antacids. Additional label directions and warnings are recommended (see Section 9.2) including directions to ask a doctor before if taking macrolide antibioics and not to take with fruit juice. Allegra ODT should be dosed on an empty stomach.*

5 Sources of Clinical Data

The Integrated Summary of Safety comprises safety information from 124 studies associated with the fexofenadine mono product at all approved and evaluated dose levels and for all approved and evaluated indications. The safety data collected from the clinical trials of fexofenadine mono-products included adverse events, results of clinical laboratory, vital signs, and electrocardiogram [ECG] evaluations. These data were maintained in a Global Integrated Safety Database (GIDB). For analyses of each of the safety variables, the study data were pooled by study categories. The following three study categories and sub-categories were defined:

A. Biopharmaceutics and pharmacokinetic studies:
1. Adult subjects
2. Pediatric subjects younger than 12 years of age (ie, <12 years of age)

B. Pharmacodynamic studies:
1. Adult subjects
2. Pediatric subjects younger than 12 years of age

C. Efficacy and safety studies:
1. Pivotal controlled studies in adult subjects
2. Other controlled studies in adult subjects
3. Pivotal controlled studies in pediatric subjects younger than 12 years of age
4. Other controlled studies in pediatric subjects younger than 12 years of age
5. Long-term safety studies in adult subjects

D. Postmarketing data:
1. The Sanofi-aventis pharmacovigilance database, spontaneous case reports with fexofenadine as a suspect drug received between 25 July 1996 and 30 September 2009;
2. FDA AERS database, spontaneous reports from 1 February 1969 to 30 June 2009
3. WHO UMC database, spontaneous reports from 1 January 1967 to 31 September 2009
4. Safety update, Sanofi Aventis pharmacovigilance database from 1 October 2009 to 31 March 2010

5.1 Table of Studies/Clinical Trials

Table 4 lists the studies contributing to the GIDB, which included the safety data from 136 unique studies (124 studies of fexofenadine monoproduct). These include the studies previously submitted to fexofenadine NDAs as well as studies submitted to fexofenadine INDs (various formulations). The safety data from postmarketing studies conducted in the US not conducted under fexofenadine INDs submitted to the FDA, and from clinical studies submitted in Europe and Japan to gain marketing approval, are also included in the GIDB. Three studies looking at developing new formulations developed in Japan are not integrated into the GIDB. No serious or unexpected events were reported in these three studies.

The two left hand columns in Table 4 contain codes describing the type of clinical trial (efficacy, safety, pharmacodynamic, bioavailability; long term or not; adult or pediatric) as listed at the bottom of the Table. The shaded rows indicate pivotal efficacy and safety studies supporting the original NDAs for fexofenadine prescription use. The product formulations studied in the trials are coded in the right hand column.

Table 4 Clinical Trials in the Integrated Safety Database (GIDB)

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
8	A	PJPR0033	Pilot relative bioavailability study of MDL 16,455A in several different sustained release and immediate release formulations (Parts One and Two)	x
8	A	PJPR0068	Multiple dose pharmacokinetics of fexofenadine administered once every twenty-four hours compared to once every twelve hours	x
8	A	PJPR0071	Relative bioavailability of prototype fexofenadine hydrochloride tablets in normal healthy male subjects	x
8	A	PJPR0076	Bioavailability of fexofenadine hydrochloride capsules coadministered with applesauce and of prototype formulations for pediatric use	a/b
8	A	M016455/1122 *	A study of the safety and pharmacokinetics of once-daily repeated oral administration of fexofenadine hydrochloride (180 mg) for 7 days in healthy adult males	c
8	A	PJPR0083	A bioavailability study of fexofenadine SR preparations in healthy, male subjects	x
8	A	PJPR0098B	Single and multiple dose pharmacokinetics of fexofenadine hydrochloride 120 mg tablets in healthy male subjects	x
8	A	M016455/J001 *	Phase I single dose administration study in Japan	b
8	A	M016455/J002 *	Phase I repeated dose administration study in Japan	b
8	A	M016455T/1001	An open label, bioavailability study of fexofenadine HCl 60 mg capsules administered orally in food delivery vehicles in fasting healthy adult male subjects	a/b
9	A	PJPR0086	Relative bioavailability and food effect study of prototype fexofenadine HCl small-size tablet formulations	x
9	A	PJPR0080	Pilot Bioavailability Study of Fexofenadine HCl (b) (4) Tablet Formulations	x
9	A	PJPR0099	Pilot Bioavailability Study of fexofenadine HCl Solution and Raspberry Suspension Formulations	x
9	A	PJPR0108	Pilot bioavailability study of prototype fexofenadine HCl (b) (4) and suspension formulations in healthy male subjects	x
9	A	PJPR0111	Pilot Bioavailability Study of Two Prototype Fexofenadine HCl Solution Formulations in Healthy Male Subjects	x
9	A	M016455H/1130	An Open Label, Randomized Pilot Bioavailability Study of Fexofenadine HCl (30 mg (b) (4) Formulations in Fasting Healthy Male Subjects	x
9	A	M016455I/1001	An open label, randomized pilot bioavailability study of four prototype fexofenadine HCl suspension formulations in fasting healthy male subjects	x
9	A	M016455I/1002	An open label, randomized pilot bioavailability study of prototype fexofenadine HCl liquid suspension formulations in healthy subjects	g

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
9	A	M016455I/1116	Open Label, Randomized Pilot Bioavailability Study of Eight Prototype Fexofenadine HCl Suspension Formulations in Fasting Healthy Male Subjects	x
9	A	M016455I/1121	A Pilot Bioequivalence Study of Single Doses of Fexofenadine HCl 60 mg Given Orally as 6 mg/mL and 9 mg/mL Suspensions and the Lactose-Free Tablet in Fasting Healthy Adult Male Subjects	x
8	B	PJPR0015	Relative bioavailability of MDL 16,455A prototype tablet and capsule formulations in healthy volunteers	x
8	B	PJPR0025	Pivotal bioavailability and bioequivalence study of the MDL 16,455A final formulation	b
8	B	PJPR0026	Interim Report on the Effect of Food on the Production Scale Capsule Formulation From the Pharmacokinetic Study PJPR0026	b
8	B	PJPR0029	Pivotal bioequivalence study of MDL 16,455A instant release tablets	x
8	B	PJPR0045	Pivotal bioequivalence study of 180 mg fexofenadine hydrochloride tablet formulations	c
8	B	PJPR0062	The effect of food on the bioavailability of fexofenadine hydrochloride 180 mg lactose-free tablets	c
8	B	PJPR0094/F1094	Pivotal bioequivalence study of 60 mg fexofenadine hydrochloride tablet formulation	b
8	B	PJPR0098A	The effect of food on the bioavailability of fexofenadine hydrochloride 120 mg lactose-free tablets in healthy male subjects	x
8	B	M016455H/1004	An Open Label, Randomized Pilot Bioavailability Study of Fexofenadine HCl Fast-Disintegrating Tablet Formulations (30 mg) in Healthy Subjects	f
8	B	M016455H/1007	Two-way Crossover, Randomized, Open-label Pivotal Bioequivalence Study Comparing the Fexofenadine Hydrochloride Orally Disintegrating Tablet (ODT) Formulation (30 mg) to the Marketed Allegra Tablet (30 mg) in Healthy Adult Subjects	f
8	B	M016455H/1008	Two-way Crossover, Randomized, Open-label Study Comparing the Bioavailability of the Fexofenadine Hydrochloride Orally Disintegrating Tablet (ODT) Formulation (30 mg) Given With and Without Water to Healthy Adult Subjects	f
8	B	M016455I/1003	Two-way Crossover, Randomized, Open-label Pivotal Study Comparing the Bioavailability of Fexofenadine Hydrochloride Suspension in Fed and Fasted Healthy Adult Subjects	g
8	B	M016455I/1004	Two-way Crossover, Randomized, Open-label Pivotal Bioequivalence Study Comparing the Fexofenadine Hydrochloride Suspension to the Marketed Allegra Tablet in Healthy Adult Subjects	g
8	B	M016455J/1104 *	Pivotal Bioequivalence Study of 60 mg Fexofenadine Hydrochloride: Peach Oblong vs. White Round Tablets	x
8	B	M016455Q/1124 *	Bioequivalence study of fexofenadine hydrochloride (MDL 16,455A) 60 mg tablets and 180 mg tablets	c
9	B	M016455Q/1125 *	Bioequivalence study of fexofenadine hydrochloride (MDL 16,455A) 60 mg tablets and 120 mg tablets	x
11	C	DDPR0003	Relative bioavailability of prototype fexofenadine HCl/ pseudoephedrine HCl combination tablets in healthy, normal male volunteers	x

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
11	C	PJPR0038	Bioavailability of fexofenadine and pseudoephedrine combination formulations in healthy, male volunteers	d
11	C	M016455D/1115	Pilot Bioavailability and Food Effect Study of Prototype Fexofenadine-D Tablet and Capsule Formulations in Healthy Male Subjects	x
11	D	DDPR0001	Pivotal Bioequivalence of 60 mg Fexofenadine HCl/ 120 mg Pseudoephedrine HCl Combination Product	d
11	D	DDPR0002	The effect of food on the pharmacokinetics of fexofenadine/pseudoephedrine combination product	d
11	D	DDPR0005	Single dose bioequivalence of 60 mg fexofenadine HCl/ 120 mg pseudoephedrine HCl combination product in healthy male volunteers	d
11	D	M016455S/1001	A Pivotal /Steady-State Bioequivalence Study of 180 mg Fexofenadine HCl – 240 mg Pseudoephedrine HCl Combination Tablets in Fasting Healthy Subjects	e
11	D	M106455S/1002	An open label, randomized study to assess the effect of food on the pharmacokinetics of 180 mg fexofenadine-240 mg pseudoephedrine combination tablets in healthy subjects	e
8	E	PJPR0008	Pharmacokinetics and metabolism of [14C]MDL 16,455A in healthy, male volunteers	b
8	E	PJPR0011	Single and multiple dose pharmacokinetics of oral MDL 16,455A in healthy male volunteers	b
10	F	M016455I/1005	A multicenter study to assess the safety and pharmacokinetics of open-label 30 mg single dose fexofenadine hydrochloride oral suspension (6 mg/mL) in pediatric subjects 2 to 5 years of age	g
10	F	M016455I/1114	A multicenter study of the pharmacokinetics of oral fexofenadine hydrochloride administered as a granulation powder in applesauce to children from 2 through 5 years of age	a/g
10	F	M016455T/1123	A multicenter study of single escalating dose safety and pharmacokinetics of oral fexofenadine hydrochloride in children from 6 months to 2 years of age	a/g
8	G	M016455/4124 *	A randomized, double-blind, repeat-dose, crossover study to evaluate the pharmacokinetics (PK), safety, and tolerability of desloratadine (CLARINEX®) compared to fexofenadine (ALLEGRA®) in healthy adults who have been identified as slow metabolizers for desloratadine	c
8	G	PJPR0013	Pharmacokinetics of MDL 16,455A in subjects with renal impairment	b
8	G	PJPR0020	Pharmacokinetics of single oral dose of MDL 16,455A in healthy elderly volunteers	b
8	G	PJPR0021	Pharmacokinetics of single oral dose of MDL 16,455A in subjects with various degrees of liver failure	b
8	H	M016455/1E08	A randomized, open-label, parallel-group study to determine the effect of antacid use on the pharmacokinetics of fexofenadine, loratadine, and cetirizine	c
8	H	PJPR0022	Effect of gastric pH on the pharmacokinetics of MDL 16,455 following a single oral dose of MDL 16,455A in healthy male volunteers	b
8	H	M016455J/1105 *	Drug-drug interactions of fexofenadine HCl and erythromycin in healthy volunteers	b

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
8	H	PJPR0018	Effect of erythromycin on the pharmacokinetics of MDL 16,455A	b
8	H	PJPR0028	Effect of ketoconazole on the pharmacokinetics of MDL 16,455A	b
11	I	PJPR0043	Effect of pseudoephedrine on the pharmacokinetics of fexofenadine	d
9	J	PJPR0055	Randomized, double-blind, crossover comparison of fexofenadine, loratadine, and placebo: Suppressive effects on histamine-induced wheals and flares during 24 hours in healthy subjects	b
9	J	PJPR0059	A comparison of fexofenadine, terfenadine, loratadine, and placebo in suppression of histamine-induced wheal and flare	b
9	J	PJPR0090	Single center, randomized, double-blind, crossover study comparing the effects of a single dose of fexofenadine HCl 180 mg, diphenhydramine HCl 50 mg, and placebo on cognitive performance in naval flight personnel	c
9	J	M016455/4123 *	A double-blind, controlled, parallel-group, randomized, monocentric, comparative study of suppression of wheal and flare induced by increasing doses of histamine after oral administration of fexofenadine 180 mg versus loratadine 10 mg versus desloratadine 5 mg versus placebo during 7 days in healthy volunteer subjects: relation with plasma and tissue concentrations.	c
9	J	PJPR0002	Acute dose tolerance of MDL 16,455A in healthy male volunteers	b
9	J	PJPR0003	Subchronic dose tolerance study of MDL 16,455A in healthy male subjects	b
9	J	PJPR0007	A double-blind, randomized, placebo-controlled, four-period crossover pharmacodynamic and safety study of MDL 16,455A in normal subjects	b
9	J	M016455/4120 *	A Comparison of Fexofenadine HCl 180 mg, Loratadine 10 mg and Placebo in Suppression of Skin Wheal and Flare Induced by Histamine	c
9	J	M016455A/4136 *	Safety of Fexofenadine Hydrochloride in Elderly Patients with Allergic Rhinitis	b
9	J	M016455A/4139 *	Single center, randomized, double-blind, crossover study comparing the effects of single-dose fexofenadine HCl 180 mg, cetirizine 10 mg, and placebo on cognitive performance in naval flight personnel	c
9	J	M016455A/4141	A randomized, open-label, single-dose, crossover study to determine the effect of eight ounces of grapefruit juice on fexofenadine 180 mg inhibition of induced wheal and flare	c
9	J	M016455A/4143	Comparative study evaluating the effects of fexofenadine HCl 180 mg with grapefruit juice versus placebo with grapefruit juice in a skin wheal and flare challenge model	c
9	J	M016455A/4144	Comparative study evaluating the effects of fexofenadine HCl 180 mg with orange juice versus placebo with orange juice in a skin wheal and flare challenge model	c
9	J	M016455A/4145	A Comparison of Fexofenadine HCl 180 mg, Desloratadine 5 mg and Placebo in Suppression of Wheal and Flare Induced by Histamine	c
9	J	M016455I/1120 *	Pharmacokinetics and pharmacodynamics of oral fexofenadine hydrochloride tablets administered to healthy adult male subjects.	a
9	J	M016455I/1118	An Open-Label, Randomized, Crossover Study to Evaluate the Pharmacokinetics and Pharmacodynamics of 40, 80, and 160 mg Oral Fexofenadine Hydrochloride Suspension in Healthy Adult Male Subjects	x

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
9	J	M016455/J003 *	Histamine intradermal challenge testing in Japan	b
9	J	M016455/J006 *	Double-blind, randomized study of the pharmacokinetics of MDL 16,455 and suppression of the histamine-induced skin reaction following single oral doses of MDL 16,455A and terfenadine in healthy adult male volunteers	b
9	K	PJPR0047	Effect of fexofenadine on histamine induced sinonasal reflex	b
9	K	M016455/4049	A single-center, randomized, double-blind, placebo-controlled study evaluating the dose response of fexofenadine (60 mg, 120 mg, 360 mg BID) on mediator release following nasal provocation test with ragweed allergen	b
9	K	M016455/4051	Comparison of the effect of fexofenadine 60 mg, diphenhydramine 50 mg and alcohol on driving performance	b
9	K	M016455/4052	Effect of ragweed allergy and the treatment of allergy symptoms with fexofenadine HCl or clemastine on Scholastic Aptitude Test (SAT) scores	b
9	K	PJPR0060	The duration of inhibition of ragweed and histamine skin prick test reaction after a six-day administration of fexofenadine HCl 60 mg BID in ragweed allergic patients	b
9	K	M016455/4102	Comparison of the effect of fexofenadine 180 mg, diphenhydramine 50 mg, and placebo on driving performance	c
9	K	M016455/4104	Multicenter, Double-Blind, Randomized Comparison of the Efficacy, Onset of Action and Safety of a Single Dose of Fexofenadine 180 mg vs. Loratadine 10 mg vs. Placebo in Treating Seasonal Allergic Rhinitis in an Outdoor Environment	c
9	K	M016455/4119 *	Single-center, double-blind, randomized, parallel study comparing onset of action, efficacy and safety of a single-dose of fexofenadine HCl (Allegra®) 180 mg and placebo in treating seasonal allergic rhinitis subjects in an environmental exposure unit	c
9	K	PJPR0017	A placebo-controlled double-blind, randomized, parallel study in an environmental exposure unit characterizing the onset of action, efficacy, and safety of a single dose of 60 mg or 120 mg MDL 16,455A in patients with fall allergies	b
9	K	M016455A/4149	Single-center, double-blind, randomized, parallel study comparing onset of action, efficacy and safety of a single-dose of fexofenadine hydrochloride (HCl) 180 mg versus montelukast Na 10 mg and placebo in treating seasonal allergic rhinitis subjects in an allergen exposure unit (Study I)	c
9	K	PJPR0091	A double-blind, randomized, placebo-controlled, parallel study in an environmental exposure unit characterizing onset of action, efficacy and safety of a single dose of 120 mg, 180 mg, or 240 mg fexofenadine HCl in patients with fall allergies	c
9	K	PJPR0048	The effect of fexofenadine on nasal allergen challenge in patients with allergic rhinitis and mild to moderate asthma	b
9	K	PJPR0050	The effect of fexofenadine on pulmonary function, methacholine challenge and hypertonic (4.5%) saline challenge in mild to moderate adult asthmatics	b

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
10	L	M016455I/1119 *	Pharmacokinetics and pharmacodynamics of oral fexofenadine hydrochloride tablets administered to children from 6 through 11 years of age.	a
10	L	PJPR0037	Pharmacokinetics and pharmacodynamics of fexofenadine hydrochloride in 6 to 12 year old pediatric patients with allergic rhinitis	a
10	L	M016455I/1117	Pharmacokinetics and Pharmacodynamics of Oral Fexofenadine Hydrochloride Suspension Administered to Children from 6 through 11 Years of Age	x
12	M	M016455D/4001	Single-center double-blind, randomized, parallel study comparing onset of action, efficacy and safety of a single-dose of Allegra-D (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) and placebo in treating seasonal allergic rhinitis subjects in an allergen exposure unit II	d
12	M	M016455D/4110	Single-center, double-blind, randomized, parallel study comparing onset of action, efficacy and safety of a single-dose of Allegra-D™ (fexofenadine 60 mg and pseudoephedrine 120mg) and placebo in treating seasonal allergic rhinitis subjects in an environmental exposure unit	d
1	N	PJPR0009	A placebo-controlled, double-blind, randomized parallel study comparing the safety and efficacy of four dosage strengths of MDL 16,455A in the treatment of spring allergies–I	b
1	N	PJPR0010	A placebo-controlled, double-blind, randomized parallel study comparing the safety and efficacy of four dosage strengths of MDL 16,455A in the treatment of spring allergies-II	b
1	N	PJPR0023	A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of three dosage strengths of MDL 16,455A (60, 120, & 240 mg BID) in the treatment of fall allergies	b
1	N	PJPR0024	A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of three dosage strengths of MDL 16,455A (40, 60, & 120 mg BID) in the treatment of fall allergies	b
1	N	M016455A/4121	A phase IIIa, multicenter, randomized, double-blind, parallel-group, placebo-controlled study on the efficacy and safety of fexofenadine HCl 180 mg once daily in chronic idiopathic urticaria	c
1	N	PJPR0039	A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of four dosage strengths of fexofenadine HCl (20, 60, 120, & 240 mg BID) in the treatment of chronic idiopathic urticaria	b
1	N	PJPR0067	A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of four dosage strengths of fexofenadine HCl (20, 60, 120, & 240 mg BID) in the treatment of chronic idiopathic urticaria	b
1	N	PJPR0081	A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of fexofenadine HCl 120 mg and 180 mg QD in the treatment of autumn seasonal allergic rhinitis	c
3	O	PJPR0053	A double-blind, randomized study comparing the efficacy and safety of fexofenadine and placebo in Black patients with seasonal allergic rhinitis	b
3	O	PJPR0092	Safety evaluation of once daily dosing of fexofenadine HCl 180mg in subjects with seasonal allergic rhinitis and concomitant mild to moderate asthma	c

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
3	O	PJPR0054	Comparison of fexofenadine versus loratadine in seasonal allergic rhinitis	b
3	O	PJPR0056 *	Comparison of fexofenadine (60 mg BID) versus loratadine (10 mg QD) in seasonal allergic rhinitis	b
3	O	M016455A/4122	A double-blind, double-dummy, parallel-group, multi-center, randomized study of fexofenadine HCl 180 mg vs cetirizine HCl 10 mg in subjects with moderate to severe seasonal allergic rhinitis (SAR) during the fall or winter/spring allergy season	c
3	O	PJPR0019	A multicentre, double-blind, randomised, placebo-controlled, parallel group study comparing the efficacy and safety of four dosage regimes of fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria	c
3	O	PJPR0032	A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of two dosage strengths of fexofenadine hydrochloride (120, and 180 mg once a day) versus cetirizine (10 mg once a day) in the treatment of seasonal allergic rhinitis (SAR)	c
3	O	PJPR0061	A multicentre, double-blind, randomised, parallel-group comparative study of the efficacy and safety of two dosage strengths of fexofenadine hydrochloride (HCl) versus placebo in the treatment of subjects with seasonal allergic rhinitis (SAR)	c
3	O	JTAM202 *	Double-blind dose-finding study of MDL 16,455A in perennial nasal allergies	b
3	O	JTAM201	Double-blind dose-finding study of MDL 16,455A in chronic urticaria	b
3	O	M016455J/3106 *	Evaluation of the efficacy and safety of MDL16,455A at doses of 60 and 120 mg b.i.d. in patients with seasonal allergic rhinitis (a double-blind, placebo-controlled, randomized study)	b
3	O	PJPR0057	A double-blind, randomized, parallel study comparing the efficacy and safety of fexofenadine HCl 60 mg BID, 120 mg QD and placebo in the treatment of perennial allergic rhinitis	b
3	O	M016455M/3001	A multicenter, double-blind, randomized, parallel study comparing the efficacy and safety of fexofenadine HCl 120 mg BID, fexofenadine HCl 240 mg QD, and placebo in subjects with perennial allergic rhinitis	h
3	O	M016455M/3002	A multicenter, double-blind, randomized, parallel study comparing the efficacy and safety of fexofenadine 120 mg BID, fexofenadine 240 mg QD, and placebo in subjects with perennial allergic rhinitis	h
3	O	M016455M/3097	A Double-Blind, Randomized, Parallel Study Comparing the Efficacy and Safety of Fexofenadine HCl 120 mg QD, 180 mg QD, Cetirizine HCl 10 mg QD, and Placebo QD in the Treatment of Perennial Allergic Rhinitis.	c
3	O	M016455O/3101 *	Evaluation of the efficacy and safety of fexofenadine hydrochloride (MDL 16,455A) for the treatment of pediatric perennial allergic rhinitis (Double-blind, randomized, ketotifen fumarate-controlled, parallel comparison)	a
3	O	M016455O/3102 *	Evaluation of Efficacy and Safety of Fexofenadine Hydrochloride (MDL 16,455A) for Treatment of Pediatric Atopic Dermatitis (Double-blind, Randomized, Ketotifen Fumarate-controlled, Parallel Comparison)	a

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
3	O	M016455P/2113	A multicenter, double-blind, randomized, parallel groups, placebo-controlled pilot study to observe the effects of montelukast 10 mg in combination with fexofenadine 180 mg daily or 120 mg BID on asthma in subjects with persistent mild to moderate atopic asthma	c
3	O	M016455P/3001	A multicenter, double-blind, randomized, parallel groups placebo-controlled study to assess the efficacy and safety of fexofenadine 120 mg BID in subjects with mild to moderate persistent asthma	h
3	O	M016455P/3002	A multicenter, double-blind, randomized, parallel groups placebo-controlled study to assess the efficacy and safety of fexofenadine 120 mg BID in subjects with mild to moderate persistent asthma	h
3	O	M016455/3117 *	Evaluation of the efficacy and safety of fexofenadine hydrochloride (MDL16,455A) administered once daily at doses of 120 mg and 180 mg for the treatment of seasonal allergic rhinitis (Double blind, randomized, placebo- and bid administration-controlled study)	c
3	O	R3118	Evaluation of the efficacy and safety of fexofenadine hydrochloride (MDL16,455A) administered once daily at 120 mg and 180 mg for the treatment of chronic idiopathic urticaria (Double-blind, randomized, placebo- and bid administration-controlled trial)	c
2	P	PJPR0066/77	A Double-blind Randomized, Placebo-controlled Parallel Study Comparing the Efficacy and Safety of Three Dosage Strengths of Fexofenadine HCl (15, 30 and 60 mg BID) in Pediatric Patients (Ages 6 to 11 Years) in the Treatment of Seasonal Allergic Rhinitis	a
4	Q	M016455C/3212	A double-blind, randomized, placebo-controlled, parallel group study assessing the efficacy and safety of oral fexofenadine HCl tablets 30 mg twice a day in pediatric subjects (6 to 11 years) in the treatment of seasonal allergic rhinitis.	a
4	Q	M016455I/3112	A multicenter, double-blind, randomized, placebo-controlled, parallel study to assess the safety and tolerability of fexofenadine HCl 30 mg twice a day during treatment of children 2 through 5 years of age with allergic rhinitis	a/g
4	Q	M016455O/3101*	Evaluation of the efficacy and safety of fexofenadine hydrochloride (MDL 16,455A) for the treatment of pediatric perennial allergic rhinitis (Double-blind, randomized, ketotifen fumarate-controlled, parallel comparison)	a
4	Q	M016455O/3102 *	Evaluation of Efficacy and Safety of Fexofenadine Hydrochloride (MDL 16,455A) for Treatment of Pediatric Atopic Dermatitis (Double-blind, Randomized, Ketotifen Fumarate-controlled, Parallel Comparison)	a
4	Q	M016455T/3001	A multicenter, double-blind, randomized, placebo-controlled, parallel study to assess the safety and tolerability of fexofenadine HCl 15 mg in children with allergic rhinitis	a/g
4	Q	M016455T/3002	A multicenter, double-blind, randomized, placebo-controlled, parallel study to assess the safety and tolerability of fexofenadine HCl 30 mg in children with allergic rhinitis	a/g
6	R	PJPR0035	"A comparative study of the safety and efficacy of a twice-daily fexofenadine HCl 60 mg pseudoephedrine HCl 120 mg combination versus its components alone in the management of ragweed seasonal allergy"	d
5	S	PJPR0027	A twelve-month safety/tolerance study of 240 mg MDL 16,455A QD and placebo QD in normal healthy subjects	h

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
5	S	PJPR0031	A six-month safety/tolerance study of 60 mg MDL 16,455A BID and placebo BID in normal subjects	b
5	S	M016455P/3003	A multicenter, open-label, randomized, parallel group study to assess the long-term safety performance of fexofenadine compared to montelukast in subjects with asthma	h

* 1 of 25 synopsis submitted in NDA 201-613 sequence 0000 as per FDA request of December 14, 2010 as an appendix to the ISS

A Biopharmaceutic studies - Bioavailability studies, mono products, adult subjects and patients, Module 5.3.1.1
B Biopharmaceutic studies - Comparative bioavailability and bioequivalence studies, mono-products, in adult subjects, Module 5.3.1.2
C Biopharmaceutic studies - Bioavailability studies in adult subjects – fixed-dose combination products with pseudoephedrine, Module 5.3.1.1
D Biopharmaceutic studies - Comparative bioavailability and bioequivalence studies in adult subjects – fixed-dose combinations with pseudoephedrine, Module 5.3.1.2
E Human pharmacokinetic studies – Healthy subject pharmacokinetic and initial tolerability studies, mono-products, adult subjects and patients, Module 5.3.3.1
F Human pharmacokinetic studies – Patient pharmacokinetic and initial tolerability study, mono-products, pediatric patients, Module 5.3.3.2
G Human pharmacokinetic studies – Intrinsic factor pharmacokinetics studies, mono-product, Module 5.3.3.3
H Human pharmacokinetic studies – Extrinsic factor pharmacokinetics studies, mono-product, Module 5.3.3.4
I Human pharmacokinetic studies – Extrinsic factor pharmacokinetic studies in adults, fixed-dose combination products with pseudoephedrine, Module 5.3.3.4
J Human pharmacodynamic studies - Healthy subject pharmacodynamic and pharmacokinetic/pharmacodynamic studies, mono-products, adult subjects and patients, Module 5.3.4.1
K Human pharmacodynamic studies - Patient pharmacodynamic and pharmacokinetic/pharmacodynamic studies, mono-products, adults, Module 5.3.4.2
L Human pharmacodynamic studies - Patient pharmacodynamic and pharmacokinetic/pharmacodynamic studies, mono-products, pediatric patients, Module 5.3.4.2
M Human pharmacodynamic studies - Patient pharmacodynamic and pharmacokinetic/pharmacodynamic studies in adults – fixed-dose combination products with pseudoephedrine, Module 5.3.4.2
N Efficacy and safety studies – Pivotal controlled studies in adult patients, mono-products, Module 5.3.5.1
O Efficacy and safety studies – Other controlled studies in adult patients, mono-products, Module 5.3.5.1
P Efficacy and safety studies – Pivotal controlled studies in pediatric patients younger than 12 years of age, mono-products, Module 5.3.5.1
Q Efficacy and safety studies – Other controlled studies in pediatric patients younger than 12 years of age, mono-products, Module 5.3.5.1
R Efficacy and safety studies – Other controlled studies in adult patients, fixed-dose combination products with pseudoephedrine, Module 5.3.5.1
S Efficacy and safety studies – Long-term safety studies in adult patients, mono-products, Module 5.3.5.1

Shaded rows indicate pivotal efficacy and safety studies supporting original NDA approvals for fexofenadine prescription use
1 Pivotal Controlled Adults
2 Pivotal Controlled Peds
3 Other Controlled Adults
4 Other Controlled Peds
5 Long term
6 Other Allegra D
7 Not applicable
8 Pivotal Clin Pharm Adults
9 Other Clin Pharm Adults
10 Clin Pharm Peds
11 Allegra D Pivotal Clin Pharm
12 Allegra D Other Clin Pharm

Study category NDA	Study category CTD	Study/protocol number	Study title	US or non-US Formulation
a US Formulation 30 mg tablet/capsule b US Formulation 60 mg tablet/capsule c US Formulation 180 mg tablet d US Formulation fixed dose combination fexofenadine 60 mg/pseudoephedrine 120 mg e US Formulation fixed dose combination fexofenadine 180 mg/pseudoephedrine 240 mg f US Formulation 30 mg orally disintegrating tablet g US Formulation oral suspension h US Formulation supportive 120 and 240 mg x Developmental or non-US Formulation				
NDA = New Drug Application CTD = Common Technical Document MDL 16,455(A) = M016455 = fexofenadine hydrochloride				

Post-marketing safety data were collected by the Sponsor in the Global Pharmacovigilance database. The review of these data is given in Section 8.

Three studies of new formulations in Japan were not included in the GIDB. No serious events were observed in them.

Post-marketing safety data were also collected from outside databases (Food and Drug Administration's Adverse Event Reporting System [FDA AERS] and World Health Organization - The Uppsala Monitoring Centre [WHO UMC] Database. The review of these data is also given in Section 8.

5.2 Review Strategy

This review will focus on safety. Much of the safety data has been submitted in previous NDAs. Efficacy for SAR and CIU has been demonstrated previously and will not be discussed again here. The Division of Pulmonary Allergy and Rheumatology Products (DPARP) is conducting the review of 4 PAR studies to support the sell copy claim of "indoor and outdoor allergies" on the label. This review will concentrate on the safety and serious AEs. Cardiology has been consulted to review the ECG and QT data in addition to spontaneously reported postmarketing cardiac AEs. The Office of Surveillance and Epidemiology (OSE) has been consulted to also look at the AERS postmarketing cardiac, hepatic, drug interaction, and data mining results.

5.3 Discussion of Individual Studies/Clinical Trials

The sponsor is seeking a label claim for "indoor and outdoor allergies". Four perennial allergic rhinitis (PAR) studies (M016455M/3001, M016455M/3002, M016455M/3097,

and PJPR0057) are being reviewed by The Division of Pulmonary Allergy and Rheumatology Products (DPARP). These studies will not be reviewed separately here.

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.

A total of 40 efficacy and safety studies were conducted. Studies M016455O/3101 and M016455O/3102 were counted twice each as both studies included adult and pediatric subjects as defined for this assessment of safety. A total of 33 studies were in the adult population and a total of 7 studies were in the pediatric population. Studies in the adult population consisted of 8 pivotal studies, 22 other types of controlled studies, and 3 long-term safety studies. Studies in the pediatric population consisted of 1 pivotal study and 6 other types of controlled studies.

Safety data and adverse events from many of the trials mentioned above have been submitted previously (discussed individually or pooled) under NDA 20-625, NDA 20-872, NDA 21-909, and NDA 21-963. Adverse events in the following studies, organized by study category, have not been submitted under an IND, NDA, or supplement to an NDA referenced in this submission:

- Biopharmaceutics and human pharmacokinetic studies in adult subjects (M016455/J001, M016455/J002, M016455/1122, M016455J/1104, M016455Q/1124, M016455Q/1125, M016455/4124, and M016455/1105,
- Pharmacodynamic studies in adult subjects (M016455I/1120, M016455/4119, M016455/4120, M016455/4123, M016455/4136, M016455A/4139, M016455/J003, and M016455/J006
- Biopharmaceutics and pharmacokinetics in pediatric subjects (M016455I/1119)
- Other controlled studies in adult subjects (PJPR0056, M016455/3106, M016455/3117, JTAM-CL-202, M016455O/3101 [12 years of age and older], M016455O/3102 [12 years of age and older])
- Other controlled studies in pediatric subjects younger than 12 years of age (M016455O/3101 [younger than 12 years of age], M016455O/3102 [younger than 12 years of age])

Also M016455P/3003 a controlled study in adult asthma sufferers, was not previously submitted.

6 Review of Efficacy

Efficacy Summary

See DPARP review.

6.1 Indication

Not applicable

6.1.1 Methods

Not applicable

6.1.2 Demographics

Not applicable

6.1.3 Subject Disposition

Not applicable

6.1.4 Analysis of Primary Endpoint(s)

Not applicable

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

Not applicable

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

Not applicable

7 Review of Safety

Safety Summary

This Integrated Summary of Safety is based on analyses of safety data of the mono products captured in a Global Integrated Database (GIDB). The safety data in this GIDB are the safety data from 136 unique studies using various mono-products and fixed-dose combination products of fexofenadine and pseudoephedrine hydrochloride. The studies have previously been submitted in the 4 NDAs and in supplements to these NDAs listed above and the 2 NDAs for the fixed-dose combination products. The GIDB also includes safety data from additional studies, conducted under Investigational New Drug application (IND) 43,573, IND 51,709, and IND 48,486, that evaluated formulations related to the capsule or tablet or that evaluated the efficacy and safety of fexofenadine in the approved indications of SAR or CIU.

7.1 Methods

There are 23 studies listed below in Section 7.3, and the four PAR studies mentioned above in Section 5.3, which have not been submitted previously in an NDA. These studies will not be reviewed individually here. The Sponsor has pooled the safety data from these trials with that from the trials previously submitted in NDAs into the GIDB which is reviewed below.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 4 lists the clinical trials in the GIDB which provided safety data in the present submission.

7.1.2 Categorization of Adverse Events

The Sponsor applied ICH criteria (International Conference on Harmonization E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) to reporting of adverse events in all fexofenadine clinical studies included in the present submission. Adverse events, including treatment-emergent adverse events (TEAEs) and serious adverse events, were monitored throughout all studies. All adverse events, regardless of their seriousness or relationship to the study medication, were collected by

open questioning from the time of informed consent to the end-of-study and recorded in the case report form. Adverse events in individual trials were coded using the then-current version of the applicable coding dictionary (e.g., Hoechst Adverse Reaction Terminology System, Merrell Dow version of the World Health Organization Reaction Terminology Dictionary, Marion Merrell Dow version of the World Health Organization Reaction Terminology Dictionary, The Japanese Adverse Reaction Terminology Dictionary, and the Medical Dictionary for Regulatory Activities [MedDRA]).

For this submission, all adverse events in the GIDB were recoded to MedDRA version 12.0. Adverse event data, including all TEAEs, serious adverse events, and TEAEs leading to discontinuation, were integrated for each of the study categories listed above (See Section 5, and Table4), combining all adult-controlled studies and all pediatric-controlled studies. Treatment-emergent adverse events were also summarized by system organ class for the combined controlled studies in adult subjects and the controlled studies in pediatric subjects.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See section 7.2.

7.2 Adequacy of Safety Assessments

In clinical trials, a total of 18,361 subjects have been exposed to fexofenadine, and 910 subjects have been exposed to the fixed-dose combinations of fexofenadine and pseudoephedrine, compared to 6397 subjects exposed to placebo. A total of 4640 subjects in the adult population were exposed to doses of fexofenadine that were greater than 180 mg, but less than 180 mg BID. In addition, 438 adult subjects were exposed to doses of fexofenadine that were greater than or equal to 180 mg BID (23 subjects in biopharmaceutics and pharmacokinetic studies, 96 in pharmacodynamic studies and 319 in efficacy and safety studies).

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the pivotal controlled studies in adult subjects (Table 5), a total of 3874 subjects were exposed to fexofenadine for a mean of 16.62 days. The mean exposure in the fexofenadine 60 mg BID treatment group was similar (16.51 days), while the mean exposure in the fexofenadine 180 mg QD treatment group was higher (18.52 days). A total of 1226 subjects were exposed to placebo for a mean of 16.01 days.

Table 5 Summary of exposure to fexofenadine in pivotal controlled studies in adult subjects

		Fexofenadine					
Summary statistics	Placebo (N=1236)	<60 mg BID (N=1117)	60 mg BID (N=871)	120 - 180 mg daily (N=681)	180 mg QD (N=450)	>180 mg daily (N=782)	Total (N=3901)
Number of subjects (n)	1226	1111	864	676	450	773	3874
Mean ± SD (days)	16.01 ± 6.61	15.79 ± 6.35	16.51 ± 6.74	13.70 ± 2.18	18.52 ± 7.27	19.37 ± 8.50	16.62 ± 6.83
Median (days)	14.00	14.00	14.00	14.00	15.00	14.00	14.00
Min : Max (days)	1.0 : 36.0	1.0 : 73.0	1.0 : 37.0	1.0 : 28.0	1.0 : 37.0	2.0 : 60.0	1.0 : 73.0

Min = minimum; Max = maximum; N = total number of subjects/subjects; n = number of subjects/subjects with data.
Source: Appendix 5.3.5.3.1.4

In the other controlled studies in adult subjects (Table 6), a total of 8263 subjects were exposed to fexofenadine for a mean of 28.79 days. The dose groups of interest, fexofenadine 60 mg BID and 180 mg QD were exposed for means of 16.64 and 27.9 days, respectively. A total of 1330 subjects were exposed to other treatments which included cetirizine, loratadine, and ketotifen for a mean of 24.57 days.

Table 6 Summary of exposure to fexofenadine in other controlled studies in adult subjects

		Fexofenadine						
Summary statistics	Placebo (N=3578)	<60 mg BID (N=679)	60 mg BID (N=1458)	120-180 mg daily (N=1544)	180 mg QD (N=1339)	>180 mg daily (N=3276)	Total (N=8296)	Other (N=1330)
Number of subjects (n)	3566	667	1455	1530	1335	3276	8263	1323
Mean ± SD (days)	33.70 ± 24.47	12.64 ± 7.18	16.64 ± 6.75	23.70 ± 17.14	27.90 ± 17.79	40.22 ± 25.57	28.79 ± 21.93	24.57 ± 16.70
Median (days)	29.00	12.00	15.00	15.00	15.00	29.00	27.00	15.00
Min : Max (days)	1.0 : 124.0	1.0 : 49.0	1.0 : 46.0	1.0 : 85.0	1.0 : 62.0	1.0 : 120.0	1.0 : 120.0	1.0 : 68.0

Min = minimum; Max = maximum; N = total number of subjects/subjects; n = number of subjects/subjects with data.
Other includes 10 mg cetirizine, 10 mg loratadine, and 1 g ketotifen.
Source: Appendix 5.3.5.3.1.6

In the pivotal studies in children (Table 7), a total of 646 pediatric subjects were exposed to fexofenadine for a mean of 15.51 days in combined Studies PJPR0066/77. The studies also included a fexofenadine 60 mg BID dose group, which is higher than the recommended total daily dose of fexofenadine in the pediatric population. In these combined studies, 229 pediatric subjects were exposed to placebo for a mean of 15.43 days. A total of 5 children under 5 years of age were exposed to fexofenadine at any dose. A total of 614 children from 5 to 12 years of age were exposed to fexofenadine at doses of 15 mg BID to 60 mg BID.

Table 7 Summary of exposure to fexofenadine in pivotal controlled studies PJPR0066/77 in pediatric subjects

		Placebo	Fexofenadine			
Summary statistics		(N=229)	15 mg BID (N=224)	30 mg BID (N=209)	60 mg BID (N=213)	Total (N=646)
Number of subjects (n)		229	224	209	213	646
Mean ± SD (days)		15.43 ± 2.04	15.49 ± 2.23	15.39 ± 1.87	15.66 ± 1.79	15.51 ± 1.98
Median (days)		15.00	15.00	15.00	15.00	15.00
Min : Max (days)		3.0 : 22.0	1.0 : 22.0	2.0 : 19.0	4.0 : 20.0	1.0 : 22.0
Min = minimum; Max = maximum; N = total number of subjects/subjects; n = number of subjects/subjects with data. Source: Appendix 5.3.5.3.1.5						
Age group (years)						
≥2 to ≤5	n (%)	0	3 (1.3)	1 (0.5)	1 (0.5)	5 (0.8)
≥6 to ≤12	n (%)	229 (100)	221 (98.7)	208 (99.5)	212 (99.5)	614 (99.2)

In the other controlled studies in pediatric subjects (Table 8), a total of 986 subjects were exposed to fexofenadine for a mean of 15.03 days. Subjects exposed to fexofenadine 15 mg BID were between the ages of 6 months to younger than 2 years of age, inclusive, and subjects exposed to fexofenadine 30 mg BID were between the ages of 6 months to younger than 12 years of age, inclusive. A total of 108 subjects were exposed to ketotifen for a mean of 28.39 days and 892 subjects were exposed to placebo for a mean of 13.26 days

Table 8 Summary of exposure to fexofenadine in other controlled studies in pediatric subjects

		Placebo	Fexofenadine			Other
Summary statistics		(N=901)	15 mg BID (N=85)	30 mg BID (N=904)	Total (N=989)	(N=108)
Number of subjects (n)		892	84	902	986	108
Mean ± SD (days)		13.26 ± 3.65	8.24 ± 1.22	15.66 ± 5.48	15.03 ± 5.64	28.39 ± 2.54
Median (days)		15.00	8.00	15.00	15.00	29.00
Min : Max (days)		1.0 : 29.0	3.0 : 11.0	1.0 : 29.0	1.0 : 29.0	4.0 : 29.0
Min = minimum; Max = maximum; N = total number of subjects/subjects; n = number of subjects/subjects with data. Other includes 1 g ketotifen. Source: Appendix 5.3.5.3.1.7						
Age group (years)						
<2	n (%)	199 (22.1)	85 (100.0)	108 (11.9)	193 (19.5)	0
≥2 to ≤5	n (%)	232 (25.7)	0	221 (24.4)	221 (22.3)	0
≥6 to ≤12	n (%)	470 (52.2)	0	575 (63.6)	575 (58.1)	108 (100)

A total of 193 children < 2 years of age was exposed to fexofenadine at any dose. Two hundred and twenty one children from 2 to ≤ 5 were exposed to fexofenadine 30 mg BID,

and 575 children aged ≥ 6 and ≤ 12 were exposed to 30 mg BID which is the prescription dose in children 2 to 12 years of age.

In the long-term safety studies in adult subjects (Table 9), a total of 1109 subjects were exposed to fexofenadine for a mean of 259.63 days. The majority, a total of 901 subjects, were exposed to a total daily dose of 240 mg fexofenadine, which is higher than the recommended total daily dose for fexofenadine in adult subjects. Also in long-term studies 444 subjects were exposed to placebo for a mean of 232.24 days and 220 were exposed to montelukast for a mean of 302.71 days.

Table 9 Exposure to fexofenadine in long-term safety studies in adult subjects

	Placebo	Fexofenadine			Other
Summary statistics	(N=453)	60 mg BID (N=220)	>180 mg daily (N=901)	Total (N=1121)	(N=220)
Number of subjects (n)	444	216	893	1109	220
Mean ± SD (days)	232.24 ± 107.45	158.03 ± 41.25	284.21± 117.99	259.63 ± 118.47	302.71 ± 107.73
Median (days)	182.00	172.00	357.00	339.00	358.00
Min : Max (days)	1.0 : 427.0	8.0 : 205.0	1.0 : 392.0	1.0 : 392.0	1.0 : 375.0

Other includes 5 mg and 10 mg montelukast.
Min = minimum; Max = maximum; N = total number of subjects/subjects; n = number of subjects/subjects with data.
Source: Appendix 5.3.5.3.1.8

7.2.2 Explorations for Dose Response

The Sponsor analyzed the pooled incidence of TEAEs in the adult population, including all pivotal controlled and other controlled studies, by dose group. The analysis revealed that the 3 most frequently cited TEAEs, in decreasing order, were headache, nasopharyngitis, and oropharyngeal pain. An increase in the number of subjects reporting TEAEs was found in comparing doses of fexofenadine from180 mg QD to 360 mg QD, versus doses > 360 mg QD, suggesting a dose relationship (for additional discussion, see Section 7.3.1). However, upon examination of individual TEAEs, no obvious dose relationship was observed, except perhaps for headache which was more common at doses >360 mg QD (above the recommended dose in this application).

MO Comment *There is no clear dose relation in the incidence of TEAEs.*

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology section and Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See Section 2.4.

7.3 Major Safety Results

The clinical trial safety database for this application comprised 136 unique studies with a total of 18361 subjects exposed to fexofenadine. In the biopharmaceutics and pharmacokinetic, as well as the pharmacodynamic studies categories, adverse events that occurred at any dose of fexofenadine are combined into the "fexofenadine" group. Subjects who participated in multiple studies within a study category and were exposed to the same treatment (fexofenadine in the clinical pharmacology studies) or the same fexofenadine dose (for the controlled studies) are counted only once in the total number of subjects. However, for those subjects, all adverse events from all studies in which they participated have been included in the analyses.

A standardized definition of treatment-emergent adverse event (TEAE) is used in the safety analyses. All adverse events have been categorized as pretreatment, on-treatment, and post-treatment adverse events using the following definitions:

Pre-treatment adverse events have been defined as adverse events that started before the first dose of the double-blind study medication and did not worsen in intensity (severity or frequency) after the first dose of double-blind study medication.

On-treatment adverse events have been defined as:

- Adverse events that started or increased in intensity from the time of the first dose of double-blind study medication up to 3 days following the last dose of double-blind study medication, regardless of relationship to study medication.
- In crossover studies, the on-treatment period for a given treatment or dose was defined as the period from the time of dosing to the time of subsequent dosing. The on-treatment period, therefore, included the washout period between treatments or doses regardless of whether the subject received placebo during this period or no study medication at all. The on-treatment period for the last treatment or dose was defined as up to 3 days or 72 hours following the last dose of study medication.

- Adverse events that started more than 3 days or 72 hours after the last dose of double-blind study medication and were assessed by the Investigator as being "possibly related" to the study medication, or were serious adverse events.
- Post-treatment adverse events have been defined as adverse events that (1) started more than 3 days or 72 hours after the last dose of double-blind study medication and were assessed by the Investigator as being "not related" to study medication, and (2) were not serious.

Adverse events that started prior to randomization and continued without worsening during the double-blind treatment period, or that started after completion of the study, do not meet the definition of treatment-emergent and are not included in the analyses. However, they are included in the subject listings of adverse events and marked as not treatment-emergent.

The most common treatment-emergent adverse events are summarized by category of study in Tables 10-16 and are similar across all the categories. Table 10 gives the pooled TEAEs for biopharmaceutics and pharmacokinetic studies, and Table 11 gives them for pharmacodynamic studies.

Table 10 Treatment-emergent adverse events in biopharmaceutics and pharmacokinetic studies in adult subjects (cut-off: incidence of at least 0.5%)

MedDRA preferred term	Fexofenadine (N=1175)
Number (%) of subjects with TEAEs	232 (19.74%)
Headache	60 (5.11%)
Nausea	16 (1.36%)
Haematocrit decreased	12 (1.02%)
Blood bicarbonate increased	11 (0.94%)
Somnolence	11 (0.94%)
Dizziness	10 (0.85%)
Monocyte count increased	7 (0.60%)
Blood phosphorus increased	6 (0.51%)
Diarrhoea	6 (0.51%)
Syncope	6 (0.51%)
Upper respiratory tract infection	6 (0.51%)

Includes data from safety evaluable subjects in Biopharmaceutics and Human PK Studies. Presented are TEAEs that occurred in at least 0.5% of all subjects treated with fexofenadine HCl, sorted by frequency.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext.sas OUT=REPORT/OUTPUT/ae0075intxt_j.rtf (16NOV2009 - 20:00)
Source: Appendix 5.3.5.3.3.1

MO Comment *The blood draws for the trials may have contributed to decreased hematocrits in* Table 10. *The GIDB indicates that the syncope cases in* Table 10 *were nonserious and did not cause subjects to withdraw from the study. Descriptions provided for two of the syncope cases in* Table 10 *included vasovagal response and hypoglycemia.*

Table 11 Summary of treatment-emergent adverse events in pharmacodynamic studies in adult subjects

MedDRA preferred term	Fexofenadine (N=1800)
Number (%) of subjects with TEAEs	207 (11.50%)
Headache	66 (3.67%)
Somnolence	16 (0.89%)
Dizziness	14 (0.78%)
Nausea	14 (0.78%)
Back pain	9 (0.50%)

Includes data from safety evaluable subjects in Human PD Studies. Presented are TEAEs that occurred in at least 0.5% of all subjects treated with fexofenadine HCl, sorted by frequency.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext.sas OUT=REPORT/OUTPUT/ae0076intxt_j.rtf (16NOV2009 - 20:01)
Source: Appendix 5.3.5.3.3.5

An analysis of TEAEs, in which all biopharmaceutics, pharmacokinetic, and pharmacodynamic studies in the adult population were pooled, was performed. These analyses revealed that the most frequently cited TEAEs, were headache, nausea, and somnolence. No obvious dose relationship was observed for these TEAEs, except perhaps for headache which was more common at doses of fexofenadine of 180 mg BID or higher.

The pooled analysis of TEAEs in all biopharmaceutics, pharmacokinetic, and pharmacodynamic studies in the pediatric population is shown in Table 12. The incidences of these events are not causes for concern.

Table 12 Summary of treatment-emergent adverse events in biopharmaceutics, pharmacokinetic, and pharmacodynamic studies in pediatric subjects (cut-off: incidence of at least 1%)

MedDRA preferred term	Fexofenadine (N=214)
Number (%) of subjects with TEAEs	68 (31.78%)
Abdominal pain	7 (3.27%)
Somnolence	6 (2.80%)
Viral infection	5 (2.34%)
Lymphadenopathy	4 (1.87%)
Nausea	4 (1.87%)
Rhinorrhoea	4 (1.87%)
Cough	3 (1.40%)
Headache	3 (1.40%)
Venous insufficiency	3 (1.40%)

Includes data from safety evaluable subjects in Biopharmaceutics and Human PK and PD Studies. Presented are TEAEs that occurred in at least 1% of all subjects treated with fexofenadine HCl, sorted by frequency.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext.sas OUT=REPORT/OUTPUT/ae0077intxt_j.rtf (16NOV2009 - 20:01)
Source: Appendix 5.3.5.3.3.10

Table **13** summarizes TEAEs in pivotal, placebo-controlled studies in adult subjects. For each MedDRA Primary System Organ Class, the incidences are compared for placebo, for six dose groups (<60 mg BID, 60 mg BID, 120 to 180 mg daily, 180 mg QD, 180 to 360 mg daily, and >360 mg daily), and for fexofenadine total (all groups combined) in the pooled pivotal trials. In Table 14, the TEAEs are shown in similar format for the pooled pivotal and other controlled studies in adult subjects, comparing placebo, the same six dose groups, and fexofenadine total.

None of the TEAEs had a difference of 1 percentage point or more between the percentages in the placebo and the total fexofenadine treatment group. TEAEs reported in greater percentages in the fexofenadine 180 mg QD treatment group compared to the placebo group, by a difference of 1 percentage point or more, were headache, back pain, nasopharyngitis, and myalgia. No differences in percentages of 1 percentage point or more were found between the fexofenadine 60 mg BID and placebo treatment groups or the fexofenadine 120 to 180 mg daily and placebo treatment groups.

MO Comment *Sponsor analyses of TEAEs in the adult population, in which all pivotal controlled studies were pooled, revealed that the four most frequently cited TEAEs, in decreasing order, were headache, nasopharyngitis, oropharyngeal pain and nausea. The incidences of these events were similar for the study drugs and for placebo. For example,* Table 13 *shows that headache was reported by 8.09% of 1236 subjects given placebo, and by 8.92% of 3901 subjects on study drug (not statistically significant).*

The reviewer analyzed the pooled adverse event incidences in

Table 13 and Table 14 to examine possible dose dependences for all TEAEs, for headaches, and for somnolence.

Table 13 Summary of treatment-emergent adverse events in pivotal controlled studies in adult subjects versus dosing group (cut-off: incidence of at least 1% in any of the fexofenadine treatment groups)

Primary System Organ Class MedDRA preferred term	Placebo (N=1236)	Fexofenadine <60 mg BID (N=1117)	60 mg BID (N=871)	120 - 180 mg daily (N=681)	180 mg QD (N=450)	>180 - <360 mg daily (N=463)	>=360 mg daily (N=319)	Total (N=3901)
Number (%) of subjects with TEAEs	460 (37.22%)	392 (35.09%)	330 (37.89%)	183 (26.87%)	138 (30.67%)	194 (41.90%)	147 (46.08%)	1384 (35.48%)
Infections and infestations	100 (8.09%)	77 (6.89%)	63 (7.23%)	33 (4.85%)	36 (8.00%)	54 (11.66%)	40 (12.54%)	303 (7.77%)
Nasopharyngitis	19 (1.54%)	16 (1.43%)	14 (1.61%)	7 (1.03%)	12 (2.67%)	11 (2.38%)	13 (4.08%)	73 (1.87%)
Upper respiratory tract infection	17 (1.38%)	15 (1.34%)	6 (0.69%)	5 (0.73%)	6 (1.33%)	12 (2.59%)	6 (1.88%)	50 (1.28%)
Influenza	6 (0.49%)	9 (0.81%)	9 (1.03%)	2 (0.29%)	2 (0.44%)	5 (1.08%)	5 (1.57%)	32 (0.82%)
Gastroenteritis viral	8 (0.65%)	5 (0.45%)	5 (0.57%)	1 (0.15%)	3 (0.67%)	3 (0.65%)	6 (1.88%)	23 (0.59%)
Psychiatric disorders	11 (0.89%)	18 (1.61%)	11 (1.26%)	8 (1.17%)	3 (0.67%)	8 (1.73%)	8 (2.51%)	56 (1.44%)
Insomnia	6 (0.49%)	5 (0.45%)	5 (0.57%)	5 (0.73%)	1 (0.22%)	6 (1.30%)	5 (1.57%)	27 (0.69%)
Nervous system disorders	138 (11.17%)	126 (11.28%)	105 (12.06%)	57 (8.37%)	43 (9.56%)	72 (15.55%)	52 (16.30%)	455 (11.66%)
Headache	100 (8.09%)	105 (9.40%)	74 (8.50%)	41 (6.02%)	36 (8.00%)	54 (11.66%)	38 (11.91%)	348 (8.92%)
Sinus headache	6 (0.49%)	11 (0.98%)	10 (1.15%)	4 (0.59%)	2 (0.44%)	6 (1.30%)	6 (1.88%)	39 (1.00%)
Dizziness	12 (0.97%)	4 (0.36%)	8 (0.92%)	5 (0.73%)	4 (0.89%)	8 (1.73%)	3 (0.94%)	32 (0.82%)

Primary System Organ Class MedDRA preferred term	Placebo (N=1236)	Fexofenadine <60 mg BID (N=1117)	60 mg BID (N=871)	120 - 180 mg daily (N=681)	180 mg QD (N=450)	>180 - <360 mg daily (N=463)	>=360 mg daily (N=319)	Total (N=3901)
Somnolence	3 (0.24%)	7 (0.63%)	10 (1.15%)	4 (0.59%)	3 (0.67%)	4 (0.86%)	3 (0.94%)	31 (0.79%)
Eye disorders	7 (0.57%)	12 (1.07%)	8 (0.92%)	4 (0.59%)	4 (0.89%)	5 (1.08%)	3 (0.94%)	36 (0.92%)
Ear and labyrinth disorders	11 (0.89%)	11 (0.98%)	9 (1.03%)	0	2 (0.44%)	1 (0.22%)	4 (1.25%)	27 (0.69%)
Respiratory, thoracic and mediastinal disorders	82 (6.63%)	64 (5.73%)	51 (5.86%)	31 (4.55%)	26 (5.78%)	26 (5.62%)	27 (8.46%)	225 (5.77%)
Oropharyngeal pain	25 (2.02%)	23 (2.06%)	16 (1.84%)	10 (1.47%)	6 (1.33%)	9 (1.94%)	12 (3.76%)	76 (1.95%)
Epistaxis	8 (0.65%)	8 (0.72%)	8 (0.92%)	5 (0.73%)	5 (1.11%)	2 (0.43%)	2 (0.63%)	30 (0.77%)
Gastrointestinal disorders	72 (5.83%)	69 (6.18%)	62 (7.12%)	26 (3.82%)	20 (4.44%)	29 (6.26%)	34 (10.66%)	240 (6.15%)
Nausea	21 (1.70%)	21 (1.88%)	16 (1.84%)	4 (0.59%)	1 (0.22%)	8 (1.73%)	12 (3.76%)	62 (1.59%)
Diarrhoea	9 (0.73%)	15 (1.34%)	9 (1.03%)	2 (0.29%)	1 (0.22%)	3 (0.65%)	6 (1.88%)	36 (0.92%)
Abdominal discomfort	5 (0.40%)	8 (0.72%)	11 (1.26%)	4 (0.59%)	2 (0.44%)	2 (0.43%)	3 (0.94%)	30 (0.77%)
Abdominal pain upper	10 (0.81%)	13 (1.16%)	3 (0.34%)	2 (0.29%)	3 (0.67%)	2 (0.43%)	4 (1.25%)	27 (0.69%)
Dyspepsia	12 (0.97%)	5 (0.45%)	7 (0.80%)	2 (0.29%)	3 (0.67%)	6 (1.30%)	4 (1.25%)	27 (0.69%)

Primary System Organ Class MedDRA preferred term	Placebo (N=1236)	Fexofenadine <60 mg BID (N=1117)	60 mg BID (N=871)	120 - 180 mg daily (N=681)	180 mg QD (N=450)	>180 - <360 mg daily (N=463)	>=360 mg daily (N=319)	Total (N=3901)
Skin and subcutaneous tissue disorders	36 (2.91%)	16 (1.43%)	12 (1.38%)	8 (1.17%)	9 (2.00%)	10 (2.16%)	8 (2.51%)	63 (1.61%)
Musculoskeletal and connective tissue disorders	40 (3.24%)	45 (4.03%)	38 (4.36%)	21 (3.08%)	23 (5.11%)	15 (3.24%)	19 (5.96%)	161 (4.13%)
Myalgia	10 (0.81%)	15 (1.34%)	11 (1.26%)	5 (0.73%)	6 (1.33%)	6 (1.30%)	7 (2.19%)	50 (1.28%)
Back pain	7 (0.57%)	13 (1.16%)	6 (0.69%)	9 (1.32%)	9 (2.00%)	4 (0.86%)	8 (2.51%)	49 (1.26%)
Reproductive system and breast disorders	13 (1.05%)	12 (1.07%)	14 (1.61%)	6 (0.88%)	1 (0.22%)	8 (1.73%)	7 (2.19%)	48 (1.23%)
Dysmenorrhoea	11 (0.89%)	5 (0.45%)	12 (1.38%)	6 (0.88%)	1 (0.22%)	7 (1.51%)	5 (1.57%)	36 (0.92%)
General disorders and administration site conditions	40 (3.24%)	29 (2.60%)	25 (2.87%)	20 (2.94%)	8 (1.78%)	24 (5.18%)	8 (2.51%)	114 (2.92%)
Fatigue	8 (0.65%)	6 (0.54%)	8 (0.92%)	8 (1.17%)	2 (0.44%)	6 (1.30%)	3 (0.94%)	33 (0.85%)
Pyrexia	4 (0.32%)	2 (0.18%)	1 (0.11%)	4 (0.59%)	1 (0.22%)	5 (1.08%)	0	13 (0.33%)
Investigations	36 (2.91%)	34 (3.04%)	40 (4.59%)	7 (1.03%)	2 (0.44%)	24 (5.18%)	14 (4.39%)	121 (3.10%)
White blood cell count decreased	5 (0.40%)	3 (0.27%)	6 (0.69%)	0	0	6 (1.30%)	2 (0.63%)	17 (0.44%)

Primary System Organ Class MedDRA preferred term	Placebo (N=1236)	Fexofenadine <60 mg BID (N=1117)	60 mg BID (N=871)	120 - 180 mg daily (N=681)	180 mg QD (N=450)	>180 - <360 mg daily (N=463)	>=360 mg daily (N=319)	Total (N=3901)
Alanine aminotransferase increased	2 (0.16%)	2 (0.18%)	9 (1.03%)	3 (0.44%)	0	1 (0.22%)	1 (0.31%)	16 (0.41%)
Blood triglycerides increased	5 (0.40%)	4 (0.36%)	4 (0.46%)	0	0	2 (0.43%)	4 (1.25%)	14 (0.36%)
Blood calcium decreased	2 (0.16%)	2 (0.18%)	4 (0.46%)	0	0	5 (1.08%)	0	11 (0.28%)
Injury, poisoning and procedural complications	23 (1.86%)	10 (0.90%)	12 (1.38%)	8 (1.17%)	7 (1.56%)	7 (1.51%)	8 (2.51%)	52 (1.33%)

Includes data from safety evaluable subjects in Pivotal Controlled Studies. Presented are TEAEs that occurred in at least 1% of subjects in any of the fexofenadine treatment groups grouped by SOC. TEAEs are sorted by frequency in the total fexofenadine HCl group. SOCs are sorted in internationally agreed order.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext_hd.sas OUT=REPORT/OUTPUT/ae0925intxt_i.rtf (21JAN2010 - 21:59)
Source: Appendix 5.3.5.3.3.20

Table 14 Summary of treatment-emergent adverse events in pivotal and other controlled studies in adult subjects receiving doses of 180 mg twice daily or higher (cut-off: incidence of at least 1% in any of the fexofenadine treatment groups)

Primary System Organ Class MedDRA preferred term	Placebo (N=4808)	Fexofenadine <60 mg BID (N=1796)	60 mg BID (N=2329)	120 - 180 mg daily (N=2224)	180 mg QD (N=1788)	>180 - <360 mg daily (N=3739)	>=360 mg daily (N=319)	Total (N=12195)	Other (N=1330)
Number (%) of subjects with TEAEs	1832 (38.10%)	633 (35.24%)	750 (32.20%)	759 (34.13%)	659 (36.86%)	1388 (37.12%)	147 (46.08%)	4336 (35.56%)	470 (35.34%)
Infections and infestations	572 (11.90%)	114 (6.35%)	164 (7.04%)	190 (8.54%)	206 (11.52%)	528 (14.12%)	40 (12.54%)	1242 (10.18%)	138 (10.38%)
Nasopharyngitis	147 (3.06%)	35 (1.95%)	56 (2.40%)	56 (2.52%)	58 (3.24%)	160 (4.28%)	13 (4.08%)	378 (3.10%)	35 (2.63%)
Upper respiratory tract infection	96 (2.00%)	15 (0.84%)	19 (0.82%)	33 (1.48%)	47 (2.63%)	89 (2.38%)	6 (1.88%)	209 (1.71%)	29 (2.18%)
Influenza	41 (0.85%)	10 (0.56%)	19 (0.82%)	23 (1.03%)	18 (1.01%)	45 (1.20%)	5 (1.57%)	120 (0.98%)	17 (1.28%)
Sinusitis	77 (1.60%)	3 (0.17%)	10 (0.43%)	8 (0.36%)	28 (1.57%)	59 (1.58%)	2 (0.63%)	110 (0.90%)	14 (1.05%)
Gastroenteritis viral	32 (0.67%)	5 (0.28%)	9 (0.39%)	4 (0.18%)	6 (0.34%)	21 (0.56%)	6 (1.88%)	51 (0.42%)	7 (0.53%)
Psychiatric disorders	42 (0.87%)	22 (1.22%)	22 (0.94%)	15 (0.67%)	16 (0.89%)	36 (0.96%)	8 (2.51%)	119 (0.98%)	10 (0.75%)
Insomnia	23 (0.48%)	7 (0.39%)	11 (0.47%)	9 (0.40%)	8 (0.45%)	19 (0.51%)	5 (1.57%)	59 (0.48%)	6 (0.45%)

Primary System Organ Class MedDRA preferred term	Placebo (N=4808)	Fexofenadine <60 mg BID (N=1796)	Fexofenadine 60 mg BID (N=2329)	Fexofenadine 120 - 180 mg daily (N=2224)	Fexofenadine 180 mg QD (N=1788)	Fexofenadine >180 - <360 mg daily (N=3739)	Fexofenadine >=360 mg daily (N=319)	Fexofenadine Total (N=12195)	Other (N=1330)
Nervous system disorders	552 (11.48%)	240 (13.36%)	244 (10.48%)	263 (11.83%)	206 (11.52%)	417 (11.15%)	52 (16.30%)	1422 (11.66%)	159 (11.95%)
Headache	419 (8.71%)	181 (10.08%)	158 (6.78%)	195 (8.77%)	156 (8.72%)	296 (7.92%)	38 (11.91%)	1024 (8.40%)	92 (6.92%)
Somnolence	31 (0.64%)	34 (1.89%)	57 (2.45%)	29 (1.30%)	24 (1.34%)	35 (0.94%)	3 (0.94%)	182 (1.49%)	42 (3.16%)
Sinus headache	40 (0.83%)	12 (0.67%)	16 (0.69%)	8 (0.36%)	13 (0.73%)	39 (1.04%)	6 (1.88%)	94 (0.77%)	8 (0.60%)
Eye disorders	47 (0.98%)	22 (1.22%)	16 (0.69%)	19 (0.85%)	20 (1.12%)	33 (0.88%)	3 (0.94%)	113 (0.93%)	11 (0.83%)
Ear and labyrinth disorders	42 (0.87%)	14 (0.78%)	15 (0.64%)	15 (0.67%)	13 (0.73%)	28 (0.75%)	4 (1.25%)	89 (0.73%)	9 (0.68%)
Respiratory, thoracic and mediastinal disorders	393 (8.17%)	105 (5.85%)	113 (4.85%)	129 (5.80%)	106 (5.93%)	260 (6.95%)	27 (8.46%)	740 (6.07%)	81 (6.09%)
Oropharyngeal pain	99 (2.06%)	36 (2.00%)	32 (1.37%)	44 (1.98%)	40 (2.24%)	78 (2.09%)	12 (3.76%)	242 (1.98%)	21 (1.58%)
Epistaxis	42 (0.87%)	14 (0.78%)	24 (1.03%)	24 (1.08%)	17 (0.95%)	37 (0.99%)	2 (0.63%)	118 (0.97%)	11 (0.83%)
Cough	57 (1.19%)	19 (1.06%)	11 (0.47%)	26 (1.17%)	11 (0.62%)	27 (0.72%)	3 (0.94%)	97 (0.80%)	20 (1.50%)

Primary System Organ Class MedDRA preferred term	Placebo (N=4808)	Fexofenadine <60 mg BID (N=1796)	60 mg BID (N=2329)	120 - 180 mg daily (N=2224)	180 mg QD (N=1788)	>180 - <360 mg daily (N=3739)	>=360 mg daily (N=319)	Total (N=12195)	Other (N=1330)
Asthma	55 (1.14%)	9 (0.50%)	8 (0.34%)	8 (0.36%)	11 (0.62%)	39 (1.04%)	1 (0.31%)	76 (0.62%)	7 (0.53%)
Gastrointestinal disorders	290 (6.03%)	126 (7.02%)	132 (5.67%)	114 (5.13%)	100 (5.59%)	232 (6.20%)	34 (10.66%)	738 (6.05%)	77 (5.79%)
Nausea	69 (1.44%)	39 (2.17%)	29 (1.25%)	25 (1.12%)	19 (1.06%)	38 (1.02%)	12 (3.76%)	162 (1.33%)	21 (1.58%)
Diarrhoea	50 (1.04%)	26 (1.45%)	25 (1.07%)	14 (0.63%)	11 (0.62%)	53 (1.42%)	6 (1.88%)	135 (1.11%)	9 (0.68%)
Abdominal pain upper	34 (0.71%)	18 (1.00%)	14 (0.60%)	17 (0.76%)	8 (0.45%)	22 (0.59%)	4 (1.25%)	83 (0.68%)	9 (0.68%)
Dyspepsia	35 (0.73%)	9 (0.50%)	9 (0.39%)	12 (0.54%)	9 (0.50%)	23 (0.62%)	4 (1.25%)	66 (0.54%)	5 (0.38%)
Skin and subcutaneous tissue disorders	117 (2.43%)	36 (2.00%)	24 (1.03%)	44 (1.98%)	30 (1.68%)	61 (1.63%)	8 (2.51%)	203 (1.66%)	15 (1.13%)
Musculoskeletal and connective tissue disorders	168 (3.49%)	55 (3.06%)	54 (2.32%)	60 (2.70%)	94 (5.26%)	144 (3.85%)	19 (5.96%)	426 (3.49%)	28 (2.11%)
Back pain	55 (1.14%)	15 (0.84%)	12 (0.52%)	26 (1.17%)	36 (2.01%)	52 (1.39%)	8 (2.51%)	149 (1.22%)	9 (0.68%)
Myalgia	34 (0.71%)	15 (0.84%)	15 (0.64%)	11 (0.49%)	19 (1.06%)	30 (0.80%)	7 (2.19%)	97 (0.80%)	2 (0.15%)

Primary System Organ Class MedDRA preferred term	Placebo (N=4808)	Fexofenadine <60 mg BID (N=1796)	60 mg BID (N=2329)	120 - 180 mg daily (N=2224)	180 mg QD (N=1788)	>180 - <360 mg daily (N=3739)	>=360 mg daily (N=319)	Total (N=12195)	Other (N=1330)
Reproductive system and breast disorders	56 (1.16%)	17 (0.95%)	22 (0.94%)	11 (0.49%)	11 (0.62%)	42 (1.12%)	7 (2.19%)	110 (0.90%)	6 (0.45%)
Dysmenorrhoea	42 (0.87%)	9 (0.50%)	15 (0.64%)	9 (0.40%)	8 (0.45%)	32 (0.86%)	5 (1.57%)	78 (0.64%)	6 (0.45%)
General disorders and administration site conditions	153 (3.18%)	58 (3.23%)	62 (2.66%)	74 (3.33%)	64 (3.58%)	121 (3.24%)	8 (2.51%)	387 (3.17%)	43 (3.23%)
Fatigue	27 (0.56%)	12 (0.67%)	14 (0.60%)	23 (1.03%)	7 (0.39%)	20 (0.53%)	3 (0.94%)	79 (0.65%)	13 (0.98%)
Investigations	128 (2.66%)	57 (3.17%)	106 (4.55%)	56 (2.52%)	43 (2.40%)	88 (2.35%)	14 (4.39%)	364 (2.98%)	19 (1.43%)
Blood triglycerides increased	11 (0.23%)	4 (0.22%)	6 (0.26%)	1 (<0.1%)	1 (<0.1%)	8 (0.21%)	4 (1.25%)	24 (0.20%)	3 (0.23%)
Injury, poisoning and procedural complications	85 (1.77%)	13 (0.72%)	24 (1.03%)	28 (1.26%)	30 (1.68%)	62 (1.66%)	8 (2.51%)	165 (1.35%)	20 (1.50%)

Includes data from safety evaluable subjects in All Controlled Studies. Presented are TEAEs that occurred in at least 1% of subjects in any of the fexofenadine treatment groups grouped by SOC. TEAEs are sorted by frequency in the total fexofenadine HCl group. SOCs are sorted in internationally agreed order.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext_hd.sas OUT=REPORT/OUTPUT/ae0926intxt_i.rtf (21JAN2010 - 22:04)
Source: Appendix 5.3.5.3.3.34

For Table 13*, with the pooled safety results for all pivotal controlled trials, the reported incidences of TEAEs were highest (46% and 42%) in the two highest dose groups (above 180 mg daily). The differences among dose groups are statistically significant (p< 0.0001). The incidences of headaches were also highest in the two highest dose groups (p=0.0094). Although the higher than 180 mg treatment groups had the highest percentage of subjects who had TEAEs, the 180 mg QD and 120 to 180 mg treatment groups had the lowest percentages of subjects who had TEAEs, indicating that the incidence of TEAEs was not consistently dose dependent.*

Similar analyses were performed on Table 14 *which pooled safety results for all the controlled trials (pivotal and other). Again the highest rates of TEAEs were reported in the two highest dose groups (p< 0.0001). The incidence of headaches also varied across dose groups and was statistically significant (p=0.0014), although the dose dependence is less clear (the incidence in the second highest dose group, 180 to 360 mg daily, was less than for placebo).*

Although these tests reached statistical significance, it is cautioned that numerous individual trials were pooled for each of Table 13 *and* Table 14*, and the differences in TEAE rates may reflect differences in the trials.*

Hence the clinical trial data do not provide clear evidence for dose-dependence in the incidence of TEAEs, and headache in particular, in view of the differences in the results of various trials. Many of the trials pooled for Table 13 *and* Table 14 *have previously been reviewed for one or more of the fexofenadine NDAs* (Table 1).

Somnolence is the fifth most frequent TEAE in all controlled studies after headache, nasopharyngeal pain, oropharyngeal pain, and upper respiratory infection (Sponsor Table 5.3.5.3.3.33). Although the incidence of somnolence was generally low in the adult population, it was significantly different than placebo when examined in the controlled studies. The incidence of somnolence as a TEAE in Table 14 *was significantly greater (p<0.001) for the total fexofenadine group (182/12195 subjects, 1.5%) versus placebo (31/4803 subjects, 0.64%). Somnolence was also significantly greater in the total fexofenadine groups than in the placebo group for the studies in Table 13 (although not shown there as the incidences did not reach 1%). However, the reporting rate of somnolence was lower in the pivotal trials of* Table 13 *(total, 0.79%) than in the pivotal-plus-other trials of* Table 14 *(total, 1.49%). The trials in* Table 13 *are included in those of* Table 14*, so the difference is caused by a larger reporting rate in the other (not pivotal) controlled trials. Moreover, the incidence of somnolence did not exhibit a consistent dose dependence: in* Table 13 *and in* Table 14*, it was lower for the 120-180 mg QD and 180 mg QD groups than it was for the <60 mg BID and 60 mg BID groups.*

Table 15 shows the pooled results for TEAEs in pivotal, controlled pediatric trials (see Table 7 for a summary of exposures). Subjects were aged 6 to 11 years old.

In the analysis of the pivotal controlled combined studies in pediatric subjects, the percentage of subjects who reported at least 1 TEAE was similar between the total fexofenadine treatment group (34.67%) and placebo treatment group (35.37%). Similar to the studies in adult subjects,

the percentages of TEAEs across the 3 dose groups did not indicate that the incidences of TEAEs were dose dependent.

Treatment-emergent adverse events that occurred in the total fexofenadine treatment group at incidences greater than 1% and notably higher than the respective incidences in the placebo group were, in descending order in the total fexofenadine group, cough, pyrexia, upper respiratory tract infection, viral infection, nausea, and otitis media.

Table 15 Summary of treatment-emergent adverse events in pivotal controlled combined studies PJPR0066/77 in pediatric subjects (cut-off: incidence of at least 1% in the fexofenadine 30 mg twice a day or total groups)

		Fexofenadine			
Primary System Organ Class MedDRA preferred term	Placebo (N=229)	15 mg BID (N=224)	30 mg BID (N=209)	60 mg BID (N=213)	Total (N=646)
Number (%) of subjects with TEAEs	81 (35.37%)	76 (33.93%)	75 (35.89%)	73 (34.27%)	224 (34.67%)
Infections and infestations	23 (10.04%)	21 (9.38%)	19 (9.09%)	13 (6.10%)	53 (8.20%)
Upper respiratory tract infection	2 (0.87%)	4 (1.79%)	6 (2.87%)	1 (0.47%)	11 (1.70%)
Nasopharyngitis	2 (0.87%)	4 (1.79%)	2 (0.96%)	2 (0.94%)	8 (1.24%)
Viral infection	0	4 (1.79%)	1 (0.48%)	3 (1.41%)	8 (1.24%)
Otitis media	0	1 (0.45%)	5 (2.39%)	1 (0.47%)	7 (1.08%)
Psychiatric disorders	1 (0.44%)	4 (1.79%)	1 (0.48%)	2 (0.94%)	7 (1.08%)

Primary System Organ Class MedDRA preferred term	Placebo (N=229)	Fexofenadine 15 mg BID (N=224)	Fexofenadine 30 mg BID (N=209)	Fexofenadine 60 mg BID (N=213)	Fexofenadine Total (N=646)
Nervous system disorders	21 (9.17%)	18 (8.04%)	16 (7.66%)	26 (12.21%)	60 (9.29%)
Headache	17 (7.42%)	17 (7.59%)	15 (7.18%)	22 (10.33%)	54 (8.36%)
Respiratory, thoracic and mediastinal disorders	19 (8.30%)	16 (7.14%)	16 (7.66%)	14 (6.57%)	46 (7.12%)
Oropharyngeal pain	7 (3.06%)	7 (3.13%)	5 (2.39%)	4 (1.88%)	16 (2.48%)
Cough	3 (1.31%)	3 (1.34%)	8 (3.83%)	4 (1.88%)	15 (2.32%)
Epistaxis	3 (1.31%)	4 (1.79%)	3 (1.44%)	3 (1.41%)	10 (1.55%)
Wheezing	1 (0.44%)	0	3 (1.44%)	3 (1.41%)	6 (0.93%)
Gastrointestinal disorders	13 (5.68%)	15 (6.70%)	17 (8.13%)	12 (5.63%)	44 (6.81%)
Abdominal pain upper	8 (3.49%)	5 (2.23%)	4 (1.91%)	5 (2.35%)	14 (2.17%)
Nausea	0	1 (0.45%)	3 (1.44%)	3 (1.41%)	7 (1.08%)
Diarrhoea	1 (0.44%)	2 (0.89%)	3 (1.44%)	0	5 (0.77%)
Skin and subcutaneous tissue disorders	2 (0.87%)	2 (0.89%)	5 (2.39%)	5 (2.35%)	12 (1.86%)
Musculoskeletal and connective tissue disorders	4 (1.75%)	2 (0.89%)	6 (2.87%)	7 (3.29%)	15 (2.32%)
General disorders and administration site conditions	3 (1.31%)	7 (3.13%)	11 (5.26%)	9 (4.23%)	27 (4.18%)
Pyrexia	2 (0.87%)	4 (1.79%)	5 (2.39%)	3 (1.41%)	12 (1.86%)
Injury, poisoning and procedural complications	4 (1.75%)	6 (2.68%)	3 (1.44%)	6 (2.82%)	15 (2.32%)

Includes data from safety evaluable subjects in study PJPR0066/77. Presented are TEAEs that occurred in at least 1% of subjects in either of the following 2 treatment groups: total fexofenadine HCl, fexofenadine HCl 30 mg BID grouped by SOC. TEAEs are sorted by frequency in the total fexofenadine HCl group. SOCs are sorted in internationally agreed order.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext2_soc.sas OUT=REPORT/OUTPUT/ae0061intxt_i.rtf (04DEC2009 - 12:49)
Source: Appendix 5.3.5.3.3.22

Table 16 shows the pooled results for TEAEs in other (not pivotal), controlled pediatric trials (see Table 8 for exposure). The subjects were as young as 6 months of age.

Table 16 Summary of treatment-emergent adverse events in other controlled studies in pediatric subjects (cut-off: incidence of at least 1% in the fexofenadine 30 mg twice a day or total treatment groups)

Primary System Organ Class MedDRA preferred term	Placebo (N=901)	Fexofenadine 15 mg BID (N=85)	Fexofenadine 30 mg BID (N=904)	Fexofenadine Total (N=989)	Other (N=108)
Number (%) of subjects with TEAEs	311 (34.52%)	34 (40.00%)	285 (31.53%)	319 (32.25%)	53 (49.07%)
Infections and infestations	101 (11.21%)	11 (12.94%)	93 (10.29%)	104 (10.52%)	20 (18.52%)
Nasopharyngitis	9 (1.00%)	0	25 (2.77%)	25 (2.53%)	10 (9.26%)
Otitis media	15 (1.66%)	3 (3.53%)	16 (1.77%)	19 (1.92%)	0
Sinusitis	2 (0.22%)	1 (1.18%)	10 (1.11%)	11 (1.11%)	0
Upper respiratory tract infection	19 (2.11%)	1 (1.18%)	10 (1.11%)	11 (1.11%)	0
Nervous system disorders	30 (3.33%)	1 (1.18%)	44 (4.87%)	45 (4.55%)	11 (10.19%)
Headache	22 (2.44%)	0	32 (3.54%)	32 (3.24%)	1 (0.93%)
Ear and labyrinth disorders	15 (1.66%)	1 (1.18%)	10 (1.11%)	11 (1.11%)	0
Respiratory, thoracic and mediastinal disorders	81 (8.99%)	5 (5.88%)	79 (8.74%)	84 (8.49%)	15 (13.89%)
Cough	17 (1.89%)	2 (2.35%)	23 (2.54%)	25 (2.53%)	1 (0.93%)
Epistaxis	10 (1.11%)	0	11 (1.22%)	11 (1.11%)	3 (2.78%)
Oropharyngeal pain	7 (0.78%)	0	11 (1.22%)	11 (1.11%)	1 (0.93%)
Asthma	18 (2.00%)	0	10 (1.11%)	10 (1.01%)	4 (3.70%)
Gastrointestinal disorders	76 (8.44%)	18 (21.18%)	72 (7.96%)	90 (9.10%)	4 (3.70%)
Vomiting	38 (4.22%)	12 (14.12%)	21 (2.32%)	33 (3.34%)	0
Diarrhoea	12 (1.33%)	4 (4.71%)	11 (1.22%)	15 (1.52%)	3 (2.78%)
Skin and subcutaneous tissue disorders	25 (2.77%)	5 (5.88%)	24 (2.65%)	29 (2.93%)	2 (1.85%)

Primary System Organ Class MedDRA preferred term	Placebo (N=901)	Fexofenadine 15 mg BID (N=85)	Fexofenadine 30 mg BID (N=904)	Fexofenadine Total (N=989)	Other (N=108)
General disorders and administration site conditions	37 (4.11%)	1 (1.18%)	34 (3.76%)	35 (3.54%)	0
Pyrexia	31 (3.44%)	1 (1.18%)	25 (2.77%)	26 (2.63%)	0
Investigations	5 (0.55%)	1 (1.18%)	12 (1.33%)	13 (1.31%)	10 (9.26%)
Injury, poisoning and procedural complications	24 (2.66%)	1 (1.18%)	18 (1.99%)	19 (1.92%)	4 (3.70%)

Includes data from safety evaluable subjects in Other Controlled Studies. Presented are TEAEs that occurred in at least 1% of subjects in either of the following 2 treatment groups: total fexofenadine HCl, fexofenadine HCl 30 mg BID grouped by SOC. TEAEs are sorted by frequency in the total fexofenadine HCl group. SOCs are sorted in internationally agreed order.
Other is ketotifen 1 g.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext2_soc.sas OUT=REPORT/OUTPUT/ae0063intxt_i.rtf (04DEC2009 - 12:50)
Source: Appendix 5.3.5.3.3.27

MO Comment *The overall incidence of TEAEs is consistent between the pediatric pivotal trials and the other trials: for total fexofenadine 224/646 (34.6%) TEAEs in the pivotal pediatric trials of* Table 15*, versus a slightly lower value 319/989 (32.3%) in the other trials of* Table 16*. However, the reported incidences of headaches were significantly higher in the pivotal trials, 54/646 (8.36%) than in the other trials, 32/989 (3.24%).*

The other (not pivotal) controlled trials compared two fexofenadine doses, 15 mg BID and 30 mg BID. The reported incidences of headaches in these other trials were 0/85 in the lower dose group, versus 32/904 (or 3.54%) in the higher dose group. This difference is marginally significant, p=0.054 by Fisher exact. However, the trials of Table 16 *enrolled younger subjects who may be less able to complain of headache.*

*In the combined analysis of other controlled studies in pediatric subjects, the percentage of subjects who reported at least 1 TEAE was slightly lower in the total fexofenadine treatment group (32.25%) compared to the placebo treatment group (34.52%). In the other treatment group, which included subjects who received ketotifen, the percentage of subjects who reported at least 1 TEAE was 49.07%. The percentage of subjects who reported at least 1 TEAE in the fexofenadine 15 mg BID treatment group (40.00%) was higher than in the fexofenadine 30 mg BID treatment group (*Table 16*). This may be due to the younger subjects (6 months to 2 years) treated with this dose, who also reported a higher incidence of vomiting.*

As was the case for the studies in adult subjects, the incidences of TEAEs across the 3 dose groups did not display a consistent dose response effect.

The GIDB also included long term safety studies (Table 9) in adult subjects exposed to fexofenadine for six months or a year. Table 17 shows the TEAEs reported in these studies.

Table 17 TEAEs in adult long-term safety studies (incidence >2.5% in Total group)

Primary System Organ Class MedDRA preferred term	Placebo (N=453)	Fexofenadine 60 mg BID (N=220)	Fexofenadine >180 mg daily (N=901)	Fexofenadine Total (N=1121)
Number (%) of subjects with TEAEs	382 (84.33%)	161 (73.18%)	762 (84.57%)	923 (82.34%)
Infections and infestations	226 (49.89%)	71 (32.27%)	551 (61.15%)	622 (55.49%)
Upper respiratory tract infection	70 (15.45%)	22 (10.00%)	197 (21.86%)	219 (19.54%)
Nasopharyngitis	72 (15.89%)	29 (13.18%)	176 (19.53%)	205 (18.29%)
Sinusitis	28 (6.18%)	7 (3.18%)	115 (12.76%)	122 (10.88%)
Influenza	32 (7.06%)	8 (3.64%)	63 (6.99%)	71 (6.33%)
Bronchitis	8 (1.77%)	3 (1.36%)	64 (7.10%)	67 (5.98%)
Gastroenteritis viral	15 (3.31%)	4 (1.82%)	31 (3.44%)	35 (3.12%)
Urinary tract infection	11 (2.43%)	1 (0.45%)	30 (3.33%)	31 (2.77%)
Viral upper respiratory tract infection	17 (3.75%)	0	30 (3.33%)	30 (2.68%)
Psychiatric disorders	16 (3.53%)	5 (2.27%)	50 (5.55%)	55 (4.91%)
Insomnia	6 (1.32%)	3 (1.36%)	26 (2.89%)	29 (2.59%)
Nervous system disorders	134 (29.58%)	41 (18.64%)	257 (28.52%)	298 (26.58%)
Headache	109 (24.06%)	31 (14.09%)	190 (21.09%)	221 (19.71%)
Sinus headache	16 (3.53%)	2 (0.91%)	35 (3.88%)	37 (3.30%)
Respiratory, thoracic and mediastinal disorders	90 (19.87%)	32 (14.55%)	307 (34.07%)	339 (30.24%)
Asthma	0	0	102 (11.32%)	102 (9.10%)
Oropharyngeal pain	21 (4.64%)	8 (3.64%)	91 (10.10%)	99 (8.83%)
Nasal congestion	20 (4.42%)	6 (2.73%)	39 (4.33%)	45 (4.01%)
Cough	9 (1.99%)	2 (0.91%)	39 (4.33%)	41 (3.66%)
Gastrointestinal disorders	97 (21.41%)	32 (14.55%)	222 (24.64%)	254 (22.66%)
Diarrhoea	13 (2.87%)	4 (1.82%)	45 (4.99%)	49 (4.37%)
Nausea	18 (3.97%)	2 (0.91%)	42 (4.66%)	44 (3.93%)
Abdominal discomfort	13 (2.87%)	4 (1.82%)	39 (4.33%)	43 (3.84%)

Primary System Organ Class MedDRA preferred term	Placebo (N=453)	Fexofenadine 60 mg BID (N=220)	Fexofenadine >180 mg daily (N=901)	Fexofenadine Total (N=1121)
Toothache	20 (4.42%)	6 (2.73%)	31 (3.44%)	37 (3.30%)
Dyspepsia	13 (2.87%)	3 (1.36%)	31 (3.44%)	34 (3.03%)
Abdominal pain upper	4 (0.88%)	3 (1.36%)	26 (2.89%)	29 (2.59%)
Musculoskeletal and connective tissue disorders	95 (20.97%)	37 (16.82%)	229 (25.42%)	266 (23.73%)
Back pain	36 (7.95%)	14 (6.36%)	100 (11.10%)	114 (10.17%)
Myalgia	30 (6.62%)	10 (4.55%)	44 (4.88%)	54 (4.82%)
Arthralgia	13 (2.87%)	4 (1.82%)	44 (4.88%)	48 (4.28%)
Pain in extremity	21 (4.64%)	8 (3.64%)	34 (3.77%)	42 (3.75%)
Investigations	103 (22.74%)	35 (15.91%)	120 (13.32%)	155 (13.83%)
White blood cell count decreased	33 (7.28%)	13 (5.91%)	18 (2.00%)	31 (2.77%)
Injury, poisoning and procedural complications	63 (13.91%)	18 (8.18%)	155 (17.20%)	173 (15.43%)
Muscle strain	13 (2.87%)	1 (0.45%)	33 (3.66%)	34 (3.03%)

Includes data from safety evaluable subjects in Long-Term Safety Studies. Presented are TEAEs that occurred in at least 2.5% of subjects in the total fexofenadine HCl treatment group grouped by SOC. TEAEs are sorted by frequency in the total fexofenadine HCl treatment group. SOCs are sorted in internationally agreed order.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext_soc.sas OUT=REPORT/OUTPUT/ae0066intxt_i.rtf (04DEC2009 - 12:47)
Source: Appendix 5.3.5.3.3.30

MO Comment *The fexofenadine 60 mg BID dose group comprised subjects from a 6-month Study (PJPR0031) and the >180 mg QD dose group comprised subjects from 2 studies (PJPR0027 and M016455P/3003) in which subjects were exposed to fexofenadine for up to 12 months. The placebo group is composed of subjects from Studies PJPR0031 and PJPR0027, while subjects in the comparator group in Study M016455P/3003 received montelukast.*

The percentages of subjects who experienced TEAEs were similar between the fexofenadine greater than 180 mg daily (84.57%) and the placebo (84.33%) treatment groups, while the percentage in the fexofenadine 60 mg BID (73.18%) treatment group was lower. Although the long term reporting rate of TEAEs increased with fexofenadine dose, the rate reported for the fexofenadine 60 mg BID group was lower than that for placebo. The apparent dose dependence in the pooled studies may be due to the shorter treatment period of Study PJPR0031, which confounds any dose dependence because the higher dose group also used drug for a longer time.

The Sponsor concluded that fexofenadine was generally well tolerated by adult subjects, 12 years of age and older, in the biopharmaceutics, pharmacokinetic, and pharmacodynamic studies at doses up to 800 mg in single-dose studies and 690 mg BID for 29 days in multiple-dose studies. Fexofenadine was also well tolerated by pediatric subjects, 6 months to younger than 12 years of age, in pharmacokinetic and pharmacodynamic studies at doses up to 60 mg.

Likewise, in pivotal and other controlled studies in adult subjects who had SAR, PAR, CIU, or asthma, fexofenadine was generally well tolerated at doses up to 240 mg BID. In addition, in

pediatric subjects 6 months to younger than 12 years of age who had allergic rhinitis or SAR, fexofenadine was generally well tolerated at doses up to 60 mg BID. The most frequently reported TEAE across all studies was headache.

The adverse event profile of fexofenadine in adult subjects in the other controlled studies confirms that the drug was very well tolerated at the approved doses of 60 mg BID and 180 mg QD in support of this application, as well as doses above the recommended total daily dose of 180 mg.

The adverse event profile of fexofenadine in pediatric subjects younger than 6 years of age differs from the profile in older pediatric subjects and adult subjects, with higher percentages for TEAEs more typical for this age group. Headache, usually the most frequent TEAE associated with fexofenadine treatment, was reported less frequently as it is generally not an observable symptom and must be reported by the subject. The adverse event profile of fexofenadine in pediatric subjects 6 to 12 years of age with SAR confirms that the drug was well tolerated at the approved dose of 30 mg BID in support of this application.

The reported TEAEs in the long-term studies did not indicate any new or unexpected safety risk associated with the long-term treatment with fexofenadine. No gender, race, age, or dose relationships were observed, including at doses that would exceed the maximum recommended daily dose of 180 mg in the adult population.

MO Comment *We agree that the incidences of the most frequent TEAEs reported in the GIDB are supportive of safety of fexofenadine at the doses, for the indications, and in the adult and pediatric populations described in this application. Although the pooled safety data in the GIDB suggested that the total TEAE rate and the rate of headaches (the most frequent TEAE) were highest in the highest dose groups, neiher of these reporting rates showed a consistent dose dependence. Somnolence was also reported in the controlled clinical trials by 0.79% to 1.49% of adult subjects and was significantly greater for the total fexofenadine group than for placebo. However, the somnolence reporting rate did not exhibit a consistent dose dependence.*

7.3.1 Deaths

In the clinical trials, in the adult population only, there were four deaths. Two deaths were in the placebo group. Of the 2 subjects in the placebo group who died, one subject had a cerebrovascular accident and subsequent cardiac arrest which resulted in death, and the other was a completed suicide.

There were two deaths in the fexofenadine 60 mg bid group, one of whom did not actually receive study medication (study M016455P–3002; subject 2089-00021). The other subject who died (study PJPR0053; subject 0395-00019) in the fexofenadine 60 mg bid group suffered respiratory failure caused by bacterial pneumonia after she discontinued from the study.

Subject 0395/00019, a 38-year-old Black woman with a history of allergies, diabetes, hypertension, and obesity, completed the study study PJPR0053 on 1 May 1996 in the fexofenadine 60 bid group. She was subsequently diagnosed with bacterial pneumonia on 10

June 1996. She died on 24 June 1996 of respiratory failure secondary to overwhelming bacterial pneumonia.

MO Comment *None of the deaths can be attributed to fexofenadine.*

7.3.2 Nonfatal Serious Adverse Events

There were 117 subjects who experienced serious AEs in the controlled clinical trials in the GIDB (from a total 18361 safety evaluable subjects given fexofenadine and 6397 subjects given placebo). A total of 50 of the 117 subjects with serious AEs did not receive study medication (either received placebo, a comparitor, or were not treated). Among the 117 cases were 20 asthma cases (seven studies were performed in asthma populations); 8 cardiac cases (not including one death case, discussed in Section 7.3.1); and four cases with cholecystitis , and one with increased bilirubin who also had mononucleosis). Table 18 shows a selected set of significant serious AEs from the controlled clinical trials database of GIDB.

MO Comment *The cases listed in Table 18 are those that the Investigator assessed as related to fexofenadine, plus additional SAEs involving cardiac, hepatic, or hypersensitivity events. The latter types of AEs are of special interest and are analyzed in the postmarketing Section 8. A total of 24 cases is shown in* Table 18, *of which 13 were assessed by the Investigator as being related to study medication, including two cardiac cases and one abdominal pain:*

- **Study M016455I/1120 subject 1001-00002** Two hours after receiving 60 mg fexofenadine, hospitalized for abdominal pain, treated with morphine. During first study period subject also experienced 19 hr abdominal pain after receiving 120 mg fexofenadine.The reviewer agrees that this case is possibly related to fexofenadine.
- **Study M016455P/3003 subject 3113-00007** Open angle glaucoma on day 20 of treatment. Fexofenadine is unlikely to be related to open angle glaucoma.
- **Study M016455M/3097 subject 1062-010** After 45 days of treatment, chest pain, tachycardia and hypertension.The reviewer agrees that this case is possibly related to fexofenadine.
- **Study PJPR0053 subject 0388-00008** Atrial fibrillation on day 7 of treatment, 1 hr after dose. ECG showed atrial fibrillation. Subject was treated in the ER with IV digoxin and subject recovered without sequelae. The reviewer agrees that this case has probable relation to fexofenadine; similar cases were identified in postmarketing spontaneous reports.
- **Study M016455P/3003 subject 3104-00019** Possible disseminated herpes simplex virus on day 258 of treatment. This reviewer disagrees with the Investigator and assesses this case as unlikely to be related to fexofenadine.

Table 18 *also includes cases of interest without a causality assessment. Six cardiac events are listed, including a case of syncope and two reports of acute MI (one of which occurred after 18 days of treatment) plus three additional cases of chest pain. Also of interest are three cases involving cholecystectomy. One case involved increased bilirubin but also had mononucleosis and is therefore unlikely related to fexofenadine.*

It is noted that in 5 cases assessed as related by the investigator, the subject was on placebo. One of these cases was a completed suicide, **Study PJPR0027, subject 0204-00028.** *Placebo subjects also reported one each of hypersensitivity reaction, upper GI bleed, angioedema, and spontaneous abortion.*

In two additional cases pediatric subjects were on comparator drugs (montelukast for a 15 year old with viral syndrome; and ketotifen for a 10 year old with gastroenteritis).

There were two pediatric subjects who experienced serious AEs with fexofenadine: one case each of neutropenia and status asthmaticus. The neutropenia case is confounded because alternate explanations could account for the event; the child seroconverted for mycoplasma and influenza. The case of status asthmaticus occurred on a camping trip in a 9 yo female with a history of mild asthma, where exposure to outdoor allergens more likely triggered the asthma.

In summary, there are two cardiac SAEs possibly or probably related to fexofenadine during the clinical trial development program, in which 18361 patients were exposed to the drug.

Table 18 Significant Serious AEs from clinical trials included in GIDB

Study	Subject	Age	Sex	Treatment	Comments	Withdraw due to AE	Investigator Assessed as Related
M016455C/3212	1307-00001	10	f	Fexofenadine HCl	after 14 days treatment, neutropenia and leukopenia, asymptomatic but medically important. seroconverted for mycoplasma and influenza A-B	No	Yes
M016455I/1120	1001-00002	43	m	Fexofenadine HCl	Two hours after receiving 60 mg fexofenadine, hospitalized for abdominal pain, treated with morphine. During first study period subject also experienced 19 hr abdominal pain after receiving 120 mm fexofenadine	Yes	Yes
M016455P/3002	2090-00017	68	f	Fexofenadine HCl 120 mg BID	On day 36 of treatment, L sided chest pain. Mild left ventricular hypertrophy, cardiac enzymes negative.	Yes	
M016455P/3003	3005-00009	74	m	Fexofenadine HCl 120 mg BID	Acute myocardial infarction on Day 318. Syncope vasovagal; ventricular tachycardia developed during cardiac cath; viral infection NOS. History MI 1987; MI assessed by Investigator to be related to his underlying concomitant illness (CAD)	No	
M016455P/3003	3099-00014	49	f	Fexofenadine HCl 120 mg BID	Syncope on day 68; subject experienced blurred vision, facial numbness, intermittent orthostatic hypotension, weakness. Increased fatigue over the previous 6 weeks. Negative cardiac enzymes and ECG. Tilt table was positive. On Day 69, experienced ataxia, intermittent palpitations, lightheadedness, and mitral regurgitation. Initial treatment included oral atenolol	No	
M016455P/3003	3104-00019	45	f	Fexofenadine HCl 120 mg BID	Possible disseminated herpes simplex virus on Day 258	Yes	Yes
M016455P/3003	3113-00007	56	m	Fexofenadine HCl 120 mg BID	open angle glaucoma Day 20	Yes	Yes
M016455P/3003	3119-00057	54	m	Fexofenadine HCl 120 mg BID	Coronary artery disease Day 285 CP with dyspnea on exertion	No	
M016455M/3097	1062-010	58	m	Fexofenadine HCl 120 mg QD	after 45 days of study medication, chest pain and hypertension, admitted to r/o MI. ECG showed tachycardia. Serial ECGs and enzymes were WNL. A month later, hospitalized again with dyspnea. CXR cardiomegaly. ECG sinus rhythm with left anterior ventricular block, poor R wave progression, and nonspecific ST-T wave changes	Yes	Yes

Study	Subject	Age	Sex	Treatment	Comments	Withdraw due to AE	Investigator Assessed as Related
M016455M/3002	5028-00033	44	m	Fexofenadine HCl 240 mg QD	MI on day 18 of treatment. concomitant medication included amlodipine, simvastatin, benazepril, and metoprolol	Yes	
PJPR0027	0198-00007	59	m	Fexofenadine HCl 240 mg QD	after about 3 months treatment, chest pain. History angina	Yes	
PJPR0053	0388-00008	24	m	Fexofenadine HCl 60 mg BID	atrial fibrillation on day 7 of treatment, 1 hr after dose. ECG nonspecific ST-T changes	Yes	Yes
M016455P/3003	3079-00004	40	m	Fexofenadine HCl 120 mg BID	Acute asthma exacerbation leading to respiratory arrest, tachycardia, non-specific ST-T wave change, poor R-wave progression, and right axis deviation	No	
PJPR0066/77	0900-0021	9	F	Fexofenadine HCl 30 mg BID	Status asthmaticus (heart rate 160 bpm and oxygen saturation 88-92 mmHg) after 14 days of treatment. Patient had not needed medication for 2 years prior to treatment	Yes	
M016455P/3001	1010-00061	34	f	Fexofenadine HCl 120 mg BID	On day 2 of treatment, abdominal pain, biliary dyskinesia. Cholecystectomy	Yes	
M016455M/3001	4102-00021	81	m	Fexofenadine HCl 240 mg QD	On day 20, symptoms of chest tightness. Cholelithiasis and cholecystectomy. Fexofenadine discontinued and subject withdrawn from study. Congestive heart failure and pulmonary edema developed. Subject discharged home after 9 days hosp.	Yes	
M016455O/3101	6-104	10	f	Ketotifem fumarate syrup	gastroenteritis	No	Yes
M016455P/3003	3005-00003	15	f	Montelukast 10 mg QD	viral syndrome on day 274 with fever, severe headache, myalgia, mild runny nose, and stiff neck. event was unresolved with no follow-up deemed necessary.	Yes	Yes
M016455/4092	1133-001	28	f	Placebo	spontaneous abortion	Yes	Yes
M01645I/3112	1365-00021			Placebo	hypersensitivity	Yes	Yes
PJPR0027	0204-00028			Placebo	Death; completed suicide (gunshot)	Yes	Yes
PJPR0027	0198-00005			Placebo	upper GI bleed	Yes	Yes
PJRP0019	0117-00003			Placebo	angioedema	Yes	Yes

7.3.3 Dropouts and/or Discontinuations

Narratives for subjects who discontinued due to an adverse event were not systematically written for all studies. Therefore, line listings that represent the available data for the subjects were provided for all studies in which subjects discontinued due to an adverse event. Summaries of TEAES leading to subject discontinuation from the clinical trials are presented in the following groups:

- adult population in the biopharmaceutic, pharmacokinetic, and pharmacodynamic studies
- pediatric population in the biopharmaceutic, pharmacokinetic, and pharmacodynamic studies
- adult population in the pivotal and other controlled studies
- pediatric population in the pivotal and other controlled studies
- adult population in the long-term safety studies

In the biopharmaceutics and pharmacokinetic studies in adult subjects (Table 19), 8 subjects (less than 1%) discontinued due to a TEAE. The most common reason for discontinuation was headache, which was reported by 2 subjects. In the studies that were not previously submitted, there were no discontinuations due to TEAEs.

Table 19- Treatment-emergent adverse events leading to discontinuation in biopharmaceutics and pharmacokinetic studies in adult subjects

MedDRA preferred term	Fexofenadine (N=1175)
Number (%) of subjects with TEAEs	8 (0.68%)
Headache	2 (0.17%)
Atrioventricular block second degree	1 (<0.1%)
Ectopic pregnancy	1 (<0.1%)
Influenza	1 (<0.1%)
Nausea	1 (<0.1%)
Respiratory fume inhalation disorder	1 (<0.1%)
Thermal burn	1 (<0.1%)
Ventricular extrasystoles	1 (<0.1%)

Includes data from safety evaluable subjects in Biopharmaceutics and Human PK Studies.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext.sas OUT=REPORT/OUTPUT/ae0181intxt_i.rtf (16NOV2009 - 20:02)
Source: 5.3.5.3 Integrated Summary of Safety, Section 17 Appendices, Supporting Statistical Output [5.3.5.3.3.64]

MO Comment *Two subjects in* Table 19 *discontinued because of cardiac AEs. Subject 0209/00101 in study PJPR0033 was a 19 yo male who discontinued because of ventricular extrasystoles on the first day of treatment; the subject was referred to his own physician and the outcome is unknown. Subject 0209/00104 was a 24 yo male who discontinued because of 2nd deg AV block, also on the first day of treatment. The subject was referred to his own physician and*

the outcome is unknown. Neither subject was treated for his condition, and no further information is available.

In the pharmacodynamic studies in adult subjects (Table 20), 4 subjects (less than 0.25%) discontinued due to a TEAE. One subject in the fexofenadine 400 mg BID group discontinued due to a serious adverse event of pyloric stenosis. In the studies which were not previously submitted, 3 subjects in the fexofenadine group discontinued due to TEAEs.

Table 20 Treatment-emergent adverse events leading to discontinuation in pharmacodynamic studies in adult subjects

MedDRA preferred term	Fexofenadine (N=1800)
Number (%) of subjects with TEAEs	4 (0.22%)
Abdominal pain	1 (<0.1%)
Atrial fibrillation	1 (<0.1%)
Infectious mononucleosis	1 (<0.1%)
Pyloric stenosis	1 (<0.1%)

Includes data from safety evaluable subjects in Human PD Studies.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext.sas OUT=REPORT/OUTPUT/ae0182intxt_i.rtf (16NOV2009 - 20:02)
Source: 5.3.5.3 Integrated Summary of Safety, Section 17 Appendices, Supporting Statistical Output [5.3.5.3.3.67]

MO Comment *One subject in* Table 20 *[ID Code B-021, a 73-year-old male] discontinued pharmacodynamic study M016455A/4136 in elderly patients because of arrhythmia noted in physician's examinations and because of moderate atrial fibrillation on ECG. The subject was discontinued before treatment with fexofenadine and was exposed to placebo only during the washout period. Thus this event is not related to fexofenadine.*

In the pivotal controlled studies in adult subjects (Table 21), a greater percentage of subjects in the placebo group (32 subjects, 2.59%) discontinued due to a TEAE compared to subjects in the fexofenadine group (78 subjects, 2%; not a significant difference). In the total fexofenadine group, the main reasons for discontinuation due to a TEAE were headache and nausea, reported by 8 subjects (0.21%) each. The percentages of subjects in the placebo group who discontinued for these TEAEs were lower than in the fexofenadine group. In the fexofenadine 180 mg QD and the >180 mg QD groups, urticaria, somnolence, nausea, upper respiratory tract infection, and sinusitis were the most common TEAEs leading to discontinuation in the highest fexofenadine dose groups. The most frequently reported TEAEs leading to discontinuation in the placebo group were bronchitis and sinusitis (both at 0.24%; Table 21).

Table 21 TEAEs leading to discontinuation in pivotal controlled studies in adult subjects (cut-off: incidence of at least 3 subjects the total fexofenadine group)

		Fexofenadine					
MedDRA preferred term	Placebo (N=1236)	<60 mg BID (N=1117)	60 mg BID (N=871)	120 - 180 mg daily (N=681)	180 mg QD (N=450)	>180 mg daily (N=782)	Total (N=3901)
Number (%) of subjects with TEAEs	32 (2.59%)	26 (2.33%)	20 (2.30%)	9 (1.32%)	10 (2.22%)	13 (1.66%)	78 (2.00%)
Headache	2 (0.16%)	4 (0.36%)	2 (0.23%)	1 (0.15%)	0	1 (0.13%)	8 (0.21%)
Nausea	1 (<0.1%)	1 (<0.1%)	4 (0.46%)	1 (0.15%)	0	2 (0.26%)	8 (0.21%)
Upper respiratory tract infection	2 (0.16%)	1 (<0.1%)	1 (0.11%)	2 (0.29%)	2 (0.44%)	1 (0.13%)	7 (0.18%)
Urticaria	2 (0.16%)	2 (0.18%)	0	0	2 (0.44%)	2 (0.26%)	6 (0.15%)
Sinusitis	3 (0.24%)	0	2 (0.23%)	0	3 (0.67%)	0	5 (0.13%)
Somnolence	0	0	2 (0.23%)	0	1 (0.22%)	2 (0.26%)	5 (0.13%)
Bronchitis	3 (0.24%)	3 (0.27%)	0	0	0	1 (0.13%)	4 (0.10%)
Diarrhoea	0	0	2 (0.23%)	1 (0.15%)	0	1 (0.13%)	4 (0.10%)
Asthma	1 (<0.1%)	1 (<0.1%)	0	1 (0.15%)	1 (0.22%)	0	3 (<0.1%)
Otitis media	1 (<0.1%)	1 (<0.1%)	0	2 (0.29%)	0	0	3 (<0.1%)

Includes data from safety evaluable subjects in Pivotal Controlled Studies. Presented are TEAEs that occurred in at least 3 fexofenadine HCl-treated subjects, sorted by frequency in the total fexofenadine HCl group.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext.sas OUT=REPORT/OUTPUT/ae0191intxt_i.rtf (16NOV2009 - 20:03)
Source: 5.3.5.3 Integrated Summary of Safety, Section 17 Appendices, Supporting Statistical Output [5.3.5.3.3.74]

In the other controlled studies in adult subjects (Table 22), the percentage of subjects who discontinued due to a TEAE was higher in the placebo treatment group (126 subjects, 3.52%) compared to the total fexofenadine (219 subjects, 2.64%) and other treatment groups (23 subjects, 1.73%). In the total fexofenadine and placebo groups, the TEAE that most frequently resulted in discontinuation was asthma. This was the most common TEAE that resulted in discontinuation in the fexofenadine >180 mg treatment group only. The most frequently cited TEAEs that resulted in discontinuation in the fexofenadine treatment groups varied and included seasonal allergy <60 mg BID), nasopharyngitis (60 mg BID), nausea (120 to 180 mg daily), and upper respiratory tract infection (>180 mg daily). In the "Other" treatment group, the most frequently cited TEAE that resulted in discontinuation was upper respiratory tract infection.

In other controlled studies which were not previously submitted (namely, study PJPR0056, M016455J/3106, M016455/3117, JTAM-CL-202, M016455O/3101 (≥12 yrs) and M016455O/3102 (≥12 yrs); from table 5.3.5.3.3.78 in the ISS appendix not shown here), the percentage of subjects who discontinued due to a TEAE was higher in the total fexofenadine treatment group than in the placebo group. The most common reason for discontinuation due to a TEAE in the fexofenadine treatment groups was nasopharyngitis.

MO Comment *In Table 22, of 26 subjects in the fexofenadine group who discontinued for a TEAE of asthma, 22 were in the >180 mg fexofenadine group. However, these were asthma studies (M016455P/3001 and M016455P/3002) which tested a dose of 120 mg BID, so the prevalence of asthma sufferers in the fexofenadine group was biased to larger dose groups.*

Table 22 TEAEs leading to discontinuation in other controlled studies in adult subjects (cut-off: incidence of at least 3 subjects in the total fexofenadine group)

		Fexofenadine						
MedDRA preferred term	Placebo (N=3578)	<60 mg BID (N=679)	60 mg BID (N=1458)	120 - 180 mg daily (N=1544)	180 mg QD (N=1339)	>180 mg daily (N=3276)	Total (N=8296)	Other (N=1330)
Number (%) of subjects with TEAEs	126 (3.52%)	11 (1.62%)	21 (1.44%)	50 (3.24%)	35 (2.61%)	102 (3.11%)	219 (2.64%)	23 (1.73%)
Asthma	29 (0.81%)	1 (0.15%)	0	2 (0.13%)	1 (<0.1%)	22 (0.67%)	26 (0.31%)	1 (<0.1%)
Upper respiratory tract infection	12 (0.34%)	0	0	3 (0.19%)	5 (0.37%)	16 (0.49%)	24 (0.29%)	3 (0.23%)
Sinusitis	13 (0.36%)	0	1 (<0.1%)	2 (0.13%)	2 (0.15%)	14 (0.43%)	19 (0.23%)	2 (0.15%)
Bronchitis	9 (0.25%)	0	2 (0.14%)	3 (0.19%)	3 (0.22%)	7 (0.21%)	15 (0.18%)	0
Headache	8 (0.22%)	1 (0.15%)	2 (0.14%)	7 (0.45%)	2 (0.15%)	2 (<0.1%)	14 (0.17%)	2 (0.15%)
Nasopharyngitis	1 (<0.1%)	1 (0.15%)	3 (0.21%)	2 (0.13%)	3 (0.22%)	5 (0.15%)	14 (0.17%)	2 (0.15%)
Nausea	4 (0.11%)	1 (0.15%)	1 (<0.1%)	4 (0.26%)	0	2 (<0.1%)	8 (<0.1%)	0
Dizziness	2 (<0.1%)	1 (0.15%)	2 (0.14%)	2 (0.13%)	2 (0.15%)	0	7 (<0.1%)	1 (<0.1%)
Hypersensitivity	0	0	1 (<0.1%)	1 (<0.1%)	2 (0.15%)	3 (<0.1%)	7 (<0.1%)	2 (0.15%)
Cough	0	0	0	1 (<0.1%)	0	5 (0.15%)	6 (<0.1%)	0
Influenza	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)	2 (0.15%)	2 (<0.1%)	6 (<0.1%)	0
Urticaria	10 (0.28%)	1 (0.15%)	0	1 (<0.1%)	1 (<0.1%)	3 (<0.1%)	6 (<0.1%)	0
Oropharyngeal pain	1 (<0.1%)	0	1 (<0.1%)	2 (0.13%)	0	2 (<0.1%)	5 (<0.1%)	0
Seasonal allergy	7 (0.20%)	2 (0.29%)	0	3 (0.19%)	0	0	5 (<0.1%)	0
Abdominal pain upper	0	0	0	3 (0.19%)	0	1 (<0.1%)	4 (<0.1%)	1 (<0.1%)
Chest pain	0	0	0	1 (<0.1%)	0	3 (<0.1%)	4 (<0.1%)	0
Diarrhoea	1 (<0.1%)	0	1 (<0.1%)	2 (0.13%)	1 (<0.1%)	0	4 (<0.1%)	0
Pyrexia	0	0	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)	4 (<0.1%)	0
Feeling hot	0	1 (0.15%)	0	0	2 (0.15%)	0	3 (<0.1%)	0
Gastroenteritis	1 (<0.1%)	0	0	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	3 (<0.1%)	0
Pruritus	1 (<0.1%)	1 (0.15%)	0	1 (<0.1%)	1 (<0.1%)	0	3 (<0.1%)	0
Rash	1 (<0.1%)	0	0	2 (0.13%)	1 (<0.1%)	0	3 (<0.1%)	0
Vomiting	1 (<0.1%)	1 (0.15%)	0	1 (<0.1%)	0	1 (<0.1%)	3 (<0.1%)	0

Includes data from safety evaluable subjects in Other Controlled Studies. Presented are TEAEs that occurred in at least 3 fexofenadine HCl-treated subjects, sorted by frequency in the total fexofenadine HCl group.
Other includes cetirizine 10 mg, loratadine 10 mg, and ketotifen 1 g.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext.sas OUT=REPORT/OUTPUT/ae0193intxt_i.rtf (16NOV2009 - 20:03)
Source: 5.3.5.3 Integrated Summary of Safety, Section 17 Appendices, Supporting Statistical Output [5.3.5.3.3.77]

In the pivotal controlled studies PJPR0066/77 in pediatric subjects (Table 23), the percentage of subjects who discontinued due to a TEAE was higher in the placebo treatment group (5 subjects, 2.18%) than in the total fexofenadine group (5 subjects, 0.77%). One subject in the fexofenadine group discontinued due to asthma, while in the placebo group, 2 subjects did so.

Table 23 Treatment-emergent adverse events leading to discontinuation in pivotal controlled combined Studies PJPR0066/77 in pediatric subjects

		Fexofenadine			
MedDRA preferred term	Placebo (N=229)	15 mg BID (N=224)	30 mg BID (N=209)	60 mg BID (N=213)	Total (N=646)
Number (%) of subjects with TEAEs	5 (2.18%)	1 (0.45%)	3 (1.44%)	1 (0.47%)	5 (0.77%)
Ear infection	0	0	1 (0.48%)	0	1 (0.15%)
Nasal oedema	0	0	0	1 (0.47%)	1 (0.15%)
Otitis media	0	0	1 (0.48%)	0	1 (0.15%)
Status asthmaticus	0	0	1 (0.48%)	0	1 (0.15%)
Viral infection	0	1 (0.45%)	0	0	1 (0.15%)
Asthma	2 (0.87%)	0	0	0	0
Pharyngitis	1 (0.44%)	0	0	0	0
Sinusitis	3 (1.31%)	0	0	0	0

Includes data from safety evaluable subjects in study PJPR0066/77. Presented are TEAEs that occurred in any fexofenadine HCl-treated subject.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext.sas OUT=REPORT/OUTPUT/ae0192intxt_i.rtf (16NOV2009 - 20:04)
Source: 5.3.5.3 Integrated Summary of Safety, Section 17 Appendices, Supporting Statistical Output [5.3.5.3.3.76]

In the other controlled studies in pediatric subjects (Table 24), the percentage of subjects who discontinued due to a TEAE was higher in the placebo group (26 subjects, 2.89%) than in the total fexofenadine (23 subjects, 2.33%) and other groups (1 subject, 0.93%). In the total fexofenadine group, asthma was the most frequently cited TEAE that resulted in discontinuation (reported for 4 subjects only in the fexofenadine 30 mg BID group). There were two discontinuations due to asthma in the placebo treatment group. Also in the placebo group, there were 2 discontinuations due to urticaria versus one in the fexofenadine group given 30 mg BID. In the pediatric studies which were not previously submitted (namely, M016455O/3101 (<12 yrs) and M016455O/3102 (<12 yrs); from table 5.3.5.3.3.80 in the ISS appendix not shown here), 3 subjects discontinued due to TEAEs of asthma, bronchitis, and urticaria, respectively.

Table 24 Treatment-emergent adverse events leading to discontinuation in other controlled studies in pediatric subjects

MedDRA preferred term	Placebo (N=901)	Fexofenadine 15 mg BID (N=85)	Fexofenadine 30 mg BID (N=904)	Fexofenadine Total (N=989)	Other (N=108)
Number (%) of subjects with TEAEs	26 (2.89%)	3 (3.53%)	20 (2.21%)	23 (2.33%)	1 (0.93%)
Asthma	2 (0.22%)	0	4 (0.44%)	4 (0.40%)	1 (0.93%)
Gastroenteritis viral	0	1 (1.18%)	2 (0.22%)	3 (0.30%)	0
Otitis media	3 (0.33%)	1 (1.18%)	2 (0.22%)	3 (0.30%)	0
Abdominal pain upper	1 (0.11%)	0	1 (0.11%)	1 (0.10%)	0
Bronchitis	1 (0.11%)	0	1 (0.11%)	1 (0.10%)	0
Cough	2 (0.22%)	1 (1.18%)	0	1 (0.10%)	0
Ear infection	1 (0.11%)	1 (1.18%)	0	1 (0.10%)	0
Pneumonia	1 (0.11%)	0	1 (0.11%)	1 (0.10%)	0
Sinusitis	1 (0.11%)	1 (1.18%)	0	1 (0.10%)	0
Urticaria	2 (0.22%)	0	1 (0.11%)	1 (0.10%)	0
Viral infection	2 (0.22%)	0	1 (0.11%)	1 (0.10%)	0
Vomiting	1 (0.11%)	0	1 (0.11%)	1 (0.10%)	0
Overdose	2 (0.22%)	0	0	0	0
Upper respiratory tract infection	5 (0.55%)	0	0	0	0

Includes data from safety evaluable subjects in Other Controlled Studies. Presented are TEAEs that occurred at least 2 subjects, sorted by frequency in the total fexofenadine HCl group.
Other is ketotifen 1 g.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext2.sas OUT=REPORT/OUTPUT/ae0194intxt_i.rtf (16NOV2009 - 20:13)
Source: 5.3.5.3 Integrated Summary of Safety, Section 17 Appendices, Supporting Statistical Output [5.3.5.3.3.79]

In long term safety studies in adult subjects (Table 25), the percentage of subjects who discontinued due to a TEAE was higher in the placebo group (31 subjects, 6.84%) than in the total fexofenadine group (58 subjects, 5.17%, which included 35 subjects from the long-term safety study in subjects with asthma, M016455P/3003). In the fexofenadine treatment groups, the most common TEAEs that resulted in discontinuation were asthma and headache. Asthma was cited as a reason for discontinuation in the fexofenadine > 180 mg daily treatment group only. Reports of headache and increased hepatic enzymes as TEAEs leading to discontinuation occurred at similar rates in the placebo treatment group when compared with the >180 mg QD fexofenadine group.

Table 25 Treatment-emergent adverse events leading to discontinuation in long-term safety studies in adult subjects

		Fexofenadine		
MedDRA preferred term	Placebo (N=453)	60 mg BID (N=220)	>180 mg daily (N=901)	Total (N=1121)
Number (%) of subjects with TEAEs	31 (6.84%)	9 (4.09%)	49 (5.44%)	58 (5.17%)
Asthma	0	0	12 (1.33%)	12 (1.07%)
Headache	3 (0.66%)	1 (0.45%)	5 (0.55%)	6 (0.54%)
Gastrooesophageal reflux disease	0	0	2 (0.22%)	2 (0.18%)
Hepatic enzyme increased	0	0	2 (0.22%)	2 (0.18%)
Sinusitis	0	0	2 (0.22%)	2 (0.18%)
Alanine aminotransferase increased	3 (0.66%)	0	0	0
Depression	4 (0.88%)	0	0	0
Dry skin	2 (0.44%)	0	0	0
Palpitations	2 (0.44%)	0	0	0

Includes data from safety evaluable subjects in Long-Term Safety Studies. Presented are TEAEs that occurred in at least 2 subjects in any treatment group, sorted by frequency in the total fexofenadine HCl group.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/ae_intext2.sas OUT=REPORT/OUTPUT/ae0197intxt_i.rtf (16NOV2009 - 20:13)
Source: 5.3.5.3 Integrated Summary of Safety, Section 17 Appendices, Supporting Statistical Output [5.3.5.3.3.81]

7.3.4 Significant Adverse Events

The most common TEAEs reported in the controlled trials in adults were analyzed in

Table 13 and in Table 14 for incidence of at least 1% in any fexofenadine treatment group. The TEAEs leading to discontinuation were analyzed in Table 21 and in Table 22 for incidence of at least three subjects in the total fexofenadine group (all dose groups). This section will analyze significant TEAEs in adult populations, including somnolence, syncope and loss of consciousness (these preferred terms were combined), and cardiac preferred terms. These significant AEs include both non-serious and serious events.

The complete listing of TEAEs in the pivotal and other controlled trials in adult subjects with all dose groups including those above 180 mg BID (the same dataset as in Table 14), was analyzed by the reviewer to extract specific terms and specific dose groups (placebo, 60 mg BID, 180 mg QD, >180 mg QD, and total fexofenadine which includes all the other dose groups in Table 14). The numbers of cases reporting selected TEAEs is shown in Table 26 by dose group.

Table 26 Cases with Selected TEAEs in pivotal and other controlled trials in adults

Primary System Organ Class PT	Placebo group (N=4808)	60 mg BID group (N=2329)	180 mg QD group (N=1788)	>180 mg QD group (N=4058)	Total fexofenadine (N=12195)
Somnolence	31 (0.64%)	57* (2.45%)	24* (1.34%)	38 (0.94%)	182* (1.49%)
Syncope & Loss of consciousness	1	0	0	4	6
Cardiac terms	9	5	6	19*	36

* significant versus placebo (P<0.05); numbers derived fron Sponsor Table 5.3.5.3.3.32
Subjects are counted once per preferred term

MO Comment *A significantly greater incidence of somnolence (p<0.001) is found in the total fexofenadine group compared to placebo, for pivotal and other controlled trials. Likewise the incidence of somnolence was higher for each of the 60mg BID and 180mg BID groups versus placebo. However, the incidence of somnolence was higher in the 60 mg BID group than in the 180 mg QD group, so there was not consistent evidence for dose dependence. The incidences of syncope and loss of consciousness (terms combined) are not significantly different for placebo and fexofenadine groups. Also, the incidences of cardiac terms (including palpitations, tachycardia, bradycardia, and other events) was significantly higher in the >180 mg QD fexofenadine dose groups than in the placebo group.*

A similar analysis was performed for the dataset of long-term safety studies in adult subjects (the same dataset as in Table 17, which shows only TEAEs with incidence >2.5%). In addition to somnolence, syncope/loss of consciousness and cardiac terms as above, the reviewer also looked at hypertension. The numbers of cases with these selected TEAEs is shown in Table 27.

Table 27 Cases with Selected TEAEs in long term safety studies in adults

Primary System Organ Class PT	Placebo group (N=453)	60 mg BID group (N=220)	>180 mg QD group (N=901)	Total fexofenadine (N=1121)
Somnolence	1	1	5	6
Syncope and Loss of consciousness	1	0	5	5
Cardiac terms	7	1*	23*	24
Hypertension	0*	0	11	11*
Headache	109	31*	190*	221

* significant pair-wise comparison (P<0.05); numbers derived fron Sponsor Table 5.3.5.3.3.30

MO Comment *A significantly greater incidence of hypertension (p=0.04, Fisher Exact test) is found in the total fexofenadine group compared to placebo, in the long term safety trials in adults. However, the incidence of somnolence was similar in the placebo and fexofenadine groups (and as noted above, lower than in the controlled trials of* Table 26*). The incidence of headache was significantly higher (p=0.02), and that of cardiac disorders was marginally higher (Fisher's p=0.066), in the higher dose group compared to the 60 mg bid dose group.*

About half of the cardiac disorder reports were tachycardia or palpitations, with three reports of 1st degree AV block and individual reports of acute MI with ventricular tachycardia during a catheterization procedure, atrial fibrillation and left bundle branch block. However, the evidence for dose dependence in these TEAEs is confounded by the longer study duration in the higher dose group. In addition, one of the long term studies was performed in an asthma population, comparing fexofenadine 120 mg BID with montelukast.

In summary, there is evidence from the pivotal and other controlled clinical trials that the reporting rates of somnolence were higher in the 60 mg BID, 180 mg QD, and total fexofenadine groups than for placebo. In addition, the reporting rate of cardiac terms was higher for the >180 mg QD group than for placebo (above the recommended dose for fexofenadine). The increase in TEAEs with dose in the long term safety studies in adults, notably for cardiac TEAEs and for headache, was confounded by the longer study duration in the larger dose group.

The GIDB dataset was further analyzed for cardiac AEs. Table 28 shows the numbers of cardiac AE terms reported in the database.

Table 28 Cardiac AEs All Fexofenadine Groups, Clinical Trials Database

Cardiac SOC Preferred Term	Number of reports, total fexofenadine group (N=18361)	Other* (N=1658)	Placebo (N=6397)
Acute myocardial infarction	1	0	0
Angina pectoris	5	0	0
Aortic valve incompetence	1	0	0
Arrhythmia	1	0	0
Arrhythmia supraventricular	1	0	0
Atrial fibrillation	4	0	0
Atrioventricular block first degree	8	0	3
Atrioventricular block second degree	1	0	0
Bundle branch block left	0	1	0
Bundle branch block right	4	0	1
Cardiac arrest	0	0	1
Cardiac failure congestive	1	0	0
Cardiac flutter	1	0	0
Cardiomegaly	1	0	0
Conduction disorder	4	0	0

Cardiac SOC Preferred Term	Number of reports, total fexofenadine group (N=18361)	Other* (N=1658)	Placebo (N=6397)
Coronary artery disease	1	0	0
Diastolic dysfunction	1	0	0
Extrasystoles	2	1	0
Left atrial hypertrophy	1	0	0
Left ventricular hypertrophy	1	0	0
Mitral valve incompetence	1	0	0
Myocardial infarction	1	0	1
Myocardial ischaemia	3	0	0
Nodal rhythm	1	0	0
Palpitations	34	5	10
Sinus arrhythmia	2	0	0
Sinus bradycardia	12	0	0
Sinus tachycardia	3	1	0
Supraventricular extrasystoles	2	1	0
Tachycardia	19	1	5
Ventricular extrasystoles	6	0	0
Ventricular tachycardia	1	0	0
Wandering pacemaker	0	0	1
TOTAL	124	10	22

*Other includes montelukast, cetirizine and ketotifen.

MO Comment *The numbers of cardiac AE terms reported in the total fexofenadine group, 124 AEs from 18361 subjects, was significantly higher than for placebo (22 AEs from 6397 subjects, p=0.0029), but was not significantly different from the "other" group (p=0.73). For atrial fibrillation, there were two reports from one subject.*

The clinical trials safety database (total of 18361 patients) shows that cardiac AEs were reported more frequently in the fexofenadine groups than in placebo.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable

7.4 Supportive Safety Results

Not applicable

7.4.1 Common Adverse Events

See Section 7.3 for common treatment emergent adverse events. From Sponsor Table 5.3.5.3.3.23 Other Controlled Studies – Mono Products, the most common adverse events occurring at more than 1% of the reported AEs are headache, nasopharyngitis, oropharyngeal

pain, upper respiratory tract infection, somnolence, backpain, nausea, diarrhea, sinusitis, epistaxis, and influenza. Somnolence was reported by 1.82% in the total fexofenadine group.

7.4.2 Laboratory Findings

The Sponsor compared laboratory evaluations at baseline and at endpoints (usually end of study values). Baseline was defined as the last assessment prior to the start of treatment, and endpoint was defined as the day of the last non-missing post-baseline observation. If a subject had multiple values on the same day for a given variable at baseline or endpoint, the mean of these values was used in the calculation of summary statistics for baseline, endpoint, and change from baseline. Predefined changes abnormal (PCAs), predefined changes abnormal at last evaluation (LPCAs), and clinically significantly abnormal (CSA) changes were determined using the baseline value or the average baseline value (as appropriate), and the individual post-baseline values.

The laboratory studies differed across different studies, but generally included a CBC and chemistries. The primary difference was that the white blood count differential was not performed in each study.

In the pivotal and other controlled studies, mean changes from baseline to endpoint were generally small. There were no meaningful differences between the changes in the fexofenadine dose groups and the placebo group. In the pivotal and other controlled studies in pediatric subjects, mean changes from baseline to endpoint were generally small. There were no meaningful differences between the changes in the fexofenadine dose groups or the overall fexofenadine group and the placebo group.

In the long-term safety studies, mean changes from baseline to endpoint were generally small. There were no meaningful differences between the mean changes in the fexofenadine dose groups or the overall fexofenadine group and the placebo group. However, a small fraction of subjects had larger changes that met the predefined criteria for PCA, LPCA and CSA.

The numbers of subjects with serum chemistry variables meeting PCA and LPCA criteria were low for most variables, with the exception of SGOT (serum glutamic oxaloacetic transaminase or AST) and SGPT (serum glutamic pyruvic transaminase or ALT). Table 29 shows that SGPT changes meeting PCA were greater for the higher dose fexofenadine group than for placebo (p=0.028), but changes meeting CSA were not significantly different from placebo.

Table 29 Long Term Safety Studies in Adults, Abnormal Laboratory Changes

	placebo N=434	60 mg BID N=213	>180 mg QD N=851	Total fexofenadine N=1064	Other N=210
SGOT					
PCA increase > 22	8	4	29	33	7

LPCA increase > 22	2	2	8	10	0
CSA value > 3 ULN	1	1	2	3	3
SGPT					
PCA increase > 28	13*	7	50	57*	18
LPCA increase > 28	4	3	11	14	2
CSA value > 3 ULN	2	2	8	10	2

*pair wise comparison, p<0.05

MO Comment: *The lab data set was examined for subjects with 3X upper limit of normal (ULN) SGPT and 2X ULN total bilirubin to see if there were potential Hy's cases in the database. Three cases were considered. One of these cases was treated with placebo. One of the cases had Gilbert Syndrome, with an elevated bilirubin at baseline; transaminases were also elevated at baseline. The bilirubin increased to levels consistent with Gilbert's with improvement of transaminase levels after treatment. The last case also had elevated bilirubin and transaminases at baseline and had decreases in all 3 labs after treatment. None of these cases met Hy's Law criteria:*

- *In study M016455M/3001 (an efficacy and safety study of fexofenadine 120 mg BID, fexofenadine 240 mg QD, and placebo in subjects with PAR) subject 4022/00021 was a 28 yo M with a history Gilberts (Tot Bili was elevated at 30.78 at baseline and 46.17 after treatment (3-21 IU normal)). He also had elevated TA at baseline before drug administration which decreased after receiving drug; predose SGOT was 113 and 26 after treatment; SGPT was 125 predose and 36 after treatment*
- *In study PJPR0027 (a twelve-month safety/tolerance study of fexofenadine 240 mg QD and placebo QD in normal healthy subjects), subject 0199/00046 was a 24 yoM whose bilirubin went from 27 to 44 on placebo Treatment. His SGOT was 15 to 52, SGPT 17 to 124, and alk phos was normal*
- *In study PJPR0032 (an efficacy and safety study of fexofenadine (120, and 180 mg once a day versus cetirizine) subject 0430/00018 was a 34 yo M with elevated bilirubin at baseline of 58 and 51 post treatment; SGOT and SGPT were also higher at baseline than after treatment, normal alk phos*

In summary, the clinical trials safety database does not reveal evidence for significant liver toxicity.

7.4.3 Vital Signs

In the pivotal and other controlled studies in adults, the percentages of adult subjects with vital sign values meeting the criteria for PCA or LPCA were generally low (less than 1% in any treatment group). No subject had vital sign values that were clinically significantly abnormal. The criteria were: for PCA, a decrease >15 bpm in heart rate; for LPCA the same at the last visit; and for CSA, LPCA as well as PCA at >50% visits.

In the pivotal, controlled, combined pediatric studies PJPR0066/77, the percentages of subjects with values meeting the criteria for PCA or LPCA were low (less than 1% in any treatment group) for systolic and diastolic blood pressure. Percentages of PCA and LPCA decreases were higher for heart rate. However, there was no difference between the percentages in the overall fexofenadine treatment froup and the placebo group. No subject had vital sign data the met the CSA criteria for clinical significance.

In the other controlled studies in pediatric subjects, the percentages of subjects with values meeting the criteria for PCA or LPCA were low (approximately 1% or less in any treatment group). There were no meaningful differences between the percentages in the fexofenadine dose groups, the overall fexofenadine treatment group, and the placebo group. No subject had vital sign values that were clinically significantly abnormal.

7.4.4 Electrocardiograms (ECGs)

The DCRP QT interdisciplinary review stated that the available clinical trials data suggest that fexofenadine is unlikely to be associated with large changes in QTc interval. After a review of the literature, the non-clinical data, the clinical trial data, and the post-marketing experience, the DCRP QT clinical reviewer concluded that a TQT study of fexofenadine is not necessary. See DCRP QT interdisciplinary reviews.

7.4.5 Special Safety Studies/Clinical Trials

Pharmacodynamic study PJPR0007 in adult subjects was performed to examine the QT interval. See DCRP QT interdisciplinary review.

7.4.6 Immunogenicity

NA

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The review of the available safety data did not indicate any consistent relationship between the dose of fexofenadine and any of the safety findings including adverse event rates, laboratory, ECG, or vital sign assessments.

7.5.2 Time Dependency for Adverse Events

NA

7.5.3 Drug-Demographic Interactions

Elderly

Few subjects 65 years of age and older were enrolled in the studies included in the ISS. The pharmacokinetics and safety of fexofenadine 80 mg in healthy elderly subjects were evaluated in study PJPR0020. The study was an open-label, single-dose study of 20 subjects (11 male and 9 female) who all completed the study. Adjusted mean exposure was about 62.5% higher and mean C_{max} was about 68.1% higher than that in young subjects from separate studies.

Three subjects reported headache as a TEAE. One subject [0128/00003] had an abnormal ECG at poststudy. Based on the poststudy machine read data, the Investigator reported this as multiple ventricular premature complexes (extrasystole), and QT prolongation. Additionally, this subject had an abnormal ECG at predose, which was diagnosed as first-degree atrioventricular block. These ECGs were reread by an outside consultant cardiologist who indicated that all ECGs had ventricular premature beats and suggestion of U-waves, and thus ruled out fexofenadine as the cause of any changes in the ECG. There were no relevant changes in laboratory evaluations, vital signs measurements, or ECG variables.

MO Comment *The prescription label states that since peak plasma levels are greater in older subjects ≥ 65 years of age and since elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Clinical pharmacology recommends that individuals aged 65 and older should ask their doctor before use. This reviewer agrees (see Section 9.2).*

Long-term adverse effects

Adverse event, laboratory, ECG, and vital sign safety data from the long-term studies PJPR0031, PJPR0027, and M016455P/3003 have been analyzed by gender, race, and age subgroups. Results of these analyses did not indicate any long-term adverse effects associated with the long-term treatment of up to 12 months with fexofenadine at a dose that exceeds the currently approved highest QD dose of 180 mg.

The subgroup analyses of the long-term studies using the predefined criteria allow conclusions from the subgroup analyses by gender only. Female subjects reported more adverse events and, thus, the reporting rates for individual adverse events including the most frequently reported adverse events were higher in female subjects than in male subjects. The subgroups by race were too small for the subgroups of Black subjects, Asian/Oriental subjects, and subjects of other races. For the subgroup analyses by age, there were only 25 subjects on fexofenadine and 1 on placebo who were 65 years of age and older.

Pediatrics

Results of the clinical pharmacology studies in pediatric subjects and the pivotal and other controlled studies in pediatric subjects 6 months to 11 years of age can be summarized as follows:

- The analyses of TEAEs did not reveal any particular safety risk for pediatric subjects 6 months to 11 years of age at doses up to 60 mg BID.
- The results of the analyses of laboratory ECG and vital sign data did not show any relevant changes following treatment with fexofenadine at doses up to 60 mg BID and in subjects as young as 6 months.

7.5.4 Drug-Disease Interactions

Renally impaired

The objective of study PJPR0013 was to examine the impact of various degrees of renal impairment on the absorption and disposition of fexofenadine. The study was conducted as a stratified, open-label, single 80 mg dose study of 29 subjects 26 to 68 years of age assigned to one of 3 renal function groups based on creatinine clearance. The groups were defined as:

- Group I, subjects with mild-to-moderate renal impairment: creatinine clearance between 41 and 80 mL/min
- Group II, subjects with moderate-to-severe renal impairment: creatinine clearance between 11 and 40 mL/min
- Group III, subjects with end-stage renal disease between their scheduled dialysis periods (dialysis subjects): creatinine clearance 10 mL/min or less

In subjects with mild-to-severe renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy subjects. Peak plasma levels in subjects on dialysis were 82% greater and the half-life was 31% longer than observed in healthy subjects. A total of 12 of the 29 subjects reported a TEAE. The most frequently reported TEAE was headache, which was reported by 5 subjects. None of the subjects discontinued the study due to an adverse event.

Although fexofenadine doses of up to 690 mg BID for 4 weeks have been tolerated in a small number of healthy subjects, based on increases in bioavailability and half-life observed in subjects with varying degrees of renal impairment, a dose of 30 or 60 mg once daily is recommended as the starting dose in pediatric or adult subjects respectively, with decreased renal function in the approved prescription labeling for fexofenadine.

Hepatically impaired

The objective of study PJPR0021 was to characterize the pharmacokinetics of fexofenadine in subjects with various degrees of liver failure following administration of a single dose of fexofenadine 80 mg. The study was conducted as a stratified, open-label study of 17 subjects assigned to one of 2 hepatic function groups based on the Child-Pugh classification.

- Group I, mild-to-moderate hepatic impairment: Class A liver failure by the Child-Pugh classification
- Group II, moderate-to-severe hepatic impairment: Classes B and C1 liver failure by the Child-Pugh classification

Hepatic impairment had little impact on the pharmacokinetics of fexofenadine. Three of the 17 subjects reported a TEAE. Each individual TEAE was reported by only 1 subject. No subject discontinued from the study due to an adverse event.

7.5.5 Drug-Drug Interactions

See Section 4.4.3

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity evaluations were submitted.

7.6.2 Human Reproduction and Pregnancy Data

Fexofenadine is rated category C with respect to pregnancy risk, given an absence of controlled studies in pregnant women and a similar absence of teratogenic effect in animal studies at doses in excess of the recommended daily human dose. As such, it should only be used during pregnancy when the potential benefit exceeds potential risk.
Many of the cases reported with postmarketing use describe patients with unexpected pregnancy occurring during fexofenadine use, with noted discontinuation of fexofenadine at the time pregnancy was identified. Pregnancy or lactation exposures (307 cases) accounted for 2.1% of all spontaneous fexofenadine reports. The vast majority of cases (~82%) reported exposure without associated adverse outcomes, or adverse events without impact on the pregnancy. While 7 of the reports described complicated pregnancies (most commonly pre-eclampsia), given the frequency of these complications in general, an unexpectedly high occurrence of these events within the postmarketing exposure for fexofenadine is not noted. Similarly, the rare anomalies reported following fexofenadine intrauterine exposure reveal no specific patterns to suggest a drug effect.

7.6.3 Pediatrics and Assessment of Effects on Growth

NA

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

DRUG ABUSE LIABILITY ASSESSMENT

The Sponsor submitted a Drug Abuse Liability Assessment for mono-product fexofenadine which included a postmarketing update to 30 Sept 2009 from the FDA AERS and WHO Uppsala Monitoring Center databases. The safety profiles were compared for fexofenadine and two other

3rd generation antihistamines, loratadine and cetirizine. There were a total of 12 serious adverse event reports involving drug abuse or misuse; none had a fatal outcome.

A review of the Drug Abuse Warning Network (DAWN) database was also submitted, showing similar profiles for ER visits associated with non-medical use of fexofenadine and comparators. A review of the National Poison Data System (known as the Toxic Eexposure Surveillance System until 2006 and administered by the American Association of Poison Control Centers) showed that reasons for exposure were mostly unintentional (about 90% of cases) for fexofenadine exposure only. There were no deaths associated with fexofenadine.

A search of the Global Integrated safety Database (GIDB, see Table 4) was performed to identify reports of potential drug abuse, dependence, withdrawal, and overdose. The GIDB included the safety data from 134 unique studies: those previously submitted to fexofenadine NDAs as well as studies submitted to fexofenadine INDs (various formulations); postmarketing studies conducted in the US not conducted under fexofenadine INDs submitted to the FDA; and clinical studies submitted in Europe and Japan to gain marketing approval.

There were no cases of drug abuse or dependence identified. However, there were 4 cases reported as drug withdrawal headache in adults and 4 cases of overdose reported (1 in an adult and 3 in children), and 1 case of an adult substance abuser. The drug withdrawal headaches may have involved caffeine. The adult overdose case did not involve any AE. The substance abuser was on placebo and abused an antiperspirant.

The pharmacovigilance database was searched from fexofenadine launch through 30 September 2009 to identify reports of potential drug abuse, dependence, or withdrawal. Cases reported with a nature of event “drug abuse” were included irrespective of reported term.

Forty-six spontaneous case reports of abuse, misuse or overdose were identified.

- Thirty-two of the reports described an **intentional drug misuse**. These reports included splitting or crushing pills (6 cases), unapproved use in children (8 cases), doubling or otherwise increasing the standard dose (7 cases), ingestion of expired drug (4 cases), taking medication prescribed for another individual (3 cases), dispensing of the wrong drug (2 cases), and unspecified misuse (2 cases).
- Nine cases reported **intentional overdose**. These cases all represented either dosage increases due to perceived lack of effectiveness in controlling allergy symptoms, or intentional single episode overdoses with an intent to do self-harm.
- One case reported a drug dependence on promethazine that was unrelated to fexofenadine use. Similarly, a second report described laxative dependence in a patient on fexofenadine, with no suspected drug dependence associated with the antihistamine.

The remaining 3 cases reporting abuse, dependence, or withdrawal with fexofenadine are summarized in Table 30.

Table 30 Spontaneous reports of abuse, dependence or withdrawal

Case ID Age/sex	Adverse events (MedDRA PT)	Outcome	Comment
200110443US 63Y F	Drug withdrawal headache	Ongoing	Consumer reported worsening of sinus headaches (indication for treatment) when the medication wears off.
200214869US Unknown	Overdose[a]	Unknown	Physician reported a couple of teenagers presenting to the emergency department after "trying to get high" on 4 to 5 fexofenadine. No additional information provided.
200513082US 58Y F	Withdrawal syndrome (headache, fatigue, drug dependence)	Ongoing	Consumer with a history of atrial fibrillation requiring ablation therapy complained of headaches and increased fatigue associated with a return of allergy symptoms when she would try to stop fexofenadine; felt she was "addicted". Consumer had been taking fexofenadine for 6 years, with doses increasing from 60 mg daily to 180 mg twice daily of the treatment period. Patient was concomitantly taking Phenobarbital + atropine + scopolamine + hyoscyamine. The patient's physician could not confirm the reported events.

Unk- Unknown, F- female, M – male

[a]Reported as a drug abuse (nature of event)

In two cases, 200110443US and 200513082US, the reported withdrawal events may have reflected also the underlying disease condition. Concomitant medications may also provide an explanation in the second of these cases.

One case 200214869US appears to involve abuse of fexofenadine but is not substantiated by a physician and is poorly documented.

National Poison Data System (NPDS)

The NPDS (formerly TESS) poisoning surveillance database is collected by 61 poison control centers in the US. This database was searched for cases with exposure to fexofenadine between 1996 and 18 October 2009. The distribution of the cases was studied by age group, gender, reasons for exposure, and medical outcomes. Comparator drugs were not analyzed, as these NPDS data in the database were not available to the Sponsor.

The analyses of the NPDS database identified a total of 24,447 cases with fexofenadine used alone or in combination with other drugs or substances, from 1996 to 18 October 2009. Most of the cases, 58.98%, were in women. Among the cases with exposure to fexofenadine, 10.1% were reported in children less than 2 years of age, 29.2% in children 2 to 11 years of age, 50.6% in individuals 12 to 64 years of age, and 5.6% in persons greater than 65 years of age.

Of 24,447 cases with fexofenadine exposures, adverse drug events accounted for 3.67% of these cases, while suicidal intent was suspected in 13.69% of them. The major reasons for the cases with fexofenadine (approximately 78%) were unintentional; with 35.37% falling in the category of unintentional general, and 42.67% in the category of unintentional therapeutic error. Among 8652 cases with unintentional general, only 0.07% were identified with an outcome of major clinical effect and 10.4% with an outcome of moderate clinical effect. Of 10,432 cases with unintentional therapeutic error, only 1 case of death, 1 case with a major clinical effect, and 0.65% of cases (68) resulting in a moderate clinical effect were reported. About 62.3% of these cases (15,238) were exposed to fexofenadine use only.

For the cases reported with fexofenadine only exposure, 57.35% of them were women, 0.01% (2 cases) associated with a pregnancy exposure. About 13.9% were reported in children less than 2 years of age, 34.7% in children 2 to 11 years of age, 41.2% in individuals 12 to 64 years of age, and 5.4% in the elderly persons (≥65 years of age. In the cases of fexofenadine exposure only, most of the exposures were unintentional, with the rates of unintentional general exposure and unintentional therapeutic error at 43.15% and 46.63%, respectively. Adverse drug reactions and intentional suspected suicide accounted for 2.28% and 4.72%, respectively

Drug Abuse Warning Network (DAWN)

The DAWN surveillance system monitors drug-related ER visits and deaths. DAWN changed its case criteria and classification criteria in 2003, when the DAWN Live program was started. The Sponsor searched the DAWN records of ER visits in association with fexofenadine and comparators, cetirizine and loratadine, prior to 2003. The DAWN Live records were searched for ER visits for fexofenadine and both comparators from 2003 to 12 November 2009 (for fexofenadine), 04 December 2009 (for loratadine), or 05 December 2009 (for cetirizine). The visits were classified by type and by age group.

During the period from 1996 through 2002, a total of 1508 emergency department visits with fexofenadine mentioned were identified in the original DAWN database, with 2425 for cetirizine and 3985 for loratadine. No deaths in association with fexofenadine or comparators were reported.

During 2003 through 2009 (as previously defined in this section), 1322 emergency department visits in association with fexofenadine mentioned were reported in DAWN Live, with 1749 for cetirizine and 2756 for loratadine. Women had more emergency department visits in association with fexofenadine and comparators than men. No death in association with fexofenadine or comparators was reported.

Of all the cases with fexofenadine mentioned, 67.4% occurred in adults 18 to 64 years of age, 11.6% in children 12 to 17 years of age, 5.8% in children less than 12 years of age, and 15.2% in older patients (≥65 years of age). Of cases reported with cetirizine, 58.8% were identified among patients 18 to 64 years of age, with 11.7% among children 12 to 17 years of age, 18.6% in children less than 12 years of age, and 10.9% in older patients (≥65 years of age). Of cases reported with loratadine, about 59.5% were identified among patients 18 to 64 years of age, with 11.6% among children 12 to 17 years of age, 18.8% in children less than12 years of age, and 10.1% in older patients (≥65 years of age).

MO Comment *The DAWN data indicate that the proportion of ER visits associated with fexofenadine was lower than the comparators among the young children <6 years of age, but higher than the comparators for the proportion of ER visits associated with fexofenadine by older adults >65 years of age. However, without use data, the differences in the proportions of ER visits by age groups are not interpretable. The higher proportion of ER visits with fexofenadine use in older patients, versus the comparators, may be due to greater use of fexofenadine in that age group compared to use of the other two antihistamines. There may be greater use of loratadine and cetirizine in young children.*

The profiles of ER visits associated with fexofenadine, particularly those with nonmedical use of fexofenadine, are comparable with those associated with cetirizine or loratadine.

The Sponsor concluded that a risk management plan is not required, but pharmacovigilance will continue.

MO Comment: *A risk management plan is not required, based upon the review the NPDS poison control and DAWN emergency department databases.*

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarket Experience

Fexofenadine was first approved for marketing by Sanofi-aventis in the US on 25 July 1996 and is currently marketed in more than 100 countries worldwide, with marketed territories including North America, Eastern and Western Europe, Australia, Japan, the Middle East, Central and South America, and Africa.

Based upon available Intercontinental Medical Statistics (IMS) sales data, an estimated (b) (4) of fexofenadine were sold worldwide between 3Q1997 and 2Q2009. IMS sales data represent the amount of drug distributed to pharmacies and wholesalers. These distribution data can be used to estimate patient exposure based upon assumptions about how the drug is used. The estimate of exposure is calculated on the Defined Daily Dose (DDD), which is described by the CIOMS Working Group V as the assumed average maintenance dose per day for a drug used in its main indication in adults.

Cumulative worldwide sales of (b) (4) translate to approximately (b) (4) is the most commonly used dosage strength worldwide. This represents an estimated 32.05 million patient-years (pt-yrs) exposure since approval.

SANOFI-AVENTIS PHARMACOVIGILANCE DATABASE SEARCH

A search of the Sanofi-aventis pharmacovigilance database was performed on 12 October 2009 to identify all spontaneous case reports with fexofenadine as a suspect drug in an adverse drug reaction. The search retrieved cases received between 25 July 1996 and 30 September 2009, and included reports received from all spontaneous sources (ie, health care providers, Health Authorities, literature reports, and consumers).

For the purposes of this review, all terms captured as either a “diagnosis” or an accompanying “symptom” are presented as separate “Adverse Events” in this analysis. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0, and are presented by MedDRA Preferred Term (PT) unless otherwise specified.

OVERVIEW OF ADVERSE EVENTS

Since initial approval, a total of 14,572 spontaneous reports involving 24,945 adverse events (AEs) have been reported to Sanofi-aventis from worldwide sources. These reports were most commonly received from the United States, Japan and Canada. More than 90% of all adverse events were nonserious.

Countries with the greatest cumulative postmarketing exposure are the US (17.23 million pt-yrs), Japan (3.78 million pt-yrs), India (1.18 million pt-yrs), the United Kingdom (1.22 million pt-yrs), Australia (1.08 million pt-yrs), and France (1.06 million pt-yrs). A summary of AE reports by country of occurrence is presented below in Table 31. The vast majority of reports were received from the United States, followed by Japan and Canada.

Table 31 Spontaneous reports by country

Country[a]	No. (%) of AE reports
Total reports	14572
United States	9080 (62.3)
Japan	2330 (16.0)
Canada	948 (6.5)
United Kingdom	477 (3.3)
France	355 (2.4)
Australia	328 (2.2)
Brazil	280 (1.9)
Germany	223 (1.5)

[a] Includes countries with > 100 spontaneous AE reports

MO Comment *The rate of reporting by country was compared to the cumulative exposure to fexofenadine from above. Given that 17.23 million pt-yrs exposure in the US yielded 9080 AE reports, then 3.78 million pt-yrs exposure in Japan is expected to yield 1992= 9080*(3.78/17.23) reports, versus the 2330 actually received. Hence Japan had a higher reporting rate than the US for fexofenadine. The number is the count of AE terms and not the case count, so the difference may reflect a tendency to report more AE terms per case. Similarly, the reporting rates from UK and France are lower than from the US when scaled from the cumulative exposure (expected 643 and 559 reports, respectively). The rate of reporting from Canada is much higher than from the US relative to exposure, but the Canadian-reported cases are more often nonserious, with 1002 nonserious reports (97%) of the 1031 total. The 29 SAEs from Canada comprised a total of 14 cases, where the most frequently reported SOC was cardiac disorders (8 SAEs in 5 cases). One death case, the 15 yo Canadian girl (200212306GDDC) discussed below, accounted for the single reports of torsades, cyanosis, and ventricular fibrillation, and another case (a 48 yo male, case 200515693GDDC who took a total of three doses) accounted for the single report of ventricular tachycardia.*

In the Sanofi-aventis pharmacovigilance database, there were 24945 total AEs. Of these, there were 22626 (90.7%) nonserious AEs and 2319 (9.3%) SAEs reported. There were 946 cases with SAE reports including 44 deaths. The most commonly reported AEs were from the General disorders and administrative site conditions, Nervous system disorders, Gastrointestinal disorders, and Skin and subcutaneous tissues disorders SOCs. The most frequently reported AEs predominantly represented either a lack of effect in relieving allergy symptoms or events listed in the current US Prescribing Information (USPI) for fexofenadine. The single most commonly reported event was a lack of drug effect/drug ineffective.

The most frequently reported adverse events (from reports where a dose is given) are presented below in Table 32 by MedDRA PT for the 2 dose groups, <360 mg QD and >360mg QD. The maximum recommended daily dose in the present application is 180 mg QD. If a consumer were to take two 180 mg tablets a day instead of the recommended dosing, then a total dose of 360 mg QD would result. There were a total of 15173 AEs in 8088 case reports, of which 659 AEs were reported in 332 cases from the higher dose group.

Drug ineffective was the most commonly reported AE in both dose groups. The AEs reported more frequently from the >360mg QD dose group in Table 32 were fatigue, dry mouth, overdose events and therapeutic response unexpected (the latter reported from an investigator in Denmark using high-dose fexofenadine for dystonia).

In the higher dose group ≥ 360 mg QD, reports were more common in the following SOCs when compared to the lower dose group: General disorders and administrative site conditions, Injury poisoning and procedural complications, Investigations, and Surgical and medical procedures. In the General disorders and administrative site conditions SOC, the difference in reporting is primarily accounted for by an increased reporting of therapeutic response unexpected (57 events) in the higher dose group. All save one of the therapeutic response unexpected reports came from a prospective case control study in Denmark of fexofenadine in the treatment of dystonias (a non-company-sponsored study); the remaining case, from the US, involved use of fexofenadine in the treatment of chronic and positional vertigo in the elderly. In the Injury poisoning and procedural complications SOC, the difference is almost entirely due to increased reporting of overdose in the high dose group. Finally, in the Surgical and medical procedures SOC, off-label use is the primary term seen most commonly in the higher dose group.

The fraction of reports seen with the ≥ 360 mg dose group, as compared to the <360 mg dose groups, was not increased with respect to cardiac disorders, hepatobiliary disorders, nervous system disorders, psychiatric disorders or renal disorders.

Table 32 Adverse events by MedDRA preferred term and dose

	No. (%) of events		
MedDRA PT	**< 360mg**	**≥ 360 mg**	**Total [a]**
Total AEs	**14514**	**659**	**15173**
Total reports	**7756**	**332**	**8088**
Drug ineffective	1182 (8.1)	54 (8.2)	1236 (15.3)
Headache	606 (4.2)	19 (2.9)	625 (7.7)
Dizziness	451 (3.1)	19 (2.9)	470 (5.8)
Nausea	429 (3.0)	10 (1.5)	439 (5.4)
Somnolence	431 (3.0)	11 (1.7)	442 (5.5)
Back pain	325 (2.2)	11 (1.7)	336 (4.2)
Palpitations	251 (1.7)	2 (0.3)	253 (3.1)
Urticaria	242 (1.7)	11 (1.7)	253 (3.1)
Insomnia	263 (1.8)	5 (0.8)	268 (3.3)
Fatigue	221 (1.5)	15 (2.3)	236 (2.9)
Dyspnoea	214 (1.5)	5 (0.8)	219 (2.7)
Pruritus	204 (1.4)	8 (1.2)	212 (2.6)
Rhinorrhoea	189 (1.3)	4 (0.6)	193 (2.4)
Diarrhoea	193 (1.3)	1 (0.2)	194 (2.4)
Rash	186 (1.3)	0	186 (2.3)
Hypersensitivity	169 (1.2)	10 (1.5)	179 (2.2)
Overdose	47 (0.3)	77 (11.7)	124 (1.5)
Dry mouth	114 (0.8)	8 (1.2)	122 (1.5)
Off label use	23 (0.2)	59 (9.0)	82 (1.0)
Theraeutic response unexpected	6 (<0.1)	57 (8.6)	63 (0.8)
Accidental overdose	24 (0.2)	7 (1.1)	31 (0.4)
No adverse event	12 (0.1)	6 (1.0)	18 (0.2)

Source- Reported Adverse Events by Daily Dose_Spontaneous cases_Fexofenadine Hydrochloride, *pg. 419*
[a] Includes reports wherein a total daily dose was available (ie, cases with no dose given are not included in this by-dose analysis)
Table includes MedDRA PTs reported in > 1.0% of cases within a given dose group
Percentages calculated as number of cases in a dose group divided by the total cases for that dose group x 100

In addition to the above-mentioned search of the Sanofi-aventis pharmacovigilance database, the Sponsor provided analyses of the FDA AERS and WHO UMC extrernal databases of spontaneous reports, as well as the Drug Abuse Warning Network (DAWN) and National Poison Data System external databases (see Section 7.6.4). A data mining analysis of the FDA AERS was performed by the Sponsor for fexofenadine and for two comparator drugs, cetirizine and

loratadine, and revealed safety signals for cardiac arrhythmias and for hepatic and biliary disorders. A similar data mining analysis was performed with the WHO UMC database, also indentifying safety signals for heart rate and rhythm disorder as well as myo-endo-pericardial and valve disoders.

The Sponsor provided a safety update covering the period Oct. 1, 2009 to Mar. 31, 2010. The postmarketing data from the safety update were combined with the Sanofi-aventis pharmacovigilance database and reviewed together below.

DATA MINING BY EMPIRICAL BAYES GEOMETRIC MEAN METHOD

AERS and WHO

The Sponsor performed a data mining analysis of the FDA AERS database from 01 February 1969 (the beginning of the database) to 30 June 2009, using the Multi-item Gamma Poisson Shrinker method to search the postmarketing data for safety signals. It is a disproportionality method used to identify drug-event combinations reported more frequently than expected based on overall rates of drug-event associations in the database. The program calculates adjusted reporting ratio values, or "Empirical Bayes Geometric Mean" (EBGM) values, together with the lower and upper bounds of 95% confidence limits for these values, denoted EB05 and EB95 respectively. The EBGM values indicate the strength of the reporting relationship between a particular drug and adverse event, using the adjusted ratios of observed-to-expected counts for drug-event combinations. Signal scores (EBGM05) are defined to screen for potential safety signals. A threshold of 2 is currently used, which means that for any drug-event combination with signal scores greater than or equal to 2, that particular combination is reported at least twice as often as expected.

These analyses used the Qscan program from DrugLogic, which is based on the MedDRA preferred term. If a report included 2 different adverse events (preferred terms) from the same system organ class, the report would be counted twice under the specific system organ class in the analysis.

The EBGM analyses for all adverse events and serious adverse events in association with fexofenadine and comparators in the FDA AERS database were performed by MedDRA system organ class and high level group term. The adverse events retained for this analysis were those potentially related to the drug (ie, when the role of drug was coded as 'Suspect'). The EBGM analyses for each of the safety topics of interest including drug abuse or misuse, overdoses, drug interactions, pregnancy exposures, and drug abuse dependence and withdrawal were performed by user defined terms and selected standard MedDRA query (SMQ). The EBGM analyses for each of the adverse events of special interest including cardiac events, Torsades de Pointes, renal events, convulsions, anaphylactic reactions, somnolence, and possible drug related hepatic disorders were performed by user defined terms and selected SMQs. The EBGM analyses for all adverse events and serious adverse events in association with fexofenadine use and comparators were also performed by gender and selected age groups (<2 years, 2 to 11 years of age; over 65 years of age).

A similar data mining analyses of the WHO UMC database were performed using EBGM by Qscan to evaluate the profile of spontaneous reporting for all serious adverse events, adverse events for safety topics of interest, and adverse events of special interest associated with fexofenadine as well as with cetirizine and loratadine. The spontaneous reports from 1 January 1967 (the beginning of the WHO UMC database) to 31 September 2009 (the most recent data available for the WHO UMC database) were included.

Unlike the FDA AERS database, the WHO-adverse reaction terminology (ART) coding system is used in the WHO UMC database. The WHO-ART codes are not completely identical to MedDRA codes. Version WHO-ART 2009.3 was used for the EBGM analses. As was the case for AERS, the adverse events retained for the WHO analysis were those potentially related to the drug (ie, when the role of drug was coded as 'Suspect').

In the FDA AERS database, EBGM analyses by MedDRA high level group term revealed a safety signal for cardiac arrhythmias as well as cardiac disorder signs and symptoms associated with fexofenadine and loratadine. Further evaluation indicated that these safety signals with fexofenadine were mainly due to signals from nonspecific events. A signal was detected in AERS with the PT term "electrocardiogram QT prolonged". With loratadine, safety signals were suggested for Torsades de Pointes, ventricular tachycardia, and ventricular fibrillation.
EBGM analyses of FDA AERS reports by MedDRA high level group term for SAEs further yielded a signal for hepatic and hepatobiliary disorders with fexofenadine and loratadine. A safety signal for hepatitis acute with fexofenadine was suggested by further analyses at the MedDRA preferred term level. With loratadine, a safety signal for hepatitis acute was also detected at the MedDRA preferred term level.

From the WHO UMC database for SAEs by WHO-ART system organ class, the EBGM analyses suggested safety signals for heart rate and rhythm disorders (marginal finding) as well as myo/endo/pericardial and valve disorders in association with fexofenadine. However, a signal with loratadine for the serious adverse event of heart rate and rhythm disorders was also detected. The EBGM analyses by user defined terms revealed no safety signals for the adverse events of special interest including cardiac and ventricular arrhythmia events, renal events, hepatic events, anaphylactic reactions, and convulsions for fexofenadine or both comparators. However, safety signals for somnolence were detected with cetirizine and loratadine, but not fexofenadine.

The safety signals found by EBGM in the FDA AERS database are summarized in Table 33 by MedDRA High Level Group Term, for fexofenadine and for two comparators, cetirizine and loratadine.

MO Comment *In view of the AERS data mining results shown in* Table 33*, the reviewer examined 953 individual case reports of SAEs (comprising the 946 SAE reports in the Sponsor database plus additional cases identified in AERS and in the Sponsor safety update), in order to characterize the cardiac and hepatobiliary safety signals suggested for fexofenadine. The objectives were to identify the nature and significance of the cardiac and hepatic events that were flagged as being reported at higher than expected rates in association with fexofenadine. Cardiac safety signals from fexofenadine were mainly due to tachycardia, palpitation, and arrhythmias (see below). Specific events already determined to be of interest, such as QT*

prolongation, were also specifically examined as were SAE reports of hypersensitivity, drug interactions, and seizures.

Table 33 AERS EBGM signals by MedDRA High Level Group Term (EBGM 05≥2.0)

Drugs	SAEs by MedDRA HLGT	Observed Count	EBGM 05	EBGM	EBGM 9
Fexofenadine					
	gastrointestinal tract disorders congenital	10	7.4	13.4	24.6
	cardiac and vascular disorders congenital	20	5.5	8.5	13.1
	cardiac arrhythmias	210	3.0	3.5	4.0
	cardiac and vascular investigations (excl enzyme tests)	86	2.2	2.7	3.3
	hepatic and hepatobiliary disorders	109	2.0	2.4	2.9
Cetirizine					
	neurological disorders congenital	25	8.0	11.9	17.6
	gastrointestinal tract disorders congenital	13	4.2	7.2	12.3
	endocrine disorders congenital	3	4.0	10.8	29.3
	chromosomal abnormalities and abnormal gene carriers	9	3.8	7.2	13.6
	foetal complications	19	3.8	6.0	9.3
	musculoskeletal and connective tissue disorders congenital	22	2.7	4.1	6.2
	immunology and allergy investigations	37	2.4	3.3	4.6
	obstetric and gynaecological therapeutic procedures	29	2.2	3.2	4.6
	immune system disorders congenital	2	2.1	6.6	20.9
	skin vascular abnormalities	56	2.0	2.7	3.5
	chemical injury and poisoning	118	2.0	2.4	2.9
Loratadine					
	reproductive tract and breast disorders congenital	26	25.5	37.5	55.1
	musculoskeletal and connective tissue disorders congenital	22	4.4	6.6	10.1
	cardiac arrhythmias	472	4.2	4.6	5.1
	gastrointestinal tract disorders congenital	9	3.7	7.0	13.1
	renal and urinary tract disorders congenital	7	3.1	6.3	12.8
	cardiac and vascular investigations (excl enzyme tests)	139	2.3	2.7	3.2
	chemical injury and poisoning	87	2.1	2.6	3.2
	hepatic and hepatobiliary disorders	176	2.0	2.3	2.7

The Sponsor noted that the 10 AEs noted in Table 33 *under the SOC of "gastrointestinal tract disorders congenital" came from 5 reports, which had both gastrointestinal malformation and oesophageal atresia. These 5 reports referred to one baby born with GI malformation as well as congenital cardiac malformation. Likewise, the 20 AEs under the SOC "cardiac and vascular disorder congenital" came from 8 patients. Two appeared to be duplicate reports of the same patient who was exposed to both loratadine and fexofenadine. The baby had congenital heart disease and pulmonary arterial atresia. Another AE report referred to an adult patient who had bicuspid aortic valve, which is not a report of congenital anomaly associated with fexofenadine exposure in utero. The remaining five reports were for the same patient as explained earlier for*

the GI anomaly. The Sponsor concluded that the EBGM signals for the GI and cardiac congenital anomalies were not real safety signals, and the reviewer agrees.

The results of the data mining analysis of the WHO UMC spontaneous report database are summarized in Table 34. Fexofenadine safety signals were suggested for heart rate and rhythm disorders and for "myo/endo/pericardial and valve disorders".

Table 34 Data Mining Analyses by WHO ART SOC of SAEs (EBGM 05 > 2)

	SAE	Observed Count	EBGM 05	EBGM	EBGM 95
Fexofenadine	Myo/endo/pericardial & valve disorders	7	3.6	7.3	14.8
	Heart rate and rhythm disorders	9	2.4	4.4	8.3
Cetirizine	[None above EBGM 05 threshold]	–	–	–	–
Loratadine	Heart rate and rhythm disorders	51	7.3	9.7	12.8

MO Comment *The EBGM analysis of the WHO UMC database revealed a similar safety signal for cardiac SAEs as was found in the AERS data mining analysis. The OSE reviewer has also analyzed the AERS and agreed with the conclusions of the previous OSE (DDRE) safety reviews (discussed in Section 2.4).*

The Sponsor performed only the data mining analysis of the AERS and WHO databases and did not review the narrative case reports unless they were reported to Sanofi-aventis directly. The review of the Sponsor pharmacovigilance database, augmented by 3 cases of interest from the Sponsor safey update, follows. The present reviewer also searched AERS and added 4 cases to the Sponsor database, including 2 deaths.

Table 35 *summarizes the Sponsor's pharmacovigilance database (before the safety update) which has the total of 24945 AEs (2319 serious AEs) from 14572 cases (946 serious). The table also shows the selected SOCs and PTs of special interest which are specifically reviewed below. The four left-hand columns of* Table 35 *show the numbers of AE reports (cases), serious and nonserious, for the selected SOCs and PTs, without regard to causality. The two right-hand columns show the SAE cases selected for review below, referring to the summary Tables in this review and showing the numbers of SAE cases assessed as of possible, probable or higher causality. The SAEs in the review database included cases from the Sponsor safety update and from AERS.*

The reviewer assessments of causality followed the WHO system (Appendix 9.4). The assessment considers the time relation of drug use to the adverse event, the presence of underlying disease, and the use of concomitant medications. A possible assessment requires a reasonable time relation to the event, although the event could also be explained by underlying disease or use of other drugs. That is, other causes for the event or confounding factors may be present for a possible assessment, but a contribution of the drug to the event cannot be excluded. For an assessment of probable, causes for the event other than the suspect drug are unlikely, and there is a reasonable time relation to the adverse event as well as a clinically reasonable response to withdrawal of the suspect drug. For probable assessment, a positive rechallenge is not required.

Table 35. Post Marketing Serious and Nonserious AEs of Interest, Including Death Cases

	Total AEs (cases)	SAEs (cases)	Nonserious AEs (cases)	This review, Table Number	Possible probable cases
Total All SOCs	24945 (14572)	2319 (946)	22626 (13763)		#
Cardiac disorders	831 (698)	239 (177)	592 (523)	Table 40	119
tachycardia		38 (38)	105 (105)		
arrhythmia		21 (20)	56 (52)		
atrial fibrillation		26 (26)	4 (4)		
ventricular tachycardia		14 (14)	0 (0)		
ventricular fibrillation		8 (8)	0 (0)		
palpitations		29 (29)	332 (315)		
cardiac arrest		10 (10)	0 (0)		
bradycardia		13 (13)	8 (8)		
AV block complete		6 (6)	0 (0)		
QT prolonged*		16 (16)	3 (3)		
heart rate increased*		13 (12)	114 (111)		
heart rate irregular*		3 (3)	37 (36)		
loss of consciousness*		49 (48)	20 (20)		
syncope*		35 (32)	15 (15)		
Hepatobiliary disorders	162 (136)	97 (76)	65 (60)	Table 42	59
hepatic function abnormal		31 (30)	35 (35)		
jaundice		17 (17)	4 (4)		
bilirubin increased*		11 (11)	2 (2)		
Immune system disorders	413 (393)	86 (77)	327 (316)	Table 43	144
hypersensitivity		41 (38)	269 (263)		
anaphylactic reaction		28 (23)	2 (2)		
anaphylactic shock		12 (12)	1 (1)		
anaphylactoid reaction		4 (4)	1 (1)		
Skin and subcutaneous tissue disorders	2318 (1868)	269 (193)	2049 (1681)		
angioedema		31(30)	24 (22)		
Stevens Johnson		8 (8)	0 (0)		
urticaria		50 (46)	385 (370)		
dyspnea*		65 (64)	251 (246)		
Nervous system disorders	3607 (2960)	356 (253)	3251 (2724)		
convulsions		52 (48)	7 (6)		
dizziness		41 (40)	675 (650)		
somnolence		17 (17)	665 (651)		
Other SOCs	17614 (8517)	1272 (170)	16342 (8459)		
* different SOC				#added cases from AERS and Sponsor's safety update	

MO Comment Table 35 *shows selected preferred terms from Sponsor Table T1(All reported AEs), Appendix A. This Table uses the total AE numbers as given in the Sponsor Table, which do not always correspond to the sum of serious and nonserious AEs, for reasons that are not clear.*

In the Sanofi-aventis database, there were 946 SAE cases including 44 deaths. With the added cases from AERS and the Sponsor's safety update, the total postmarket database for review was 953 cases, including 46 death cases and 907 nonfatal SAE cases.

SERIOUS ADVERSE EVENTS

In the Sponsor pharmacovigilance database. SAEs were most frequently reported from the General disorders and administrative site conditions, Nervous system disorders, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, and Respiratory, thoracic and mediastinal disorders SOCs.

The most frequently reported SAEs by MedDRA PT are shown in Table 36.

Table 36 Most frequently reported serious adverse events

MedDRA preferred term	No. (%) of SAE reports
Total SAEs	**2319**
Total SAE reports	**946**
Dyspnoea	65 (3.0)
Convulsion	52 (2.2)
Urticaria	50 (2.1)
Loss of consciousness	49 (2.1)
Dizziness	41 (1.7)
Hypersensitivity	41 (1.7)
Tachycardia	38 (1.6)
Syncope	35 (1.5)
Angioedema	31 (1.3)
Hepatic function abnormal	31 (1.3)
Nausea	30 (1.2)
Palpitations	29 (1.2)
Anaphylactic reaction	28 (1.2)
Atrial fibrillation	26 (1.1)
Hypotension	25 (1.0)
Malaise	24 (1.0)
Vomiting	24 (1.0)

Source: Reported Serious Adverse Events by SOC_ Spontaneous cases_ Fexofenadine Hydrochloride, *pg. 135*
Includes AEs comprising ≥0.1% of all adverse events

As seen previously with all AE reports, the reported SAEs involve largely labeled events (eg, dizziness, hypersensitivity, angioedema, malaise, vomiting) or events possibly related to the indication for use (e.g. urticaria). The most commonly reported SAE, dyspnea, can be associated

with the allergy indication for treatment or, less commonly, can be a complication of another medical disorder (e.g. tachycardia or palpitations).

In the 946 cases from the Sponsor database reporting SAEs, the vast majority of the events were classified as serious either because of hospitalization or because the events were assessed as medically important. According to Sponsor Postmarket Review, Section 4.3.3, Table 7, the 946 SAE cases were comprised of 44 deaths, 73 life-threatening cases, 340 hospitalizations, 558 medically important cases, 11 congenital anomalies and 24 disability cases.
MO Comment *A given SAE case may fall into more than one of the above categories, so the numbers of cases in each category total to more than 946.*

Serious adverse events by dose
The most commonly reported SAEs in the Sponsor postmarketing database are presented by dose group in Table 37.

Table 37 Most common SAEs by MedDRA preferred term and dose

MedDRA PT	No. (%) of cases		
	< 360mg	≥ 360 mg	Total reports[a]
Total SAEs	**1551**	**94**	**1645**
Total reports	**611**	**36**	**647**
Dyspnoea	51 (3.3)	0	51 (3.1)
Dizziness	31 (2.0)	2 (2.1)	33 (2.0)
Loss of consciousness	33 (2.1)	2 (2.1)	35 (2.1)
Urticaria	38 (2.4)	1 (1.1)	39 (2.4)
Convulsion	29 (1.9)	2 (2.1)	31 (1.9)
Tachycardia	28 (1.8)	2 (2.1)	30c(1.8)
Hypersensitivity	28 (1.8)	3 (3.2)	31 (1.9)
Anaphylactic reaction	22 (1.4)	2 (2.1)	24 (1.4)
Syncope	22 (1.4)	2 (2.1)	24 (1.4)
Fatigue	9 (0.6)	2 (2.1)	11 (0.7)
Overdose	2 (0.1)	10 (10.6)	12 (0.7)
Electrocardiogram QT prolonged	9 (0.6)	2 (2.1)	11 (0.7)
Dry mouth	2 (0.1)	2 (2.1)	4 (0.2)
Intentional overdose	0	2 (2.1)	2 (0.1)

Source- Reported Serious Adverse Events by Daily Dose_Spontaneous cases_Fexofenadine Hydrochloride, *pg. 456*
Includes reports wherein a total daily dose information was available (ie, cases with no dose given are not included in this by-dose analysis)
Includes PTs representing at least 2% of SAEs in a dose group
Percentages calculated as number of cases in a dose group divided by the total cases for that dose group x 100

Given the limited number of SAEs in the ≥ 360 mg QD group, comparisons to be made to the <360 mg reports are limited. The reporting rate of overdose was notably higher in the ≥360 mg QD group.

CASES WITH FATAL OUTCOME

Forty-four cases in the Sponsor's postmarketing database reported SAEs with fatal outcome. Fatal report counts by age are shown below.

MO Comment: *Among the 44 reports, 3 occurred in patients taking 60 mg daily, 7 in patients taking 120 mg daily, and 7 occurred in patients taking 180 mg daily; in the remaining 27 reports, no total daily dose was provided.*

Table 38 Fatal reports by age

Age	No of Fatal Reports
< 6 mo.	1
6 mo to 17 years	1
18 years to 64 years	22
≥ 65 years	15
Age Unknown	5

Source- *Line Listing_ Reported Serious Adverse Events by Serious Criterion: Death_ Spontaneous cases_ Fexofenadine Hydrochloride,*

Fatal reports involving adults aged 18 to 64 years account for the majority of the fatal cases. Causes of death in these patients were primarily cardiac. Cases with fatal outcome among the elderly (≥ 65 years) primarily included acute myocardial infarction and cardiac arrest, with other isolated reports of liver injury, renal failure, and cerebral hemorrhage. Two of the 44 fatal case reports occurred in children. The first case (199910929RHF) involved congenital pulmonary artery stenosis in a neonate who died following attempted stenotic dilatation. The second case (200212306GDDC) reported torsades de pointes/ventricular fibrillation in a 15 year-old healthy Canadian girl.

MO Comment: *Summaries of 46 fatal cases are shown in* Table 39 *including the 44 cases from the Sponsor database. The casusality assessment follows the WHO criteria (Appendix 9.4). An asterisk is shown by causality if the cases is relatively poorly documented. The symbol # is shown if the case mentions a cardiac history. There were 3 cases with probable assessment, and two additional cases with probable causality for an SAE but not for the death (one for angioedema, one for liver disorder).There were a total of 28 death cases assessed as of probable or possible causality. Of these, 12 cases (43%) had a positive cardiac history. There were six death cases in subjects under the age of 30.*

In the following three cases, the contribution of fexofenadine to the event is probable:

> *200212306GDDC a healthy 15 year old Canadian girl who recently started fexofenadine 60 mg bid for a fly bite collapsed at a bar while with friends and was resuscitated and found to be in ventricular escape rhythm. AV dissociation, ventricular escape, rapid ventricular rhythm, ventricular tachycardia, ventricular fibrillation and asystole were also noted. The autopsy report stated no cardiovascular malformations were found, and alcohol and toxicology screens were negative. Holter monitoring of mother, sister and brother were negative as were ECGs. Torsade de pointes with ventricular fibrillation was listed as probable cause of death by the coroner.*

199920119HMRI – an 18 year old female had her second injection of DEPOPROVERA contraceptive injection on (b) (6). Nine days later she experienced arrhythmia and died suddenly. She had started fexofenadine 60 mg qd approximately one month earlier. She had taken Allegra about one year previously without problems. After her death it was determined she had Long QT syndrome (LQTS). The girl's autopsy was negative but another family member was found to have LQTS.

200115540GDDC a 26 year old male received one tablet of fexofenadine for allergic rhinitis and conjunctivitis. He was also taking prednisolone 20 mg for allergies. Other medical history is unknown. After the one dose of fexofenadine, the patient experienced shock, cardiac arrest and hypokalemia (2.63 mmol/l). He was hospitalized and died four days later. Fexofenadine may have potentiated the effect of hypokalemia.

In the following possible cases, a contribution of fexofenadine to the event cannot be excluded:

200211267JP a 26 year old male, after less than 28 days on fexofenadine for atopic dermatitis, died suddently. No autopsy was performed. The death certificate listed the cause of death as myocardial infarction. There was no history of cardiac disease and an ECG done for a work physical showed no abnormality. Concomitant medication was difluprednate ointment. PMHx included asthma as an infant but none recently.

200217201US a 28 year old male with 6 week history of cough with exercise and symptoms of runny nose and sneezing. He was on Zyrtec, nasalcort, and albuterol. He discontinued Zyrtec and started fexofenadine 180 mg qd, and flovent 220 mg per puff, 11 days prior to the event. Collapsed while playing soccer and was pronounced dead on arrival in the ER. The patient's asthma could have contributed to his death.

199920726HPD on long term sotalol therapy; died after one dose of fexofenadine; literature case [Arznei-Telegramm 9/99, Netzwerk-Bericht 10.164].

200511756JP a 50 year old male with renal failure, who received fexofenadine for 1 or 2 weeks and experienced agranulocytosis. Concomitant medications which had been taken for a long time included lansoprazole and lasix.

200910011JP a 74 year-old female with history of hypertension taking nifedipine for several years was begun on fexofenadine for pruritus. After 4 days, the pruritus resolved but malaise and jaundice developed (no values provided), so fexofenadine was discontinued. Three days later, hospitalized with AST 1962 and ALT 2250 (complete hepatic panel not provided). There was fulminant progression to encephalopathy 2 days after admission. Viral hepatitis testing for A, B, and C, EBV, and CMV were all negative, as were ANA and anti-mitochondrial AB testing. No biopsy was performed and the patient died on hospital day 5.

Table 39 *has additional possible cases in which the contribution of fexofenadine is more confounded, as well as cases which are conditional, unlikely or unrelated to fexofenadine. For the cases assessed as probable, fexofenadine is not the only explanation but others are unlikely.*

Table 39. Postmarketing Cases with Fatal Outcome

MFR report #	Age	Dose, Duration	Concomitants	History	Causality
199710771HMRI	85	PO for three days	None	DEATH NOS reported by a physician to sales rep	possible*
199810506RGB	34	120 MG QD PO; Telfast began on 30-Jul-98 and continued until (b) (4) (death)	TRIMETHOPRIM 07/13/1998 to UnknownTERBUTALINE SULFATE (BRICANYL/00199202/) 02/23/1998 to Unknown	The patient reportedly experienced ventricular tachycardia and sudden death. Post mortem report stated that the patient had been found to have arrythmogenic ventricular dysplasia. Toxicology screen pending.	Possible#
199810627RGB	51	180 MG QD PO; began 14-Aug-98 for urticaria died (b) (6)	AMITRIPTYLINE 10/??/1997 to UnknownNAPROXEN (10/??/1997 to Unknown	Post mortem report cause of death was "idiopathic cardiomyopathy". History fibromyalgia	possible#
199815655DDC	36	60 MG ONCE PO	None	Woke up coughing and gagging; sudden death. Cause of death undetermined. History hay fever and childhood asthma. In good health. No concom	possible
199911238RHF	46	120 MG/DAY PO for 4 days	PREDNISOLONE, CETRIMONIUM BROMIDE, PHENYLEPHRINEHYDROCHLORIDE, NAPHAZOLINE NITRATE 03/26/1999 to 03/29/1999 IBUPROFEN 03/26/1999 to 03/29/1999	Fatal fall. No relevant history like cardiovascular disease nor epilepsy	possible
199920119HMRI	18	Allegra 60 mg 3 weeks	LORATADINE previously; DEPO-PROVERA injection	PATIENT FOUND DEAD AT WORK ARRHYTHMIA SUDDEN DEATH QT PROLONGED..Mother and another relative have long QT syndrome. Med History included ECG QT prolonged.	Probable#
199920202RGB	39	unknown	unknown	Stab wound through heart, Fall	unrelated
199920379DDC	34	120 MG QD PO 4 days	INSULIN Unknown to 07/19/1999 FOSINOPRIL SODIUM 04/26/1999 to 07/19/1999 PRAVASTATIN ATORVASTATIN METOPROLOL AMITRIPTYLINE	Fatal MI History diabetic nephropathy (macro-albuminuria) since 1991, polyneuropathy since 1998 (diagnosis 1999), possible intermittent claudication angina pectoris polyneuropathy	possible#
199920726HPD		120 MG ONCE PO 1 hr after 1 dose	Long term therapy with SOTALOL	DEATH NOS	possible
199920910HMRI	66	PO	Unknown	IRREGULAR HEARTBEAT, SYNCOPE, DEATH. History hypertension and diabetes QT prolonged "crossed out"	possible*
199921931DDC	76	120 MG QD PO 2 doses	DIGOXIN AMLODIPINE chronically CEFTIBUTEN 2d NETILMICIN 1 day	SOMNOLENCE, CARDIAC ARREST, MI. History of obesity, hypertension, atrial fibrillation	possible#
199921935HMRI	42	PO unknown dose and duration	albuterol acetylsalicylic acid atenolol estradiol fluticasone propionate hydrochlorothiazide atorvastatin calcium	VENTRICULAR FIBRILLATION, DEATH. History dyslipidemia and hypertension (under good control)	conditional*

MFR report #	Age	Dose, Duration	Concomitants	History	Causality
200010620DDC	50	120 MG QD PO for 2 days	TOLBUTAMIDE 01/01/1999 to 12/29/1999 Duration: 51 weeks 6 daysDIGOXIN ??/??/1996 to 12/15/1999 Duration: 3 years, stopped 2 weeks before event	CARDIAC FAILURE ACUTE, TACHYCARDIA 120 beats/min, RESPIRATORY FAILURE, DYSPNOEA. Physician states that there were no rales or abnormal lung sounds on auscultation nor any pulmonary infiltrates on the chest x-ray. History diabetes, cardiomyopathy NOS. stopped digoxin 2 weeks prior to event. On fexofenadine 2 days.	Possible#
200011299HMRI	56	60 MG PRN PO one dose	azithromycin	HEART RATE INCREASED 172 bpm, CONVULSION, RESPIRATORY FAILURE, CARDIAC FAILURE, probable MI, RENAL FAILURE. DIC . History Non-Hodgkins Lymphoma. Two drugs given together, "reacted almost immediately"	possible#
200011519DDC	Old	A few days, dose unknown	Medications NOS	DEATH NOS reported by a doctor	conditional*
200011707HMRI	57	180 MG QD PO for 4 days	ISOSORBIDE MONONITRATE INSULIN ATORVASTATIN METOPROLOL TARTRATE FUROSEMIDE POTASSIUM METOLAZONE FLUOXETINE HYDROCHLORIDE GLYCERYL TRINITRATE PROZAC	MI, DEATH	possible#
200011841DDC	76	120 MG QD PO for 3 days	DIGOXIN PHENPROCOUMON SPIRONOLACTONE GLYCERYL TRINITRATE ISOSORBIDE DINITRATE LISINOPRIL LORMETAZEPAMAntacids (various)	Cause of death "myocardial infarction OR cardiac arrest". History hypertension, COPD, tachyarrhythmia,atrial fibrillation, moderate coronary stenosis	possible#
200110250JP	44	60 MG BID PO for two weeks	none	SUDDEN DEATH (during a bath, question of CO poisoning?)	conditional*
200114614US	47	60 MG BID PO 180 MG QD PO 31 weeks	AZELASTINE PSEUDOEPHEDRINE OLOPATADINE MOMETASONE	Died in sleep at home. Pathologist's diagnosis was acute dysrhythmia	possible
200115540GDDC	26	QD 40 MG PO One dose taken	prednisolone	CARDIAC ARREST, SHOCK, HYPOKALAEMIA (K = 2.63) effect may have been potentiated by fexofenadine	probable
200120305US	56	180 MG QD Poabout one year	none	FATAL CARDIAC ARRHYTHMIA. Physician said patient was a healthy athlete who had prior cardiac scan (normal), no medical history or concomitant medications	conditional*
200120306US	63	180 MG QD Poabout one year	SIMVASTATIN AMLODIPINE, BENAZEPRIL HYDROCHLORIDE NATEGLINIDE	FATAL CARDIOPULMONARY ARREST. History of hypertension and hyperlipidemia, well controlled, and uncontrolled diabetes.	Conditional*
200211267JP	26	PO for 28 days	DIFLUPREDNATE ointment	MYOCARDIAL INFARCTION suspected (no autopsy). History childhood asthma, atopic dermatitis; no abnormal ECG, cardiac history.	Possible

MFR report #	Age	Dose, Duration	Concomitants	History	Causality
200212306GDDC	15	60 MG BID PO "recent fly bite"	none	Canadian case: VENTRICULAR FIBRILLATION TORSADES DE POINTES (FATAL); coroner's report lists probable cause of death as Torsade de pointe with ventricular fibrillation	probable
200217201US	28	180 MG QD PO for 5-7 days	FLUTICASONE PROPIONATE SALBUTAMOL TRIAMCINOLONE ACETONIDE CETIRIZINE HYDROCHLORIDE OLOPATADINE HYDROCHLORIDE	Collapsed playing soccer and died. History of exercise-induced asthma.	Possible
200218074US	81	PO for one week		MYOCARDIAL INFARCTION (while playing bridge) History heart problems	possible#
200220806US	41	One dose		HYPOXIC ENCEPHALOPATHY healthy female died "in her kitchen" after first dose of fexofenadine	possible
200316549US	92	QD for 5 days		MYOCARDIAL INFARCTION 20 yr history of heart and lung disease	possible*#
200411214JP	71			AORTIC ANEURYSM RUPTURE. History of hyperlipidemia and gastric ulcer.	Unrelated
200813254US			3 glasses per day of grapefruit juice	FATAL DRUG TOXICITY (fexofenadine)	*
200914103US				DEATH NOS	*
isr 6745141-9	27		many including azithromycin, sumatriptan, zolpidem	female 27 yo QTc 459 ms. Sudden generalized loss of consciousness and sudden death likely from torsades of pointes. V fib and polymorphic v tach were noted, ECG without evidence of preexcitation, changes consistent with infarction, injury, or ischemia, and QTc of 459 msec. K was 3.1. History depression, anxiety. Two suspect concomitants azithromycin and tizanidine, possibly undiagnosed congenital long QT	possible
isr 3094131-9	80	Allegra D bid	Tenormin, Cardura, Colestid, Zestril, HCTZ, Timoptic…	sudden death (b) (6), on fexofenadine 1-2 months	*
200211847FR	77	PO	CHLORAMBUCIL; BUFLOMEDIL HYDROCHLORIDE; HYDROXYZINE HYDROCHLORIDE ACENOCOUMAROL PARACETAMOL	FATAL LIVER DAMAGE (hepatocellular damage with cholestasis)	unlikely
200713422JP	80	30 MG/DAY PO60 MG/DAY PO	Alfacalcidol, acetylsalicylic acid, lansoprazole, calcium carbonate and etizolam	JAUNDICE, CARDIAC FAILURE-FATAL, RENAL FAILURE-FATAL. History hypertension, cardiac failure, renal failure, renal CA; liver disorder occurred after the administration of fexofenadine	liver disorder probable; death unlikely.#
200910011JP	74	30 MG BID PO for 3 days	NIFEDIPINE	HEPATITIS FULMINANT FATAL. History hypertension	possible

MFR report #	Age	Dose, Duration	Concomitants	History	Causality
200311378FR	83	PO	FLUCONAZOLE CEFTRIAXONE AMPHOTERICIN B FUROSEMIDE PROSARTAN MOXONIDIN BUFLOMEDIL ALLOPURINOL LANSOPRAZOLE	DEATH ERYTHEMATOUS ERUPTION PAPULAR ERUPTION ENANTHEMA EOSINOPHILIA CUTANEOUS DESQUAMATION. History diabetes, hypertension, renal insufficiency	unlikely
200512165FR	58	PO 2 yrs	COLCHIMAX ALLOPURINOL VALSARTAN AMLODIPINE BESILATE INDAPAMIDE	FATAL STEVENS-JOHNSON SYNDROME. HEPATOMEGALY History of hypertension, congestive cardiac insufficiency, drug induced hepatitis, chronic renal failure, tobacco abuse	unlikely
200611077JP	80	60 MG/DAY PO for one days	ALLOPURINOL, SENNA, FAMOTIDINE, MOSAPRIDE CITRATE, TEPRENONE, URSODESOXYCHOLIC ACID, NICERGOLINE	ANGIOEDEMA, ACUTE CARDIAC FAILURE FATAL, HYPER-KALAEMIA. Galvanocauterization was performed 2 days prior, leading to local inflammation.	Relation to angioedema probable, to death unlikely
199812065RHF	74	PO		Chronic renal failure; died from renal failure	unlikely*
199910929RHF	1 day	120 MG QD PO (via mother)	Telfast and Loratadine and Beconase 06/17/1998 to 06/30/1998 Duration: 2 weeks	Fatal pulmonary artery stenosis congenital intrauterine growth retardation single umbilical artery	conditional*
199910966RHF	70	180 MG QD PO for 5 days	ISRADIPINE (ICAZ) ??/??/1996 to Unknown	Thrombocytopenia, fatal cerebral hemorrhage, eosinophilia. History hypertension.	Possible
200010681RGB				Death from auto accident	conditional*
200320486US	64	3 years	PREDNISONE METHOTREXATE CELECOXIB PROCHLORPERAZINE HYDROCODONE CITALOPRAM HYDROBROMIDE CHLORTHALIDONE LEVOFLOXACIN AMLODIPINE	PNEUMONIA STAPHYLOCOCCAL,HYPOTENSION, ULCER HAEMORRHAGE, SEPSIS; History RA, HT	unrelated
200511756JP	50	PO 1 to 2 weeks for eczema	LANSOPRAZOLE (TAKEPRON)FUROSEMIDEPOLAPREZINC (PROMAC)	AGRANULOCYTOSIS – FATAL. History of, renal failure. Had been stable on other medications for long time.	Possible
200714533GDDC				DEATH, HAEMOGLOBIN DECREASED, THROMBOCYTOPENIA, WHITE BLOOD CELL COUNT DECREASED	conditional*

*insufficient information.
#cardiac history

CARDIAC SERIOUS ADVERSE EVENTS

This reviewer identified 119 non-fatal cardiac SAE reports which were assessed as of possible or probable causality in the postmarketing database of 907 non-fatal cases. The Sponsor listed 203 reports of SAEs in the Sanofi-aventis database from an automated search of AE terms and without any assessment of causality. Table 40 summarizes 119 non-fatal cardiac SAE reports.

MO Comment *The reviewer identified 119 cases reporting nonfatal cardiac SAEs, in which a contribution of fexofenadine could not be excluded.* Table 40 *summarizes these cases and provides a causality assessment (see Appendix 9.4 for definitions). Of the 119 cases, there were 24 cases with a cardiac history. There were 22 cases of the 119 with the subject 30 years of age or younger, and there were 29 cases with the subject 65 years of age or older.*

Many of these cases have previously been reviewed by DCRP QT review team; the assessments in Table 40 *agree with those in the QT team review. All of the 119 cases are assessed as related, probable or possible. There are other possible causes or confounding factors present in the possible cases, but there is a reasonable time course, and a contribution of fexofenadine to the event is not excluded. For the probable cases, other causes than fexofenadine are unlikely.*

There were three cases assessed as related in which the reviewer agreed with the assessment of the physician reporter. There was one case of atrial fibrillation, one palpitations, and one supraventricular tachycardia.

There were 35 cases of the 119 where the causality was assessed as probable, including 2 atrial fibrillation and 1 ventricular fibrillation. There was one case with congenital long QT syndrome, and another report of QT pronged in a suicide attempt. There were 9 cases with tachycardia, including one ventricular and one supraventricular. There was one complete AV block and one case of second degree AV block. Examples follow:

> *isr 6771369-8 A 22 yo female took her first dose of fexofenadine 120 mg for allergic rhinitis and experienced ventricular fibrillation. Patient was successfully resuscitated and fexofenadine was stopped. Patient is recovering. Patient may have congenital long QT syndrome. Concomitant meds include an unknown drug and a contraceptive drug.*
>
> *200918166GDDC a 58 yo M who took fexofenadine for allergic rhinitis. On* (b) (6) *(the first day of treatment with fexofenadine),the patient experienced atrial fibrillation and a cerebrovascular accident. Fexofenadine was discontinued the same day. Concomitant medications were atenolol and aspirin. No mention of relevant history. The patient recovered.*
>
> *199711306HMRI Tachycardia. 36 yo M physician took one dose and had pulse >200 for 10 minutes. No concomitant medications. No cardiac history.*
>
> *199810047RGB Tachycardia. 29 yo M developed palpitations and tachycardia that resolved on discontinuation of 180 mg fexofenadine and returned on rechallenge.*
>
> *199910336RGB Supraventricular Tachycardia. 42 yo M physician after first dose of 120 mg Telfast, event occurred. No concomitant medications and no relevant history reported.*

199910873RHF malaise with brief loss of consciousness, atrial fibrillation. 35 yo M eight hours after first dose experienced malaise with brief loss of consciousness. The initial ECG in the ER was normal, then he had another episode of malaise and ECG revealed atrial fibrillation. History diabetes. No history heart disease. Cardiac ultrasound was normal. No concomitant medications noted.

199711692HMRI 1st degree AV block, chest tightness. 26 yo male developed chest tightness after one dose of 180 mg fexofenadine. ECG in ER –1st degree AV block. ECG resolved 3 days later. No cardiac history.

200511182JP AV block 2nd degree, bradycardia. About 20-Mar-2005, fexofenadine was prescribed for this 61 yo female. She felt palpitation and shortness of breath when walking and going up and down the stairs after taking the drug. On 11-Apr-2005, the patient stopped taking the fexofenadine. On (b) (6) *, the patient went to the hospital and was found to have second degree atrioventricular block and a bradycardia of 47/minute by ECG with rates going down to 20-50/minute after she was admitted. Echo findings showed mild left ventricular hypertrophy. Patient received a pacemaker and has done well. History diabetes. Concomitant meds glibenclamide fluticasone, livostin.*

There were 81 cases assessed as possible, including the following examples:

199911772RHF 53 yo M took fexofenadine 120 mg and 3 hours after the first dose presented with malaise and was hospitalized with atrial fibrillation. The atrial fibrillation resolved with medical treatment. On nadolol for hypertension. Echo was normal and holter performed the following month was normal.

200711485DE, a 15 year-old girl developed confirmed primary AV block, then asystole, following episodes of recurrent syncope during the 2 days she was treated with fexofenadine. ECG at admission was unremarkable. While convulsions were observed with arrest, these were secondary to the arrhythmia and CNS work-up was unremarkable. Continuous cardiac monitoring revealed sinus rhythm with rate of 80 beats per minute, followed by AV block with 2:1 conduction followed by asystole. No treatment was provided and the event resolved. Echocardiogram was unremarkable.

In conclusion, the reviewer examined spontaneous reports from the Sponsor pharmacovigilance database to elucidate the nature of the cardiac signal found in the EBGM analyses of AERS and WHO databases. The reviewer found 119 cases of at least possible causality where a contribution of fexofenadine to the SAE was not excluded. These were most often tachycardias, arrhythmias, and palpitations (see Table 41*) but relatively few cases involving QT prolongation. In view of the 32 million patient-yr experience with fexofenadine, the reporting rate of cardiac SAEs associated with fexofenadine is low. The finding of the QT-IRT team is that a TQT study is not needed, in view of the low pro-arrhythmic liability of fexofenadine. However, there is sufficient evidence for serious cardiac adverse events caused by fexofenadine, albeit at a very low incidence rate, that consumers should be informed about these rare cardiac events, so they know to seek medical attention if they have irregular or racing heart beats, or if they feel faint.*

Table 40. Non-fatal Cardiac SAEs, possible or probable causality

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
199910387HPD	54	m	allergic rhinitis	120 once	atrial fibrillation	after first dose, event occurred. History of asthma and hypertension (several concomitants). Required cardioversion	physician assessed as related
199911772RHF	53	m	allergic rhinitis	120 qd	atrial fibrillation, arrhythmia	3 hours after first dose, malaise, atrial fibrillation, resolved with medical treatment. On nadolol for hypertension. ECG, echo, Holter no significant findings following month.	Possible
199912441HMRI	63	m	allergy	60 qd	atrial fibrillation	after 9 months treatment, stopped fexofenadine; then on azithromycin and Sudafed 5 days, started fexofenadine for 1 dose, event occurred	possible
199920096RGB	49	f	allergic rhinitis	120 qd	atrial fibrillation	after 2 days treatment, event occurred. Many concomitants carbimazole, zolmitriptan (history hyperthyroidism)	possible
200012788DDC	50	f	urticaria	180 bid	atrial fibrillation	after one day of treatment, event occurred. Hypertension, concomitant atenolol. Ongoing	possible
200020227US	73	m		60 po	atrial fibrillation	two episodes of atrial fibrillation, second episode ECG 160 bpm. No history of CAD and stress testing negative. Concomitant aspirin.	Possible
200111000JP	76	m	urticaria	120 qd	atrial fibrillation	after 16 days treatment, patient could not measure blood pressure. ECG revealed atrial fibrillation. Concom medications chlorpheniramine, betamethasone, trapidil. History supraventricular extrasystoles. Fexofenadine discontinued, recovered with procainamide treatment	probable
200217681GDDC	68	f	skin condition	po	atrial fibrillation	Fexofenadine started 08-Aug-02 for skin allergy. On (b) (6) hospitalized for atrial fibrillation. Patient discontinued fexo, treated with Amiodarone 200mg, recovered. Concomitants prednisolone, metronidazole and chlorpheniramine	possible
200311853US	50	m			atrial fibrillation	experienced atrial fibrillation, which his cardiologist attributed to fexofenadine	possible
200114062US	59	f	allergic rhinitis	60 mg qd	Atrial fibrillation tachycardia palpitations	after one week therapy,a nurse experienced palpitations and tachycardia, ER ECG atrial fibrillation. Fexofenadine discontinued. Discharged on diltiazem. Three months later, patient stopped diltiazem, Palpitations and flutters recurred diltiazem restarted,. ECG was normal.and the events resolved	possible
200710806JP	56	m	allergic rhinitis	120 qd	atrial fibrillation	took loratadine from 13-Feb-2007 to 11-Mar-2007 and then took fexofenadine from 12-Mar-2007 to 02-Apr-2007 for rhinitis allergic. Betamethasone, d-chlorpheniramine maleate taken from 22-Mar-2007 as concomitant drug. Visited reporting physician, ECG showed atrial fibrillation on 22-Mar-2007, persisted for 4-5 hours. Disopyramide and atenolol prescribed for the event. On 03-Apr-2007, arrhythmia had appeared for an hour, visited physician, discontinued fexofenadine. 18-Apr-2007 patient continues receiving atenolol after withdrawal of fexofenadine hydrochloride and atrial fibrillation is not observed.	Possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
2010SA000514	48	m		120 qd	atrial fibrillation	one day after starting fexofenadine developed a fib. Concomitant hydrochlorothiazide, aspirin, tolbutamide, simvastatin, mometasone furoate , levocabastine (Livocab), metformin, sotalol, and enalapril. Treated with amiodarone\	possible
200918166GDDC	58	m	allergic rhinitis	po	atrial fibrillation, stroke	On (b) (6) (first day of treatment with fexofenadine), patient experienced atrial fibrillation and cerebrovascular accident. Fexo discontinued same day. Recovered	probable
199910873RHF	35	m	urticaria	po	atrial fibrillation, syncope, malaise with brief loss of consciousness	after first dose. ECG atrial fib 8 hours later. History: diabetes. No history heart disease. Cardiac ultrasound was normal. No concom medications noted.	Probable
199922129HMRI	49	m		60 once	atrial fibrillation, atrial tachycardia	49 yo physician four hours after one dose, 30 second to 10 min episodes of atrial fibrillation or tachycardia. 5 or 6 episodes that day. Has had episodes since on loratadine and has had episodes in the past.	Possible
isr 3703856_141173	54	f	allergic rhinitis	60 bid	cardiac arrest	after one month on fexofenadine, on (b) (6) cardiac arrest. Cardioversion. In ER seizures and decorticate posturing. EMT rhythm strip showed QT>500 ms. Hospitalized one week, recovered. Implanted defibrillator. EP could not recreate arrhythmia 4 days after event. Cardiac cath result “not indicative of heart disease”	probable
199811446HPD	48	f		120 qd 180 qd	cardiac dysrhythmia	after 7 days at 120 qd, dosing increased to 180 qd, two days later (premature beats) event occurred. After discontinuation, recovery in 3 days. Concomitants include salmeterol	possible
199811891HPD	45	f	allergic rhinitis	120 qd	arrhythmia	life-threatening arrhythmia occurred after 12 days treatment. No relevant history or concomitants.	Probable
199811892HPD	30	f	allergic rhinitis	120 qd	arrhythmia	life-threatening arrhythmia occurred after 15 days treatment. No relevant history or concomitants.	Probable
199813057HMRI	75	f	allergic rhinitis	60 bid	arrhythmias	after 2 months treatment. Holter monitor “positive”.Concom medications conjugated estrogens (Premarin). Patient is doctor’s mother.	Possible
199813115DDC	35	f	SAR	60 one dose	palpitations, dyspnea, chest pain	after one dose. Patient breastfeeding. No concomitant medications.	Physician assessed as related
199910057RGB	35	f	rash	120 qd	rapid pulse, irregular pulse, palpitations	within 1 hour after first dose, event occurred and lasted 3 hours. On high grapefruit diet	probable
199920036RGB	22	m	allergic rhinitis	120 qd	ventricular extrasystole	after 9 weeks treatment, no concomitant meds	possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
199920138RGB	59	f	allergic rhinitis	120 qd	ventricular extrasystole, palpitations, dyspnea, chest pain	after 5 weeks, dyspnea, palpitations and chest pain. ECG ventricular ectopics. Concomitants. Fexofenadine discontinued, event resolved	possible
199920880DDC	65		SAR	120 once	ventricular extrasystole	event was 3-4 extrasystole/minute for 12 hours, discontinued and resolved, Similar history with terfenadine.	Probable
199921584HMRI	71	f	AR and post nasal drip	60 bid	arrhythmia	During 1 year 4 months on fexofenadine, several episodes arrhythmia. Event abated after fexofenadine therapy was stopped and reappeared after reintroduction . History arrhythmia, MVP, SOB. Concom medications azelastine, clopidogrel, atenolol	probable
200117082GDDC	49	m	urticaria	180 po	palpitations	after 11 days treatment, palpitations. Fexofenadine discontinued after 18 days, event resolved.	Probable
200211307EU	40	f	allergic rhinitis	120 qd	supraventricular extrasystoles, palpitations, dizziness, hypotension	after taking 10-15 tablets over one month, hypotension, dizziness. Blood pressure below 100/40 mmHg for about one week and slowly improved. Supraventricular extrasystoles with reactive hypotension diagnosed. 24 hour ECG showed sinus rhythm with predominantly single supraventricular extrasystoles, relatively few PVCs. Incomplete BBB and normal QT	possible
200310562FR	61	f	itch	120 qd	atrial flutter	took one tablet cetirizine 31-Jan-2003 for cutaneous allergy. Experienced somnolence. On 01-Feb-2003 evening, one tablet of fexofenadine. On 02-Feb-2003, took one tablet of loratadine. On (b) (6) in ER, ECG atrial flutter. Recovered spontaneously in one hour	possible
200316601GDDC	42	f	allergic rhinitis	180 qd	palpitations, depression, suicidal ideation	Fexofenadine started 05/09/2003. visited physician 26-Jun-03; a few days earlier had palpitations and felt depressed and suicidal. Stopped fexofenadine and felt better. Had taken drugs in the previous year without problems	possible
200317848GDDC	62	m	sinusitis	po	extrasystole, malaise	took one dose fexofenadine and moxifloxacin, developed extrasystole on ECG. Fexofenadine discontinued after first dose. No rechallenge. Subject has exercise-induced ventricular bigeminy, anxious patient, previously treated with Atarax, has bronchospasm.on salbutamol as concomitant	possible
200415699GDDC	75	f	urticaria	120 qd	palpitations, malaise	On 27-Apr-04, fexofenadine started, and the patient developed malaise and palpitations the same day. Fexofenadine discontinued on 07-May-04, patient recovered.	Probable
200518308GDDC	53	f	face swelling	po	arrhythmia	patient on fexofenadine experienced arrhythmia on 24-Feb-05. fexofenadine discontinued and “there was definite improvement”	probable
200610878JP	36	f	allergic rhinitis	120 qd	palpitations, malaise	Fexofenadine started evening 10-Mar-06. 30 min after morning dose on 11-Mar-06, nausea, malaise, weakness lasting 10 hours. Next day same symptoms and also palpitations. On 15-Mar-06 palpitations aggravated. All events 30 min after dosing. fexofenadine discontinued 16-Mar-06	probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200712051DE	86	f	CIU	180 tid	ventricular extrasystole, nausea	on fexofenadine and digoxin (for years), other concomitant meds. In July 2007 experienced urticaria and given fexofenadine. Also in July, received cefaclor 500 mg for 5 days for sore throat; pantoprazole 80 mg twice per day prescribed; at that time heart examination normal and treatment with the antibiotic continued. On (b) (6) patient experienced ventricular extrasystoles and nausea lasting for approx. 12 hours. Fexofenadine and cefaclor were withdrawn. The patient recovered.	Possible
200814136GDDC		m	rhinitis	120 qd	arrhythmia	two hours after taking fexofenadine in 2007, had arrhythmia.Fexo discontinued. Drug was reintroduced and same reaction recurred (several times). Patient recovered without specific treatment except stopping fexofenadine and substitution of desloratadine. No history of adverse reaction to other drugs	probable
199920663HMRI	34	m	allergy	60 bid 60/120	first degree AV block, palpitations	after 2 weeks treatment, palpitations. Holter and ECG. Both Allegra and Allegra D. Palpitations 7 to 10 days after discontinuation of Allegra D	possible
200212265US			itch	60 prn	AV block, bradycardia	fexofenadine started for pruritus on 28-Feb-2002. Concomitant medications include levothyroxine, insulin, digoxin, carvedilol, torsemide, K, Afrin. ER ECG on (b) (6) heart block and pulse 30 bpm. Discontinued fexofenadine and all cardiac medications. Recovered	possible
200216142GDDC	30	f	allergic rhinitis	180 qd	bradycardia, RBBB, dyspnea	after 2 fexofenadine, event occurred. Normal ECG in 3 months earlier. On 24-Jun-02, ECG "sinusal bradycardia (frequency 45)" and "right branch blocked (second level)." The patient also had mild dyspnea. On 25-Jun-02, bradycardia and mild dyspnea had resolved. On 27-Jun-02 a third ECG normal	probable
200319694US	43	f	allergy	60 bid	AV block first degree, bradycardia	on routine physical and ECG in 1999, found first degree heart block. Several weeks later, dizziness and pulse 42. Discontinued fexofenadine as it was the only medication being taken, pulse normal within few days. Physician reported that ECG on 08-Jun-2001 also showed a first-degree heart block, subject unaware of bradycardia and diaphoresis	possible
200511163JP	80	m	urticaria	60 qd	bradycardia, dizziness, vomiting	started fexofenadine 04-Apr-05. developed dizziness and vomiting on 06-Apr-05 (after two tablets). Presented with pulse 45 (normally 70s to 90s). Dizziness disappeared with IV drip	possible
200511182JP	61	f	allergic rhinitis	po	AV block 2nd degree, bradycardia	About 20-Mar-2005, fexofenadine prescribed, patient felt palpitation and shortness of breath when walking and going up and down the stairs after taking the drug. On 11-Apr-2005, the patient stopped fexofenadine by her own decision. On (b) (6), the patient came to the hospital. Atrioventricular block second degree and bradycardia 47/minute by ECG with rates going down to 20-50/minute after she was admitted. Echo findings listed. Pacemaker set. Has "mild left ventricular hypertrophy" History diabetes Concom glibenclamide fluticasone, livostin	probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200611099JP	80	f	allergic rhinitis	60 qd	AV block complete	patient on fexofenadine once or twice a month, on March 31 took an extra 125 mg dose. 10 min after the dose, chest discomfort appeared which did not resolve. ECG showed complete AV block.Concomitant medications were simvastatin and terbinafine for a couple of years. Fexofenadine and terbinafine discontinued. Recovered 01-Apr-06. On the morning of 05-Apr-2006, 125 mg of Allegra was given. 1 hour later, she complained of chest discomfort and dizziness and twelve-lead resting ECG showed normal sinus rhythm. Patient instructed not to take fexofenadine. Took other meds for years	possible
200713603GDDC	47	f	urticaria	180 po	heart rate decreased	took fexofenadine from 10-Aug-2003 to 18-Aug-2003. On (b) (6), the patient experienced a fall in heartbeat to 16 beats per minute. An R-test of the heart was performed for 8 days and showed fall in heartrate. Pacemaker implanted.	Possible
200811338JP	72	f	allergic rhinitis	60 bid	AV block, complete	On 07-Feb-2008, fexofenadine hydrochloride was prescribed. On (b) (6), the patient experienced blackout and felt ill. The patient was referred to a hospital for bradycardia. The patient was diagnosed with complete atrioventricular block. A temporal pacemaker was inserted and she was hospitalized at CCU. On (b) (6), a permanent pacemaker was inserted. On (b) (6), the patient was discharged. Concomitant meds: olopatadine	probable
200913941GDDC	57	f	allergic rhinitis	120 po	bradycardia, fatigue	On 10-Apr-2009, fatigue and bradycardia (40-48 bpm). BP normal. Fexofenadine discontinued on 10-Apr-2009. On (b) (6), admitted to hospital, ECG bradycardia. The cardiologist suspected repolarization disturbance, no infarction and no hypothyroidism. On (b) (6), discharged. Health Authority(NL-LRB-86460): Conclusion in the cardiology report possible vagal reaction. The physician (patient's wife) responded to this conclusion that the symptoms did not correspond with vagal reaction (did not occur that sudden). Reporting physician believed that the 9 days of treatment probably caused the bradycardia	probable
200010908DDC	65	m	rhinitis	180 qd	bradycardia, syncope	After 4 days treatment, event occurred. fexofenadine stopped, event abated. History of rheumatic heart disease, mitral stenosis.	Possible
200011357HMRI	13			once po	bradycardia, syncope	one dose, event occurred. No relevant concomitants. No mention of relevant disease	possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200711485DE	15	f	insect bite	120 qd	AV block, bradycardia, asystole, syncope, convulsion	on 05-Jun-07 started fexofenadine after insect bite which was treated with steroid. Next day dizziness and syncope 30 sec. After the second tablet on (b) (6) she again developed dizziness, syncope, bradycardia and convulsion with enuresis and was hospitalized. EEG 45 minutes after the convulsion showed no findings. CT negative 24 hour ECG showed extrasystoles and AV block but no QT prolongation. The next day ECG was without any findings. At 4.25 pm after a preceding slowing down of heart frequency two pauses of 3.6 and 3.5 s occurred within a short interval. In further course there were no further bradyarrhythmias. There were no supraventricular/ventricular extrasystoles, no tachyarrhythmias. The AV block with the following asystole led to a short period of unconsciousness with symptomatic convulsion. In the evening there were no further pre-syncopal conditions. No further events occurred. No special countermeasures were taken. The patient only received volume replacement. Echocardiography on (b) (6) was unremarkable	possible
200221689US		f		180 qd	BP increased	[reported by consumer] After taking fexofenadine for a few days, high blood pressure (210/110). Admitted to the hospital for one day, recovered. Restarted fexofenadine, BP increased again.	Possible
200910743JP	53	m	urticaria	60 bid	brugada syndrome	received fexofenadine hydrochloride 120 mg/day orally from unknown date to 04-Sep-2006, concomitants epinastine, homochlorcyclizine and d-chlorpheniramine maleate; also H2 blocker cimetidine prescribed. The patient has originally Brugada-type wave pattern and family history of sudden death. Brugada-type wave pattern improved after four H-1 blocker and one H-2 blocker were discontinued on 04-Sep-06. implantable defibrillator given (b) (6). Brugada syndrome was diagnosed because pilsicainide load test and cardiac electrophysiological testing induced VF. On (b) (6) discharged. The Brugada-type ECG changes became augmented after starting antihistamines and they regressed after discontinuing them	possible
200111372JP	37	f	skin condition	60 qd	chest discomfort	on third day of treatment. No significant medical history, thought it was angina. D/C'd fexofenadine and it resolved	probable
200422515GDDC	48	f	allergic rhinitis	90 po	chest discomfort, dyspnea	on first day of treatment, event occurred. fexofenadine stopped and patient recovered	probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
97000459	74	f	urticaria	po	chest pain, heart rate irregular	On (b) (6) the patient was seen on an emergent basis. Since the evening of the 28th she had experienced cramps in retrosternal area. Discomfort was short-lived and radiates into back, ultrascapular, but not to jaw or down arm. Her pulse was very rapid consisting of 5 or 6 rapid beats followed by a slow down, then speeding up again. Concomitant meds: Tenormin 25/d, Dyazide 1/d, Zocor 10 hs. Outcome of the appointment: ECG showed a sinus bradycardia (rate = 56) otherwise normal, Perantine Thallium scan on (b) (6) showed no abnormalities, Prilosec 20 hs x 10 d. Personal and family history cardiac complaints. Cardiologist wrote symptoms "clearly associated with the ingestion of Allegra. If this had been a discomfort similar to what she had had in the past then clearly I would have noted that. I clearly indicated the atypical and totally different nature of her discomfort."	Probable
199710046HMRI	37	f		60 bid	cardiac dysrhythmia, irreg pulse, chest pain, possible drug interaction	Patient was given samples in the office. Took two doses of Biaxin and Allegra- began having irregular pulse and chest tightness. Stopped Allegra, sxs abated, continued Biaxin with no recurrence.	Possible
200021457DE	29	f			QT prolonged	intentional overdose 2.16 g fexofenadine with alcohol. QT 360ms evening of event and 430 ms next day. No intervention to remove unabsorbed drug. ECG normal following day. Concom drugs valproic acid, amisulpride, diazepam, levomepromazine	probable
200022718US		f			convulsion, QT prolonged	Hypertensive, with new onset seizures after one week therapy, Allegra or Allegra D. QTc 520 ms. Allegra discontinued and QTc shortened to 400 ms at discharge. Lost to follow-up	possible
200120102US	27	f	swollen eyes	180 qd	QT prolonged, dizziness, inverted t waves	after 5 doses fexofenadine over 8 days, dizziness. Fexofenadine discontinued, symptoms persisted. One week later, ECG QT >450 ms and inverted T waves all leads. No prior ECG. 12-14 days after onset Holter normal despite a few episodes of lightheadedness, stress echo normal. ECG still demonstrated inverted t waves. Symptoms were resolved. No family history of arrhythmia, sudden death, prolonged QT. Patient has not experienced symptoms previously. No fam history of cardiac disease.	Possible
200121183EU	33	m		120 qd	QT prolonged	after seven months on fexofenadine, patient had aggravated QT prolongation (peak 548 ms). Patient has slightly prolonged QTc (460) at 5 months use. fexofenadine discontinued, and QT returned to baseline over "some weeks"	possible
200410752GDDC	83	m	sweating	120 qd	QT Prolonged	patient had used fexofenadine a "long time". Prolonged QT on ECG.	Possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
2010SA010087	23	f		20 tabs	bradycardia, QT prolonged	emergency department with syncope and unconsciousness in (b) (6). She did not have any past systemic disease. Suicide attempt with fexofenadine and furosemide. Bradycardia (48/min) and markedly prolonged QTc interval (684 msec). hyponatremia, hypokalemia and hypocalcaemia. Hospitalized (b) (6). Ventricular arrhythmia not detected during the hospitalization. Recovered and discharged.	Possible
200318736GDDC	13	f		600	QT Prolonged, suicide attempt	attempted suicide with 600mg of fexofenadine, 2500mg paracetamol, 25mg of metoclopramide and tramadol (unknown dose). Developed prolonged QT interval (441 msec and pulse 100)	possible for QT
199811145RHF	79	f		120 qd	syncope, QT prolonged	after 10 days treatment, syncope. QT prolonged (520 ms). Discontinued fexofenadine, QT normal (350 ms) 2 days later. QT 480 ms two years earlier	possible
200812297GDDC	79	f	itch	120 po	QT prolonged, dizziness, RBBB, syncope	patient on fexofenadine and omeprazole experienced dizziness, nausea and syncope. EG showed prolonged QT and right bundle branch block. Fexofenadine withdrawn the same day. Corrective treatment not reported. Recovering	possible
200420324GDDC	43	f		180 qd	stroke	on fexofenadine from (b) (6), when patient hospitalized with CVA. Drug stopped, recovering	possible
199810172LCF	80	m	pruritis	120 qd	stroke, complete AV block, bradyarrhythmia	ECG normal 1 month prior to treatment. 9 days treatment, stroke, discontinued fexofenadine. History aortic stenosis. Cardiologist diagnosed AV block, set pacemaker	possible
199812436HMRI	43	f	SAR	60 bid	supraventricular tachycardia, crushing retrosternal pain, shortness of breath	after one day of treatment with Allegra and erythromycin, event occurred. Positive family history but no heart diseases.	Probable
199912274HMRI	28	f	allergy	60 qd	atrial tachycardia, dyspnea	after one week treatment, after taking Imitrex, event occurred (260 bpm), dyspneic. Both medications discontinued	possible
199922086DDC	31	f	rhinitis	60 once	supraventricular tachycardia	while also on Cipro, took one dose fexofenadine. Palpitations, shortness of breath. ECG SVT at 152/min.	possible
200520584GDDC	14	m	allergy	120 qd	supraventricular tachycardia	Fexofenadine started 03-Oct-05 (chronic use for allergy), also fluticasone for asthma. Used azithromycin 6-Oct-05 to 9-Oct-05. admitted to the hospital on (b) (6) with a severe arrhythmia (pulse 220). Cardioversion and discharged after (b) (6). Used azithromycin again 14-Nov-05 to 17-Nov-05; admitted to hospital again on (b) (6) with severe arrhythmia. Cardioversion and discharged after (b) (6) on sotalol 40 mg. On (b) (6), the patient had a third hospital admission with the same arrhythmia. The patient was again discharged after (b) (6).	Possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
199811751RHF	85	f		180 qd	syncope, fall, supraventricular tachycardia	after 13 days treatment, syncope and fall with injury; QT 520 ms pulse 50. Some days later, Holter showed supraventricular tachycardia	possible
199711494DDC	29	m	urticaria	po	syncope	12 hour after first dose. Keen jogger. ECG, echo, 24 hr monitor no findings; history mild asthma.Was felt to be vasovagal syncopal episode compounded by the URI and possibly the effects of the antihist. Cardiac w/u neg.	possible
199921064HMRI	46	m	allergy	po	syncope	reporting physician took Allegra and Allegra D for three years during fall season. Each fall after beginning Allegra, he has experienced at least one syncopal episode. Has experienced three episodes of syncope. MRI, Holter and stress test normal. Discontinued. No concomitants	possible
200113974FR	15	m	allgic rhinitis	180 qd	loss of consciousness, sweating, pallor, fall	reported by mother, took for one day, experienced loss of consciousness (which lasted 45 minutes). Recovered. Tolerated fexofenadine well previously	possible
200122703US	ped				loss of consciousness	risperidone could cause it	possible
200214859US	16	f		180 qd	loss of consciousness	started on Allegra and azithromycin, passed out next day. Other details not provided	possible
200711913JP	30	f		120 qd	loss of consciousness, amnesia	about 1 hour after taking fexofenadine on (b) (6), 10 min amnesia. Fexofenadine discontinued by patient's decision. Recovered same day.MRI negative	probable
200810968JP	9	m	allergic rhinitis	30 bid	loss of consciousness, convulsion	started fexofenadine 01-Jan-07. on (b) (6) took morning dose without reaction, took evening dose and developed convulsion and loss of consciousness. Brought to a hospital by ambulance. Regained consciousness at the hospital. No abnormality detected by blood exam or CT scan. No abnormality was found by the EEG the next day, then discharged. On clarithromycin	probable
200811247JP	66	m	allergic rhinitis	60 bid	syncope	On 19-Mar-2008: Fexofenadine was prescribed for rhinitis allergic with previouslytreated other concomitant drugs. On (b) (6): At 8:00 a m., when he was in the bathroom, the patient had feeling of dizziness and then developed syncope. The patient went to hospital, and his consciousness was clear, his pulse and blood pressure were normal. Holter monitor exam given on the (b) (6) and brain MRI given on the (b) (6) revealed no abnormality. Fexofenadine was discontinued after the event, no recurrence of syncope.	Possible
199711306HMRI	36	m	allergy	po	tachycardia	one dose. Pulse >200 bpm for 10 minutes. No concomitants	probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
199712577HPD	46	m	atopic dermatitis	180 qd	tachycardia, palpitations, arrhythmia	tingling after first dose, tachycardia after second. History of hypersensitivity to many substances; tachycardia not confirmed by ECG	probable
199810003RGB	38	f	rash	120 qd	sinus tachycardia, myocardial ischemia	1 day treatment. ECG confirmed. Concomitant oxytetracycline1 day treatment. ECG confirmed. Concomitant oxytetracycline, etynodiol diacetate (Femulen)	possible
199810047RGB	29	m	urticaria	180 qd	tachycardia	physician reported palpitations, tachycardia resolved on discontinuation and reappeared on rechallenge	probable
199910061RGB	69	f		120 qd	tachycardia, weakness	six day history of palpitations and weakness after starting fexofenadine. ECG tachycardia and fexofenadine stopped. No further symptoms. No prior history of tachycardia, palpitations or arrhythmia.	Possible
199910326RGB	55	f	itch after insect bite	180 qd	tachycardia	after one dose, several hours of tachycardia. No concom medications	possible
199910336RGB	42	m		120 qd one dose	supraventricular tachycardia	after first dose, event occurred. No concomitant medications and no relevant history reported.	Physician assessed as related
199912655DDC	47	m	allergic rhinitis	120 hs	tachycardia	after 3 days, mild tachycardia 2 hrs after dose. Recurred next two days, then discontinued and resolved. No ECG. Concomitants include etilefrin (sympathomimetic for hypotension)	possible
200010804RGB		f	allergic rhinitis	120 qd	tachycardia, dyspnea	after 3 days on fexofenadine, tachycardia, dyspnea and chest tightness. Event resolved after discontinuation of fexofenadine	possible
200011335HMRI	28	f	sinusitis	60 bid	dizziness, heart rate increased	8 days treatment. Concomitant prednisone and levofloxacin. Ongoing	possible
200113319GDDC	55	m		180 qd once	atrial tachycardia, hypertension	6 hours after first day dose of 180 mg fexofenadine, palpitations and tachycardia 220 bpm for 2 hours. BP 130/110. decreased PR on ECG. fexofenadine discontinued, recovered on IV verapamil. Previous similar event on cetirizine, 2 years prior. 12 yr history PAT, ventricular septal defect. On azithromycin	possible
200113832EU	42	f	allergy	120 qd	tachycardia	on fexofenadine 4 months, then also on erythromycin and diazepam, then 3 days later pulse increased to 100 bpm. fexofenadine discontinued (only suspect drug). Ongoing	possible
200121141FR	37	m		180 qd	tachycardia	after 6 days on fexofenadine, no concomitants, malaise and tachycardia (120-150 bpm), hospitalization, ECG. fexofenadine discontinued, event abated. No relevant history	probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200210687EU	39	f		once po	tachycardia, hypertension, dizziness	after one dose, dizzy. Presented with tachycardia (108-120 bpm) and for two hours BP (160 to 170)/(118 to 120). Concomitants included doxycycline, nedocromil and fluticasone. Fexofenadine considered only suspect drug by health authority	probable
200311819FR	46	f	itch	po	tachycardia	after one week of treatment with fexofenadine, tachycardia 120 bpm after vagal manoeuvring led to hospitalization. ECG sinusal tachycardia at 120/min with right bundle branch block incomplete. Holter showed bigeminy of supraventricular extrasystoles and a few PVCs. Exercise ECG ST depression. fexofenadine stopped one week after tachycardia episode.	Possible
199920669HMRI	30	m	allergies	60 mg	Ventricular extrasystoles	30 yo male had the onset of multiple premature ventricular ccntractions (2000 PVCs in 24 hours) during Allegra therapy. ECG shows multifocal premature ventricular contractions, no premature atrial contractions and q wave in 3, ECHO is normal.	Possible
200310661DE	44	f	urticaria	180 once	tachycardia, palpitations, arrhythmia	45 min after one dose of fexofenadine (prescribed for urticaria after wasp sting), developed palpitations and pulse 130-140 bpm lasting two hours. Normal ECG two years prior. Event abated 3 days later. Experienced tachycardias from terfenadine years prior.	Possible
200515903GDDC	43	f	allergic rhinitis		tachycardia, extrasystole	in May-2005 patient experienced tachycardia and developed ectopic beats while being treated with fexofenadine and desloratadine. She had an episode of fast regular tachycardia that lasted about 2-3 minutes at night. Desloratadine was stopped, and she was treated with atenolol and recovered. History of radiofrequency ablation of right ventricular outflow tachycardia in 1999	possible
199921074DDC	72	f	urticaria	180 qd	syncope, circulatory collapse, extrasystole, cyanosis	After one day of treatment, circulatory collapse, Fexofenadine stopped. ECG bigeminy. Recovered and normal ECG afterwards	possible
200124328GDDC	23	f		120 qd	tachycardia	While on fexofenadine , event occurred within 5 or 6 hours of taking clarithromycin. Other concomitants included salbutamol. Patient had no cardiac history	possible
200519350GDDC	41	m	skin allergy	180 qd	tachycardia, chest pain, paresthesia	after one tablet in the morning, and alcoholic drink at lunch, event occurred. No history of cardiac problem. fexofenadine discontinued. ECG normal. Recovered same day.?on levofloxacin	possible
199920900HMRI	67	f	allergic rhinitis	60 qd 60/120	hypertension, tachycardia, syncope	event after 6 days on Allegra and Allegra D (BP 233/100, HR 130; baseline BP 148/70), discontinued, event resolved	possible
200211791GDDC	31	f	allergic rhinitis	120 qd	tachycardia, syncope	on first day of fexofenadine, tachycardia, sweating, syncope. fexofenadine discontinued 2 days later, patient recovered	probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200010138HMRI	70	f	allergy	60 bid	torsade, 3rd degree AV block, ventricular tachycardia, atrial flutter	70 year old woman with underlying heart disease had dizziness and near-syncope post-treatment with fexofenadine. Complete intermittent third degree AV block, intermittent atrial fibrillation with slow ventricular response and TdP were noted on ECG and Holter. QT 513, QTc 368. Medications held. Pacemaker. Readmitted several months later with atrial flutter, pacemaker still working. ECG in 1997 also QTc 418	possible
isr 6771369-8	22	f	allergic rhinitis	120 once	ventricular fibrillation	started fexofenadine (b) (6). on first day experienced ventricular fibrillation. Fexofenadine stopped. Resuscitated, recovering. Patient may have congenital long QT. also on oral contraceptive and an unknown medicine.	Probable
200820070GDDC	46	f		120 qd	cardiac arrest, ventricular fibrillation	hospitalized (b) (6) after cardiac arrest at home. Had ventricular fibrillation and was cardioverted to sinus rhythm. Coronary Arteriography was normal. At hospitalization, serum potassium 2.6 mmol/L. The patient has been treated with fexofenadine for several years. The hypokalaemia might have caused sensitivity to fexofenadine and provoked Torsade de point ventricular fibrillation. ECG showed QT=460ms. In hospital, fexofenadine stopped, replaced with cetirizine. On (b) (6) "ECG does not for certain show prolonged QT". On (b) (6), an implantable cardioverter defibrillator (ICD) was placed and patient discharged. Continuing treatment for hypertension.	Possible
97001126	74	m	allergy	60 bid	cardiac arrest, ventricular fibrillation, coma,syncope	In addition to Allegra and clarithromycin, the patient was on augmentin, furosemide, digoxin, aspirin, potassium, metolazone, allopurinol, trazodone, hydroxyzine, isosorbide, and albuterol. About one day after last dose of fexofenadine, and after one week on clarithromycin, cardiac arrest. Patient remains in coma. Patient post-MI and renal failure	possible
200010507RGB	50	f	allergic rhinitis	120 qd	ventricular fibrillation, QT prolonged	after 8 days treatment, had ventricular fibrillation and cardiac arrest. QT prolonged after defibrillation. Many concomitants. Had taken fexofenadine seasonally for previous two years. Has pancreatitis and K of 3.3	possible
200614521GDDC	72	f	rash	180 qd	ventricular fibrillation, QT prolonged	started fexofenadine on 10-Mar-06. concomitants atenolol, furosemide, moxonidine, metformin, dosulepin, candesartan, and rosiglitazone. History allergy, diabetes, hypertension. On (b) (6), the patient experienced a prolonged QT interval and ventricular fibrillation on ECG. Hospitalized, recovered same day	possible
199910471DDC	67	m	skin condition	180 qd	QTc prolonged, ventricular fibrillation, ventricular tachycardia, collapse	event after one month treatment.QTc changes demonstrated after dechallenge and rechallenge. ECG torsade. Outside expert noted evidence for LVH and ischemic heart disease. Serum from this patient used for Scherer CR, Pinto YM et al. Biophysical J paper	possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
199711716HMRI	77	m	SAR	po	ventricular tachycardia, syncope	started fexofenadine just prior to new onset frequent ventricular arrhythmias and episodes of v tach. Discontinued fexofenadine, resolved. Cardiac history:Coronary bypass surgery but no history of arrhythmia. After event, holter monitor no significant arrhythmia. Cardiologist reported possible connection to fexofenadine	probable
200011289HMRI	36	m	allergy	60 bid	tachycardia	after two weeks treatment, event occurred. fexofenadine stopped on admission. Treated with linisopril and diltiazem. Ongoing. No sig med history or concom medications	possible
200012875DDC	55	m	skin condition	120 qd	ventricular tachycardia	after first tablet, experienced asthenia. After second tablet, tachycardia. In ER, ECG and pulse 149 bpm. fexofenadine discontinued and event abated. History MI	possible
200220947US		f		180 qd	ventricular tachycardia, palpitations, presyncope	[reported by consumer] started fexofenadine early January 2002. palpitations, presyncope in late April or early May 2002. Cardiologist diagnosed wide complex tachycardia. fexofenadine discontinued on 07-Oct-2002. Event abated, resumed workouts 5 days/week. Verapamil continued	possible
200519142GDDC	77	f	urticaria	180 qd	ventricular tachycardia, palpitations	presented on 13-Jul-05 with generalized urticaria, was put on treatment with fexofenadine. Treated with steroids. fexofenadine continued. Patient presented again 15-Jul-05 with VT 124 bpm irregular. fexofenadine discontinued, treated with atenolol, ranitidine, dipyridamole. Recovered 20-Jul-05. History HT. Concom gabapentin, rosiglitazone, hydrochlorothiazide, sulfamethoxazole, trimethoprim	possible
200916603GDDC	39	f	skin eruption	180 po	ventricular tachycardia	On 01-Jul-09 the patient developed burst of ventricular tachycardia after taking one dose of fexofenadine. Fexofenadine was discontinued on 02-Jul-09. Corrective treatment includes amiodarone. ECG, echo, TSH, blood chemistry (nos) and CBC all normal. Treating physician is a cardiologist. Patient has mild biventricular dysfunction with past history of ventricular tachycardia.	Possible
199911526HMRI	45	m	allergies	unk	Tachycardia	Patient experienced rapid heart rate (150 bpm) and a dazed state after taking one or two doses of clarithromycin. He had been taking fexofenadine for some time (not specified; dose unknown). Events lasted for one hour and resolved. The patient had no cardiac history and had taken clarithromycin two previous occasions without any problems, while not taking fexofenadine.	Probable
199811922RHF	15	f	urticaria	po	ventricular tachycardia, QT prolonged, complete AV block, bradycardia	Intentional overdose of fexofenadine, propulsid, flecainide.episode of v tach or possible torsade. Pacemaker used three days until recovery	possible
199711692HMRI	26	m	allergy	180 once	1st degree AV block, chest tightness	one dose. ECG in ER showed first degree heart block. ECG resolved 3 day later; ECG normal one year before. Concom levothyroxine	probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200317622GDDC	61	f	allergy	180 qd	ventricular tachycardia, loss of consciousness	Took first pill on 29-Jul-2003.On (b) (6), event occurred. Concomitant drugs include simvastatin, minoxidil, betamethasone valerate and ramipril. No QT (or QTc) prolongation. Polymorphic VT occurred following the 2nd 180mg pill (on the 2nd treatment day). No history of CAD and coronary cath is normal. Electrolytes were and are normal. In the 3rd day of rechallenge with the drug there is still no QT prolongation or Polymorphic VT.	Possible

The frequencies of cardiac AE terms from the SAE reports in Table 40 are shown in Table 41.

MO Comment *In the probable or possible cases reporting non-fatal cardiac SAEs, the most common SAE was tachycardia (any type other than ventricular tachycardia or supraventricular tachycardia) which was mentioned in 24 cases, followed by non-specific arrhythmias or palpitations (22 cases). Syncope was mentioned in 22 cases, most often with other cardiac events. There were a total of 17 cases that mentioned AV block (any degree) and/or bradycardia (any type). Specifically ventricular tachycardia was mentioned in 9 cases, while supraventricular tachycardia was mentioned in 5 cases. Atrial fibrillation was the fifth most common AE term with mentions in 15 cases.*

QT prolongation was relatively less common with mentions in 13 cases. There was one case of Brugada syndrome and four cases with torsade. The relatively few mentions of QT prolongation and torsade support the recommendation of the QT-IRT team that a TQT study is not needed.

Chest pain or tightness was not commonly reported, with mentions in only 5 cases.

Table 41 Frequency of Cardiac AE terms in non-fatal SAE reports

Cardiac AE Term	Number of Mentions (N=119 cases)
Tachycardia	24
Arrhythmias or palpitation	22
Syncope	22
AV block or bradycardia	17
Atrial fibrillation	15
Ventricular tachycardia	9
QT prolongation	13
Ventricular fibrillation	6
Chest pain or tightness	8
Supraventricular tachycardia	5
Hypertension or hypotension	4
Cardiac arrest	3
Torsade de pointes	4
Brugada Syndrome	1

HEPATIC SERIOUS ADVERSE EVENTS

The reviewer identified non-fatal hepatic SAE reports in the postmarketing database, including the 907 non-fatal cases from the Sponsor postmarketing database and additional cases from AERS. After a review of Medwatch reports, a total of 77 cases were found reporting nonfatal hepatic SAEs, of which 59 were assessed as of possible or probable causality.

Table 42 shows narrative summaries of the 59 non-fatal hepatic SAE reports, including 15 cases with probable causality.

Table 42 Non-fatal Hepatic SAEs. Probable or Possible Causality

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200020811GB	39	f	allergy	120 qd	hepatic function abnormal	after six months treatment, LFT and bilirubin increased. Recovered after discontinuation of fexofenadine. No concomitants or significant history; Valsartan d/c'd	possible
200110180JP	28	f	itch	60 bid	hepatic function abnormal	On fexofenadine 3 days one month prior and then three days before event. History diabetes, fatty liver, suicide attempt. On many concomitants, including cisapride, misoprostol. GOT 530 IU/L GPT 780 IU/L. bilirubin increased 1.5x.	possible
200111269JP	60	f	allergic rhinitis	120 qd	hepatic function abnormal	after several days on fexofenadine, LFTs increased GOT 19x, GPT 15x, ALP 2x, GGTP 2x, T-bili mildly elevated, 3 weeks later. Moderately severe liver injury-possibly threatening. Cholestatic injury pattern.	Possible
200210143JP	41	f	sinusitis	120 qd	liver disorder	after 11 weeks on fexofenadine, fever, jaundice, fatigue, elevated LFTs (GOT and GPT about 15x; T-Bili 10 mg/dl). Eosinophil count of 6-7%. fexofenadine discontinued, LFTs improved over next 6 weeks. DLST + for fexofenadine and cefaclor.	Probable
200812883US	34	m	SAR		hepatitis, rash, chromaturia, ocular icterus	patient on fexofenadine and no other meds developed, after a few months of treatment, chills, abdominal cramps, dark urine and erythematous rash over whole body. On presentation, mild scleral icterus; laboratory tests showed: ALP 218, AST 93, ALT 248, total bilirubin 5.7 and 12% eosinophils. Liver biopsy results revealed eosinophilic hepatitis with focal bridging fibrosis. Fexofenadine was stopped and LFTs normalized over the next few weeks. After 6 months, no meds and no recurrence. (Johal)	probable
200912535JP	64	f		po	hepatic function abnormal, bilirubin increased malaise	on fexofenadine for 3 days, presented to hospital with malaise. Laboratory data showed GOT, 263; GPT, 479; and bilirubin 3.9. Atorvastatin, carbazochrome and tranexamic acid concomitant medications. Condition improved over next two weeks.	Possible
200414364FR	76	m		1 tab qd	liver injury, bilirubin increased	since 1-Jun-04 on fexofenadine and several other meds including glimepiride. Admitted (b) (6) for jaundice, no fever, no pruritis. All meds stopped. LFTs in report. Hepatocellular injury pattern	possible
200210911JP	42	f	eczema	120 qd	hepatitis acute, jaundice, ascites, fatigue	on fexofenadine from 01/MAY/02 to 14/MAY/02, no improvement of eczema and changed to epinastine 15/MAY/02. On (b) (6) developed jaundice and fatigue, then hospitalized. IgM-HA antibody: negative, IgM-HBc antibody: negative, HCV antibody: negative, antinuclear antibody: negative. Drug induced hepatitis was suspected. See report for LFTs (bilirubin 5mg/dl, ALP 502IU/L, GOT and GPT >1100 IU/L mxed pattern of injury	possible
200310513JP	51	m	allergic rhinitis	po	jaundice	On 22-Mar-2003, started fexofenadine for 6 weeks; patient noticed urine dark, itchy urinating. On (b) (6), jaundice and hepatomegaly GOT 6x, GPT 15x T-Bil 3.9, hospitalized. On (b) (6), T-Bil was 4.0. Prednisolone started orally. On (b) (6), T-Bil was 3.8. On (b) (6), biopsy liver supported drug-induced hepatitis (no fibrosis, minor necrosis and inflammatory finding). On (b) (6), T-Bil was 2.2. Recovered from jaundice early (b) (6). Developed cystitis .Drug lymphocyte simulation test negative for fexofenadine and positive for transilast. Cholestatic pattern	possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200311569EU	52	m	urticaria	180 qd	hepatitis, jaundice	Fexofenadine started on 29 January, 2001. Symptoms appeared 1 March. On (b) (6) hospitalized with icterus. Liver examinations inconclusive (echo and CT, hepatitis serology, autoantibody, ceruloplasmin all normal), and a drug reaction suspected. Fexofenadine first stopped on 11 March, 2003 for a few days without any improvement and further on, used until (b) (6). biopsy suggested drug-induced hepatitis. All medications stopped (b) (6), including atenolol taken as long term treatment. LFTs improved: on (b) (6): ASAT 42 U/l, ALAT 42 U/l, AP 235 U/l, GGT 235 U/l, Bilirubin Total 60 umol/L. At the end of (b) (6), values had not yet completely returned to normal. Patient had no history of previous liver disorder. Cholestatic pattern Esomeprazole also suspect drug.	Possible
200410525JP	72	f	eczema	60 qd	jaundice, malaise	On 26-Jan-04 started fexofenadine. On (b) (6) developed general malaise and visited the reporting hospital. Jaundice was observed. On (b) (6) hospitalized. On (b) (6) jaundice and general malaise improved, discharged. On 12-Feb-04, drug lymphocyte stimulation test (DLST) was +.SGOT, SGPT 1500, ALP 495 bilirubin 23 mg/dL.	Probable
200413265GDDC	49	f		120 qd	hepatitis acute, jaundice	Fexofenadine prescribed for two doses only. On second day, acute hepatitis and jaundice. No liver biopsy. Antinuclear factor: +ve; immunoglobulin: normal. Event resolved after withdrawal of fexofenadine	possible
200413554JP	52	m	allergy	bid po	jaundice, chromaturia	Fexofenadine started 22 Mar-03. on (b) (6) in hospital with jaundice and chromaturia. Anorexia and pruritis two days before. Several concomitant medications Tranilast.	Possible
200420202GDDC	40	f	urticaria	120 bid	jaundice	presented with jaundice, on fexofenadine, cimetidine and other meds. All meds discontinued except an ARB (aprovel). Liver biopsy found drug-induced liver disease	possible
200611373JP	62	m	SAR	60 qd	liver disorder, jaundice	started fexofenadine 23-Mar-06. on 19-Apr-06 adbominal discomfort. On 20-Apr-06 brown-red urine. On 21-Apr-06 increased LFTs, T bili 3.6 mg/DL. fexofenadine discontinued 22-Apr-06, amlodipine continued. Ultrasound and autoantibody tests consistent with drug-induced liver injury. On 11-May-06 recovered. Cholestatic pattern.	Probable
200612483JP	62	f	sinusitis	60 bid	hepatic function abnormal, jaundice, vomiting	on 05-Jul-06, clarithromycin, Mucosta, and fexofenadine prescribed for nasal discharge. On 7-Jul-06, epigastric pain and all 3 drugs stopped by patient decision. On 9-Jul-2006, symptoms abated and started taking 3 drugs again. On 13-Jul -2006, vomited. On 19-Jul-2006, ENT and opthalmo no aggravation of sinusitis and optic neuritis. On 24-Jul-2006, epigastric discomfort persisted. On (b) (6), blood test disclosed liver disorder and she was hospitalized. Endoscopy and ultrasound. Viral antibodies, antinuclear antibody, antimitochondrial antibody negative. Jaundice was noted on (b) (6). Cholestatic injury	possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200613943JP	34	m	atopic dermatitis	120 qd	hepatic function abnormal, jaundice	started fexofenadine and Chinese herbal medicine in March 2006 for dermatitis atopic. In May 2006, generalized malaise, stomach discomfort, and coloring yellow of skin developed. In (b) (6), blood tests revealed liver disorder and jaundice. The patient was hospitalized. Fexofenadine and Chinese herbal medicine were discontinued, and close examinations did not find abnormality. Patient was released from the hospital. In August 2006, the patient started fexofenadine and Chinese herbal medicine again. In December 2006, the symptoms that similar to the ones that occurred in May developed, with liver disorder and jaundice. On (b) (6), hospitalized again. After admission, fexofenadine and Chinese herbal medicine were discontinued. Liver disorder gradually abated with bed rest, and the patient was released from the hospital on (b) (6). no LFTs reported, but jaundice	possible
200710928JP	35	f	allergy	120 qd	jaundice, liver disorder	On 13-Feb-2007: Fexofenadine started for nasal allergy. Concomitant Cefditoren pivoxil, Teprenone, sodium gualenate/Lglutamide, domperidone. On 15-Mar-07 jaundice in hands and legs. On 17-Mar-2007: antibiotic agent was prescribed for suspected hemolytic strep. Fexofenadine continued.On 19-Mar-2007: Soreness in limbs and itching aggravated. On 22-Mar-2007: liver disorder observed. On (b) (6) admitted to hospital. Biliary enzyme continually rising. Negative in various virus test and autoantibody tests. DLST on 27-Mar-2007 positive for fexofenadine. Diagnosis drug-induced liver disorder. Cholestatic injury Literature case	probable
200712489JP	27	f	eczema	120 qd	liver disorder, jaundice	Fexofenadine started 11-Aug-07. On (b) (6): visited hospital with complaint of jaundice and hospitalized. Fexofenadine discontinued (b) (6). T Bili and transaminases much improved the following week. HCV and HBV were negative. Abdominal echo and CT and MRI revealed no abnormal findings. On (b) (6): The patient was discharged from the hospital. On 22-Oct-2007: further improved: GOT was 44, GPT was 38 and total bilirubin was 0.88. Fexofenadine not given again.	Probable
200712780JP	44	f	allergic rhinitis	po	liver disorder, jaundice	In Mar-2007: Therapy with fexofenadine and pranlukast begun. In early Oct-2007: The patient experienced general malaise. On 17-Oct-2007: liver disorder was diagnosed and fexofenadine and pranlukast discontinued. On (b) (6): hospitalized. On (b) (6): Viral and auto antibody screens negative. Drug-induced liver disorder diagnosed. On (b) (6): Therapy with ursodesoxycholic acid and stronger Neo-Minophagen C.Improved with discontinuation of drugs. On (b) (6): patient discharged.	Possible
200713743GDDC	36	m	urticaria	120 qd	jaundice	Dec-0006 started fexofenadine and mequitazine. (b) (6) developed jaundice, hospitalized with liver disorder. (b) (6) started treatment with glutathione and glycyrrhizin/cysteine. Fexofenadine and mequitazine stopped in (b) (4). recovered.	Possible
200717638GDDC	19	f		120 qd	cholestasis, jaundice	In May developed cholestasis and presented with jaundice, dark colored urine, pruritis nausea, and fatigue in second half of (b) (6) fatigue, itch, dark urine and lighter stool. Nausea and vomiting. . Utrasound negative. Viral serologies, antibodies and autoimmune antibodies negative (muscle antibodies 'faintly positive'). Biopsy. Cholestatic hepatitis, very probably due to medication, Could be oral contraceptives or the antihistamines, as in both cases, cholestasis has been described.	Possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200911360JP	60	m	allergic rhinitis	60 bid	hepatic function abnormal, malaise, jaundice; mixed hepatocellular -cholestatic injury	started fexofenadine beginning Apr-09. On (b) (6), presented with malaise and jaundice. Liver disorder from blood test and hospitalized. No concomitant medications. Stronger minophagen C given IV, thereafter condition improved as of (b) (6). ultrasound hepatomegaly. No biopsy. Viral hepatitis serologies negative.Drug lymphocyte stimulation test (DLST) was positive for fexofenadine. Liver injury.Mixed hepatocellular and cholestatic injury.	Probable
199810420RGB	82	m	pruritis	120 qd	LFT abnormal, raised Alk Phos, Gamma GT	Treated with loratadine 19 days, stopped and switched to fexofenadine. After 3 days fexofenadine treatment, Alk Phos 3415 IU/L, after three weeks Gamma GT 47 IU/L, 12 days later fexofenadine discontinued, then symptoms resolved in 2 days, LFT resolving one month later. On loratadine prior to this.	Possible
199811511RHF	54	f	urticaria	180 qd	hepatitis, LFT and bili increased	LFTs normal one month prior to fexofenadine. After one month on fexofenadine, LFTs showed hepatocellular injury (also biopsy). LFTs continued to worsen on fexofenadine for another month. Discontinued, LFTs normal one month later	probable
200111291JP	67	m	allergic rhinitis	120 qd	hepatic function abnormal	after 24 days on fexofenadine, LFTs increased transaminases ~500,. All medications discontinued including gliclazide and pioglitazone, LFTs improved at discharge	possible
200111548JP	29	m	SAR	120 qd	drug induced hepatitis	after 6 weeks on fexofenadine, LFTs increased, HBs-Ag(-), HCV-Ab(-), IgM-HA(-). GOT 884, GPT1688, ALP 198, T-Bil 0.44. No concomitants. Normal 3 weeks later. With hepatocellular pattern	probable
200111781FR	53	f	urticaria	po	liver injury, angioedema	on first day of treatment, vulvar itching, plaques on face. Then lip edema and dysphagia, admission for angioedema, LFTs elevated one week later. Event abated by 18 days later. Cholestatic pattern. Also on paracetamol.	Possible
200120004JP	13	f	itch	60 qd	rash morbilliform, hepatic function abnormal	started fexofenadine developed fever same day. Next day, common cold diagnosed and fosfomycin with acetaminophen given. Next day, developed pruritic rash morbilliform, pyrexia, pyrexia. Given steroids, fever subsided. Mildly increased LFT (GGTP 2x) and HHV-6 IgG	possible
200120485JP	48	m	allergic rhinitis	60 bid	liver disorder	on 8th day with fexofenadine and montelukast, experienced fever, brown urine. Discontinued both medications. LFTs increased bilirubin 7.5 mg/dl, AST 1100 IU/L, ALT 2200 IU/L, and ALP 421. Bilirubin rose to 21 and improved over the next month to 4.4 with normalization of transaminases. Event resolved one month later. Mixed pattern	possible
200120576JP	73	m	allergic rhinitis	120 qd	hepatic function abnormal, deep venous thrombosis	after fexofenadine for 12 weeks, hepatic function disorder T-bil 2.5 . 16 days later, DVT found on echo of lower extremities. Fexofenadine discontinued after 79 days. Six weeks later, hepatic function was improved. Another month later, DVT was improved. History alcoholic liver disease, diabetes, RA. Concom meds famotidine, trandolapril.	Probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200211373JP	72	f	allergic rhinitis	120 qd	hepatic function abnormal	received fexofenadine from 15/JUL/02 to 09/SEP/02. Concomitant pravastatin from 26/NOV/99 to 09/SEP/02. On 28/AUG/02, GOT of 161 IU/L and GPT of 205. On 30/AUG/02, GOT of 104, GPT of 169, GGTP of 69, LDH of 212 and T-Bil of 0.5. On 02/SEP/02, LFT still abnormal without subjective symptom, including GOT of 115, GPT of 175, LDH of 222, T-Bil of 0.8, and G-GTP of 77. On (b) (6), hepatic function aggravated, hospitalized. GOT was 401, GPT of 613, LDH of 452, T-Bil of 1.1 and G-GTP of 97. Hepatitis D and E were negative. Drug-induced type was suspected, fexofenadine and pravastatin were discontinued. On (b) (6), hepatic function improved. GOT was 43, GPT of 65, ALP of 269 and LDH of 157. On (b) (6), discharged	possible
200310286JP	61	f	allergic rhinitis	60 bid	hepatic function abnormal	On 03-Mar-2003, started fexofenadine. On (b) (6), the patient developed urticarial eczema on face (intense pruritus) and eczema on body, with generalized malaise. No interstitial pneumonia on X-ray and no decrease of PO2. Short runs supraventricular extrasystoles on Holter. Carbamazepine and fexofenadine hydrochloride discontinued. Glutathione, glycyrrhizin, vitamin B and vitamin C were given intravenously. Betamethasone and chlorpheniramine maleate 9 tablets daily given orally. Eczema and liver function resolved, discharged (b) (6).	Possible
200310362JP	37	f	dermatitis atopic	60 bid	hepatitis	started fexofenadine 30-Nov-2002 for dermatitis atopic. Relevant concomitant medications were mequitazine and Ohrengedokuto. In the beginning of March 2003, anorexia and malaise. On (b) (6), hospitalized with severe hepatic function disorder. On 20-Mar-2003, fexofenadine, mequitazine and Ohrengedokuto stopped. On (b) (6), biopsy liver. Between (b) (6), glycyrrhizin administered intravenously. On (b) (6), discharged. See report for LFTs during event and baseline (GOT & GPT 30-40x, ALP 1.5x vs baseline; T bili 4.5.) mixed pattern	possible
200310540JP	52	f	allergic rhinitis	60 qd	hepatic function abnormal	started fexofenadine 3-Apr-2003 for 4 days. No significant medical history or concomitant medication. On (b) (6) abdominal discomfort, admitted to hospital with hepatic function disorder GOT 644, GPT 917, T-bil 1.6. On (b) (6), the event resolved. Drug-induced lymphocyte stimulation test (DLST) for fexofenadine positive. HA-antibody and IgM-HA antibody negative. Cytomegalovirus and EV virus negative. TA 15-20x ULN. No concomitants.	Probable
200310652JP	48	m	allergic rhinitis	60 qd	hepatic function abnormal	started fexofenadine Mar 2003. In Apr 2003, hepatic function disorder found and treated as outpatient. Hospitalized (b) (6) because no improvement was found in hepatic function disorder. The reporter stated he did not know the patient had been receiving fexofenadine until this date. So physician had considered it was acute aggravation of chronic hepatitis B. Fexofenadine discontinued the same day. On (b) (6) since no improvement was found(AST:288 and ALT:623), the dose of ribavirin was increased to 100ml/day. On (b) (6), since no improvement was confirmed (AST:348 and ALT:768), glutathione 200mg and liver hydrolysate (Acelart) 1 ampule were added. The hepatic function improved afterwards. On (b) (6), AST of 40 and ALT of 115.On (b) (6), the patient was discharged. Positive DLST. See report for LFTs.	Possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200310700JP	93	f	itch	120 qd	hepatic function abnormal	started fexofenadine 25-Sep-2002. She visited hospital on (b) (6) for malaise and anorexia. Examination findings: GOT:122 GPT :128 ALP:102, r-GPT:224 LDH:522 Total bilirubin 0.7. Hospitalized (b) (6), diagnosed with liver function disorder and stopped fexofenadine (b) (6). Concomitants including isosorbide, dipyridamole, furosemide continued. Steroid treatment prednisone (30 mg tid, 3 months) started, discharged from hospital (b) (6). see rpt for LFTs. Cholestatic pattern	possible
200311237JP	10	f	allergic rhinitis	120 qd	hepatic function abnormal, urine analysis abnormal	On (b) (6), 10 y.o. patient dosed olopatadine and visited the reporting hospital; olopatadine changed to fexofenadine hydrochloride. On (b) (6) t, abdominal pain and vomiting overnight, visited hospital at 5:00 am and treated with hydrocortisone, prednisolone, Stronger Neo Minophagen C, metoclopramide, and famotidine. Fexofenadine discontinued. At 10:15am, the patient re-visited the hospital, recovery observed. See report for LFTs.	Possible
200311268JP	69	f	allergic rhinitis	120 qd	hepatic function abnormal, abdominal pain	Event occurred after one week on fexofenadine, and abated after withdrawal. LFTs mildly elevated.	Probable
200312607DE	20	f	itch	qd po	hepatotoxicity nausea, vomiting	Starting on 05-Aug-2003 the patient suffered from nausea, vomiting and somnolence. Hospitalized for focal nodular hyperplasia of liver and "drug-induced toxic hepatic parenchyma damage by Telfast" from (b) (6). Mild elevation of GPT with 85 U/l. Later hospitalized due to liver damage GPT 3474with drop of liver synthesis parameters (Quick, albumin); Many investigations (see report) and "only the intake of Telfast could be found out as the cause of the liver damage according to the discharge letter". Had pruritus persisting for months with questionalble abuse of antihistaminics (fexofenadine). Abdominal ultrasound showed large mass in right lobe of liver.	Possible
200410322JP	36	m	rhinitis	120 qd	hepatic function abnormal, malaise	on 21-Jan-04 started fexofenadine, and 4 days later had anorexia and malaise. Concomitant medications diclofenac and rebamipide. Fexofenadine was discontinued. At that time his GOT was 170 and GPT 57. Both decreased to normal levels on 9-Feb-2004	Possible
200412775JP	80	f	urticaria	60 qd	hepatic function abnormal	On (b) (6) Allegra 60mg/day and Atarax 25 mg/dav were started for acute urticaria and itching. The stop dates of the drugs were (b) (6) respectively. On (b) (6), the patient developed rash that looked different from urticaria. She stopped taking Allegra at her discretion. Marked hepatic function disorder observed. On (b) (6), she was hospitalized, treated with Stronger Neo minophagen C (glychyrrhizin/glycine/cysteine combined drug) 40ml IV and Urso (ursodesoxycholic acid) 100mg x 6 tablets. Discharged on (b) (6). LFTs –transaminasesm ALP >1000, T-bil 1.6. mixed pattern	possible
200413107JP	44	m		120 qd	GGTP increased	Fexofenadine started on 11-Sep-2004 (before administration: GGTP 131, AST 24, ALT 29; on 27-Sep after administration: GGTP 208, AST 32, ALT 41). Allegra discontinued on 01-Oct. gentamicin concomitant med. Mild elevation of LFT	possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200512495JP	52	m	eczema		hepatic function abnormal	On Paruleon, Rohypnol and Goodmin for a long time. Depakene, and Tegretol were added on 29-Jul-2005, fexofenadine started 26-Aug-05. GOT 243 and GPT 370 were observed on (b) (6). The administration of Allegra, Depakene R200mg, and Tegretol 200mg was stopped. On (b) (6) GOT and GPT values decreased to 139 and 292 respectively. Recovered, discharged (b) (6) LFTs Cholestatic injury pattern. Depakene and Tegretol more suspicious for causality.	Possible
200512812JP	60	m		po	hepatic function abnormal	Hepatic function disorder GOT and GPT was 700 IU/L and 800 IU/L, respectively. Patient has recovered.	Probable
200610483JP	56	m	itch	60 bid	hepatic function abnormal	on fexofenadine from 21-Nov-2005 to 13-Dec-2005 for generalized itching. Relevant history includes gallstones, intercostal neuralgia. Concomitant diseases include Guillain-Barre syndrome and hypertension. Many concomitant meds. Abdominal pain occurred 12-Dec-2005. On 13-Dec-2005, blood test showed increased LFTs. After abdominal ultrasound (showed gallstones) and CT, antibody tests, liver injury suspected to be drug-induced. Allegra discontinued on 14-Dec-2005 and event resolved. LFTs in report. Cholestatic injury pattern	possible
200610618JP	78	m	erythroderma	120 qd	hepatic function abnormal, dermatitis exfoliative	on 26-Jan-06 started fexofenadine for pruritic rash, concomitant betamethasone. On 03-Feb-06 steroid increased. fexofenadine discontinued 04-Feb-06. On (b) (6) malaise, anorexia; hospitalized for dermatitis exfoliative with purpura. Discharged (b) (6)	possible
200612040JP	52	f	allergic rhinitis	po	hepatic function abnormal	Blood tests performed on 10-May-2006 revealed abnormal values of both AST and ALT as 186 and 416 respectively. All the medications that the patient was taking at that time were discontinued. Event resolved	possible*
200612694JP	62	m	urticaria	60 prn po	liver disorder	took fexofenadine 3/month prn through Jul-06. On (b) (6) AST of 6000 and ALT of 4000 were found. Drug-induced liver disorder was suspected. Multiple oral concomitant meds. DLST for fexofenadine negative. Viral antibodies, antinuclear antibody, antimitochondrial antibody negative. Symptoms improved with steroid pulse therapy and discharged from the hospital. The outcome was recovered on (b) (6). Fexofenadine hydrochloride was not re-administered. Hepatocellular injury	possible
200613279JP	36	f		60 qd	GGTP increased	Fexofenadine administered for 1-2 years. Presented with cough. No other drug given. Lung CT showed that there was no problem, blood test on 02-Oct-2006 showed that only gamma GTP increased to 63 (ULN 48). No abnormality was found by liver CT. Outcome of the event is not resolved as of 16-Oct-2006. liver injury category mild	possible
200711416JP	51	f	eczema	po	pyrexia, hepatic function abnormal	treated for eczema with fexofenadine, betamethasone, and heparinoid from 07-May-2007 to 15-May-2007. There was no relevant medical history or concomitant disease. An additional adverse event, hepatic function disorder, and pyrexia were experienced from 11-May-2007, with jaundice 15-May-07. Fexofenadine was not re-administered after discontinuation on 15-May-2007. the patient was recovered on 22-May-2007. No treatment was provided for these events. DLST positive only for fexofenadine. No biopsy. Viral, auto antibodies negative. Diagnosis drug-induced liver injury.	Probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200711872JP	20	m	itch	60 bid	hepatic function abnormal	Fexofenadine taken from 10-May-07 to 16 May-07 and from 27-Jun-07 to 28-Jun-07. Hospitalized (b) (6) .biopsy. DLST negative for fexofenadine and for oxatomide. Hepatic function disorder from LFTs. Treated and discharged (b) (6) . Cholestatic injury	possible
200910184JP	19	f		60 bid	hepatic function abnormal	started fexofenadine in Oct-08. on (b) (6) developed malaise, went to hospital, diagnosed with liver disorder. fexofenadine discontinued. Treated and recovered, LFT normalized (b) (6) . viral serologies, ultrasound negative. No concomitant medication. Liver injury mild	probable
200910353JP	35	m	itch	60 bid	granulocytopenia, hepatic function abnormal	On (b) (6) hospitalized with infectious endocarditis. Treated with Ampicillin, gentamicin, carperitid], furosemide and spironolactone. Started fexofenadine (b) (6) for itch (b) (6) , GOT was 75, GTP was 150, WBC was 4270 and neutrophil count was 820. fexofenadine discontinued immediately. Recovery over next 3 days with filgrastim treatment. Liver injury mild	possible
200910702JP	23	m	atopic dermatitis	60 bid	hepatic function disorder	for aggravation of atopic dermatitis, visited clinic on 14-Nov-07, fexofenadine 60 mg bid with external steroid prescribed. On 10-Dec-2007, symptom improved, fexofenadine continuously prescribed. On 14-Mar-2008, fexofenadine reduced to 60mg/day. On 28-Apr-2008, continued 60mg/day fexofenadine. On 10-Mar-2009, GOT: 563, GPT: 1512, gamma-GTP: 170. On 11-Mar-2009, the physician advised to discontinue fexofenadine. On 13-Mar-2009, the patient visited clinic, blood tests and hepatitis screenings conducted and results of blood tests showed improvement GOT and GPT, 70 and 576, respectively and viral hepatitis screenings negative. Betamethasone given. fexofenadine switched to epinastine. Patient feels well now.	Possible
200911622JP	40	f	allergy	120 qd	hepatitis acute, chromaturia	started fexofenadine 01-May-2009. From 08-May-2009, brown urine became to be observed. On (b) (6) , visited hospital with pyrexia at 38c, queasy and epigastric pain. Followed-up after prescribing internal medicines. On (b) (6) , visited hospital again with aggravated epigastric pain and jaundice. Hepatitis acute was diagnosed by CT. On (b) (6) , admitted into the reporter's hospital. All internal medications were discontinued. Rehydration. No virus infection, primary biliary cirrhosis (PBC) or autoimmune hepatitis was detected with a blood test. On 10-Jun-2009, drug-induced hepatitis was suspected as eosinophil count increased was observed. On (b) (6) , discharged. No ultrasound or biopsy. Virus and autologous antibody testing negative.	Possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200912441JP	61	f	allergic rhinitis	60 bid	liver disorder	20-Nov-2006: started fexofenadine and itavastatin for hyperlipidaemia, bronchitis chronic, and rhinitis allergic; continued without any adverse events until 01-Feb-2007. The symptoms abated. 0n (b) (6): revisited hospital with sputum and cough; fexofenadine and carbocisteine started. (b) (6): Cough persisted, and the dose of carbocisteine was increased. Also pitavastatin was started for hyperlipidaemia, revealed on blood test of (b) (6) (b) (6): Cough resolved. Patient was prescribed only fexofenadine and carbocisteine. (b) (6): blood test showed acute liver disorder. Patient had no clear symptoms. Itavastatin and fexofenadine discontinued. 05-Aug: daily glycyrrhizinate/glycine/cysteine (Stronger Neo-Minophagen C) 20 ml IV started. (b) (6): Transaminases increased to peak. (b) (6): Transaminases improved. Biliary enzyme increased developed, and the administration of Urso 150 mg/day PO was started. Over next two weeks, symptoms improved with treatment. Hepatitis virus neg	possible
200912647JP	52	f		60 bid	liver disorder	On 17-Aug-2009, developed drug-induced skin eruption (from Phenobarbitol) which could be considered as Stevens Johnson syndrome. On 14-Sep-2009, developed liver disorder, 668 of AST and 1370 of ALT. Skin eruption again aggravated. The drugs, except steroid, all discontinued. On (b) (6), admitted to hospital for aggravation of AST(=706) and ALT (=1831). Betamethasone sodium phosphate (Rinderon) 0.75 mg was switched to increased dosage of prednisolone 40 mg/day for skin eruption. On (b) (6), AST was 22 and ALT was 222, which showed improvements. Skin eruption also improved. Patient was discharged. Liver injury at least moderate. Hepatitis viral and bacterial, auto immune hepatic diseases ruled out by serum marker and diagnostic imaging. DLST +/- fexofenadine and for phenobarb	possible
200913338FR	64	m		po	cytolytic hepatitis	On 21-Aug-2009, diffuse abdominal pain with nausea and headache, took paracetamol (16g in 3 days) without medical advice. On 23-Aug-2009, despite auto-medication, symptoms persisted. Visited general practitioner, found hepatic cytolysis with ALAT at 100N, ASAT at 60N, GGT at 20N, total bilirubin at 107mcmol/L (with predominance of conjugated bilirubin), alkaline phosphatases were unremarkable and CRP increased to 63.6 mg/L. Pancreatic work up was unremarkable. Icteric acute hepatitis was diagnosed. On (b) (6), hospitalized. Hepatomegaly with cutaneo-mucous icterus. Serological analysis for hepatitis A, B, C, VIH, mycoplasm, Chlamydia, parvovirus B19, EBV, CMV, HSV1 and HSV2 were negative. Paracetamolemia was also negative but the test was performed more than 24 hours after the last intake of paracetamol. Liver ultrasound showed steatosis without dilatation of biliary duct nor liver parenchyma abnormality. Received N-acetyl-cystein as treatment, biological tests improved.	Possible

MO Comment *Of the 59 cases in the reviewer database of nonfatal hepatic SAEs, there were a total of 23 cases where there was compromise of liver function: in 17 of these cases, there was jaundice; in addition, there were 6 reports of increases in total bilirubin.*

Six non-fatal hepatic SAE reports of note involved patients on fexofenadine and no other concomitant drugs. These cases are summarized below:

200712489JP 27 yo F received fexofenadine 120 mg from 11-29 Aug 2007 for eczema. On (b) (6)*: patient visited the hospital with complaint of jaundice and was hospitalized for suspected liver disorder. SGOT was 1154. SGPT was 1428. Total bilirubin was 7.58. HCV and HBV were negative. Abdominal echo and CT and MRI revealed no abnormal findings. On* (b) (6)*, the patient was discharged from the hospital. The assessment was drug induced liver disorder and fexofenadine was discontinued 29 Aug 2007. Bilirubin and transaminases were much improved the following week. On 22-Oct-2007: further improved: GOT was 44, GPT was 38 and total bilirubin was 0.88.*

200812883US 34 yo M received fexofenadine for seasonal allergies and developed eosinophilic hepatitis. Patient was on fexofenadine and no other medications. He developed, after a few months of treatment, chills, abdominal cramps, dark urine and erythematous rash over his whole body. On presentation,he had mild scleral icterus; laboratory tests showed: ALP 218, AST 93, ALT 248, total bilirubin 5.7 and 12% eosinophils. Liver biopsy results revealed eosinophilic hepatitis with focal bridging fibrosis. Although skin prick testing was positive for common allergens, the allergist considered the most likely cause was due to a drug effect. Fexofenadine was stopped and LFTs normalized over the next few weeks. After 6 months, he was doing well with no recurrence. Patient has a history of heavy alcohol use in college. He reported no sick contacts, no over the counter medication use or active alcohol consumption. The patient presented to his primary care doctor and was found to be afebrile with stable vital signs. Physical exam showed no stigmata of chronic liver disease. Additional testing included a work up for viral hepatitis, autoimmune hepatitis, hemochromatosis and other hereditary liver conditions which were unremarkable. A right upper quadrant ultrasound did not show evidence of cholelithiasis or biliary duct dilation. The only medication he was taking, fexofenadine, was held and over the next few weeks his liver function tests returned into normal range. [Johal, A, Smith, R., Fexofenadine. First Report of Eosinophilic Hepatitis: Case Report, 73rd Annual Scientific Meeting of the American College of Gastroenterology 2008: 553.]

200911360JP 60 yo male started fexofenadine 60 mg bid from the beginning of Apr-09. On (b) (6)*,he presented with malaise and jaundice. Liver disorder from blood test and hospitalized. No concomitant medications. Stronger minophagen C given IV, thereafter condition improved as of* (b) (6)*. ultrasound hepatomegaly. No biopsy. Viral hepatitis serologies negative. Drug lymphocyte stimulation test (DLST) was positive for fexofenadine. Mixed hepatocellular and cholestatic injury.*

200910184JP 19 yo female started fexofenadine 60 mg bid in Oct-08. On (b) (6) *developed malaise, went to hospital, diagnosed with liver disorder and fexofenadine was discontinued. Treated and recovered, LFT normalized* (b) (6)*. Viral serologies,*

ultrasound negative. No concomitant medication. Drug-induced hepatic function disorder was suspected. Liver injury mild

200310540JP 52 yo female started fexofenadine on 3-Apr-2003. There was no significant medical history or concomitant medication. On (b) (6)*, she was admitted to hospital with abdominal discomfort and hepatic function disorder (GOT 644, GPT 917, T-bil 1.6). On* (b) (6)*, the event resolved. A drug-induced lymphocyte stimulation test (DLST) for fexofenadine was positive. HA-antibody and IgM-HA antibody tests were negative. Causality was assessed as probable by the reporting physician.*

200111548JP 29 yo male had drug induced hepatitis after 6 weeks on fexofenadine (LFTs increased, HBs-Ag(-), HCV-Ab(-), IgM-HA(-). GOT 884, GPT1688, ALP 198, T-Bil 0.44). No concomitant drugs. Normal 3 weeks later. Causality was assessed as probable by the reporting physician.

There were additional cases in which a likely contribution of fexofenadine to the liver injury was assessed despite the use of concomitant drugs, because of the time course. An example is:

199811511RHF 54 yo F patient with history of mastosis operated in April (normal LFTs at that time), and on medications cilazapril and theophylline for months. Since May, was treated with fexofenadine 180 mg per day for urticaria. July 21, hepatic function was checked because of asthenia, and showed AST 368, ALT 332 alk phos 440, GGT 607, total bili 28 (N<15), direct bili normal. Liver biopsy—microvesicular steatosis, lobular, portal lesions, periportal necrosis. Felt to be a drug-induced hepatitis. After fexofenadine was stopped, liver tests reportedly rapidly improved (10 days later) and returned to normal within 1 month. Also note, fexofenadine was initially continued for several weeks after the asthenia, and the LFTs worsened and normalized once fexofenadine was stopped.

In summary, the reviewer examined spontaneous reports of hepatic SAEs in the postmarket database to clarify the nature of the EBGM signal found in AERS but not in WHO. The review of serious spontaneous reports with a contribution of fexofenadine to the SAE showed that the liver injuries associated with fexofenadine are generally reversible with stopping the drug. There was only one death case where fexofenadine was possibly related to the hepatic event (case 200910011JP). The reviewer recommends informing consumers to ask their doctor if signs of jaundice or unusually dark urine appear.

HYPERSENSITIVITY SERIOUS ADVERSE EVENTS

MO Comment *In the reviewer database of 907 nonfatal SAE reports, there were a total of 156 hypersensitivity reports, of which 144 cases were assessed as of probable or possible relation to fexofenadine. A total of 56 probable or possible hypersensitivity cases were selected for presentation below in* Table 43*. Of the 56 selected cases, there were 33 cases involving anaphylactic reactions and/or shock; 16 reports of angioedema; and 7 cases of Stevens-Johnson Syndrome.*

Table 43 Non-Fatal Reports of Hypersensitivity SAEs, Possible or Probable Causality

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
199811129RHF	49	f	allergy	180 qd	allergic shock	after one tablet, hypotension and pharyngeal edema	physician assessed related
199812128RHF	17	f	allergic rhinitis	120 qd	allergic shock, syncope	after one week therapy, event occurred 20 minutes after taking the pill, treated with corticosteroid	probable
199812293HMRI	29	f	allergy	60 bid	Stevens Johnson Syndrome	after 5 days treatment. Nitrofurantoin concomitant, also discontinued.	Possible
199812739RHF	40	m	sinusitis	po	anaphylaxis	after one tablet, event occurred. Patient had taken one tablet several months earlier.Sweat, tingling, nausea, vomiting, systolic BP 60. Treated with adrenaline and steroids.No concomitant medications.	Probable
199815278DDC	36	f	allergic rhinitis	60 once	anaphylaxis, syncope	after first dose of fexofenadine, anaphylaxis. Concomitants Ceclor and herbal medicine (all discontinued together)	possible
199910396RGB		f	skin condition	120 once	anaphylactoid reaction, dyspnea	30 min after one tablet. Patient had used fexofenadine a “short time” two years earlier.	Possible
199910436HPD	26	m	urticaria	180 once	anaphylactic shock	30 min after first table. No history of allergies	probable
199910941RHF	22	f	skin condition		acute anaphylactic reaction, syncope	15 min after first dose. Took mequitazone a few days earlier	probable
199920582HMRI	38	f		po	anaphylactic reaction, skin exfoliation	two occurrences: after second dose of fexofenadine and again 2 days later. Concomitant sertraline	probable
200111023JP	63	f	urticaria	120 qd	anaphylactic shock	after one tablet fexofenadine and roxatidine, event occurred. fexofenadine discontinued.	Probable
200111307JP	56	f	allergic rhinitis	60 once	anaphylactic shock	20 min after taking one tablet, nausea, skin flushing occurred. Dyspnea 40 min later. fexofenadine discontinued, recovered on steroid therapy	probable
200111876DE	34	m	generalized itch	180 once	anaphylaxis, syncope	one hour after first dose, whole body urticaria, dyspnea and syncope. No concomitant medication.	Probable
200112654EU	49	f	urticaria	180 qd	angioedema	after 4 days treatment with fexofenadine, angioedema. Fexofenadine discontinued, recovered on steroid therapy	probable
200114034FR	24	m	cough	180 qd	angioedema	Patient no past medical history. Four hours after second dose of fexofenadine, angioedema. Steroids given, improvement. fexofenadine given again the next day, angioedema recurred, more severe.	Related

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200116009GDDC	20	f	Itch	180 qd	anaphylactic reaction	event occurred after first exposure to fexofenadine, which was given for itch from contact dermatitis. Patient has history of skin reactions to topical medications, erythromycin, benzoyl peroxide. No concomitant medications. A residual pruritis continued for 10 d	probable
200116772GDDC	26	f	allergic rhinitis	120 once	anaphylactic reaction, dyspnea	event occurred after first dose of fexofenadine, which was stopped, then event abated	Probable
200121932FR	21	f	eczema	180 once	anaphylactoid reaction	2 hours after first dose, generalized urticaria, dyspnea, edema, dysphagia. Treatment dexchlorpheniramine and methyl prednisone, recovered. Same adverse event experienced previous week 7 hours ater first use of cetirizine (10mg). Reintroduction of cetiriz	Probable
200211085JP	63	m	eczema	120 qd	Stevens Johnson Syndrome	fexofenadine one or two tablets on 10/JUN/02. developed pruritus immediately after taking fexofenadine. On 11/JUN/02, erythema appeared and pruritus aggravated. Fexofenadine discontinued 13/JUN/02. Erythema developed whole body with skin desquamation and conjunctivitis of both eyes. On (b) (6), hospitalized and received prednisolone 30mg. Three days later, erythema and skin desquamation disappeared. (b) (6), discharged	Probable
200211512JP	58	f	erythema	po	Stevens Johnson Syndrome	treated with unknown meds for allergic pharyngitis, acute sinusitis and obstruction of eustachian tube from 12/OCT/02. developed cold symptoms and took unknown OTC drug on 21/OCT/02. Erythema appeared on upper extremities and trunk on 22/OCT/02. Fexofenadine started for erythema on 23/OCT/02. erythema expanded and reporting dermatologist diagnosed Stevens Johnson Syndrome on 25/OCT/02.	Possible
200219995GDDC	3	m	atopy	30 qd	anaphylaxis, laryngospasm	On (b) (6), 30 min after first dose, the child experienced thoracic rigidity, abdominal pain, vomiting and laryngospasm. Hospitalized 24 hours, given adrenaline aminophylline and steroids. Recovered	Probable
200310369JP	56	f	urticaria	60 bid	anaphylactic shock	after 8 days on fexofenadine, palpitations, flushing. In ER, BP decreased was noted. Recovered. On 06-Mar-2003, fexofenadine was given again and event re-occurred	Probable
200310676JP	72	m	eczema	po	Stevens Johnson Syndrome	started fexofenadine 6-Jun-2003, admitted to hospital (b) (6) with facial eczema. Generalized rash and intraoral blister appeared next day. All medicines (including allopurinol and pivoxil) stopped. Treatment with betamethasone given.	Possible
200311032JP	69	f	urticaria	120 qd	dyspnea, angioedema	started fexofenadine 3-Jun-2003, within 5 minutes felt blood vessels swelling, chest pain and dyspnea. Second intake, same symptoms. fexofenadine discontinued 5-Jun. On 25-Jun, epinastine prescribed, changed to cetirizine on July 3. other concomitant medications continued	Probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200311037JP	60	m	itch	po once	shock	developed shock 20 min after first dose of fexofenadine, with nausea, pallor BP decrease. Carbenin and fexofenadine stopped. Treated with fluids, event abated.	Possible
200312497EU	36	f	allergic rhinitis	500 qd	angioedema, erythema multiforme	Started fexofenadine 25-apr-2002. On (b) (6) had headache and took one tablet aspirin 500 mg PO. Approximately 30 min thereafter, she experienced swelling lips, itch and rash on face and arms. Admitted and treated with steroids; fexofenadine stopped and replaced with cetirizine	Possible
200313298US	69	m		po	urticaria, angioedema	From 01-Apr-03 through 04-Apr-03 on fexofenadine for allergic reaction to yellow dye. Many concomitant medications. On (b) (6), the patient experienced hives and lip swelling, was hospitalized. Discontinued fexofenadine, event resolved	Possible
200314130US	25	f		30 po	anaphylactic reaction, urticaria	took one dose fexofenadine, had lunch, reaction began afterwards (pruritis, erythema, and hives on her forehead, back, and neck). After 4 hours, throat tightnening, fexofenadine discontinued by ER. Rechallenge by physician. fexofenadine 30 mg again, no reaction for 1 hr. Another fexofenadine 30 mg, hives and erythema. Treated with steroid, cetirizine and diphenhydramine. No symptoms next day	Possible
200315430GDDC	37	f	allergy	180 qd	hypersensitivity, erythema, angioedema	On 28-Apr-03 subject ate a hot dog at lunchtime and presented with periorbital and unilateral mouth edema. She received hydrocortisone and promethazine with improvement of the adverse events. Then fexofenadine one tablet taken at night. Some minutes after fexofenadine presented with contra lateral palpebral edema and increase of angioedema. Treatment with Allegra was kept until 30-Apr-03. treated with steroid injection.	Probable
200320024GDDC	42	f	urticaria	180 qd	urticaria, angioedema	on first day of treatment, developed urticaria aggravated and angioedema. fexofenadine discontinued and event resolved	Possible
200320026GDDC	24	f		180 qd	urticaria, angioedema	one hour after taking one tablet of fexofenadine, widespread urticaria and angioedema of tongue. fexofenadine discontinued the same day and patient recovered. No rechallenge	Probable
200410282JP	57	m	allergic rhinitis	120 qd	Stevens Johnson Syndrome	On 14-Jan-2004, pranlukast hydrate (Onon) and fexofenadine hydrochloride started. On 29-Jan-04 he felt chilled and took OTC cold remedy in the morning (which he usually used) and skin eruption on trunk and thighs developed in the late afternoon. On 30-Jan upper respiratory tract inflammation was diagnosed and non-pyrine preparation for cold and cefcapene pivoxil hydrochloride were prescribed from 30-Jan noon to 31-Jan morning. In the late afternoon, rash spread all over his body. On 31-Jan morning, rash appeared in the mouth. On (b) (6) afternoon, hospitalized and Stevens Johnson syndrome diagnosed. He was treated with prednisolone and is recovering from the event.	Possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200412760JP	29	f	itch	60 bid	shock	Started fexofenadine on (b) (6). mequitazine and glutathione. 2 hours after administration of the above 3 drugs, developed shock, ysrhyt, numbness, facial flushing and increased blood pressure. Hospitalized, all drugs stopped	Possible
200412827JP	50	m	urticaria	60 bid	anaphylactic reaction	15 min after taking first dose of fexofenadine, felt sick and lost consciousness. BP 80 Hospitalized, treated with steroid infusion. Recovered.	Possible
200413148JP	75	f	urticaria	120 qd	anaphylactic reaction	(b) (6), the patient developed urticaria from custard. In ER received fluid infusion, 100mg of hydrocortisone. Allegra was prescribed. (b) (6), at 14:30, she took a tablet of Allegra. An hour later, she developed nasal congestion, oedema glottis.	Possible
200510463JP	33	f	skin condition	120 qd	shock, pallor	20 min after taking one tablet, numbness and pallor, hypotension 80/50. fexofenadine discontinued, recovered	Probable
200510667EU	45	f	allergy prophylaxis	1 tab qd	hypersensitivity reaction, anaphylactic reaction	patient received fexofenadine on 3 occasions: no reaction on first exposure Dec-04, transient feeling unwell on 2nd exposure in Jan-05. On 29 January, 2005, third exposure (this report): took one tablet and after 5 minutes, fell ill, developed pruritus in hands	Probable
200510935JP	75	f	allergic rhinitis	60 qd	anaphylaxis, stridor	on (b) (6) dyspnea and generalized pruritis occurred within 2 hours after taking one tablet fexofenadine. Hospitalized with anaphylaxis, treated with steroid and oxygen	Probable
200514718GDDC	35	m		180 qd	hypersensitivity reaction, urticaria, angioedema	The patient had experienced 2 episodes of urticaria within 30 minutes of taking fexofenadine The first episode was 6 months ago. The most recent was 18-May-2005. On both occasions the patient had taken an herbal supplement in the same 24 hours. One episode caused marked angioedema and respiratory distress requiring adrenaline. The doctor rechallenged the patient with fexofenadine in a staged manner with just less than 90mg. Thirty minutes later he had florid urticaria, anxiety and starting angioedema.The patient recovered from the event.	Related
200515812GDDC	29	m	allergic rhinitis	120	hypersensitivity, rash macular, angioedema	2 weeks after starting Telfast. The pharmacist reported that the rash first appeared on the patient's legs from the groin area to the feet. The rash then appeared on his head, which then swelled into egg size lumps. The rash appeared along the torso and arms and then the neck. The rash finally appeared all over his body from head to toe. The rash increased in size to very large blotches. His lips, tongue, eyes and face swelled up and he experienced extreme itchiness. The drug was stopped in June 2005 but a re-challenge was performed where a reaction did occur. Prednisolone was given as treatment.	Probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200517374GDDC	54	f	severe allergic reaction	180 tid	anaphylactic shock	After initializing fexofenadine patient felt increasingly bad (itching, throat was closing, prickly sensation in extremities and disoriented). On (b) (6) an event of anaphylactic shock and admitted to the hospital. fexofenadine was discontinued. Treated with adrenaline	Possible
200519420GDDC	27	f	angioneurotic edema	120 qd	anaphylactic reaction, dyspnea	9 hours after taking one tablet fexofenadine, presented with dyspnea and worsening of angioneurotic edema. fexofenadine discontinued. In ER treated with steroid. Recovered next day	Probable
200610455JP	84			120 qd	dyspnea, shock	started fexofenadine (b) (6). event occurred next day. Hospitalized, outcome not reported	Possible
200610772JP	38	f	cough	60 qd	angioedema, rash	Fexofenadine started 10-Feb-06 for atopic cough. Rash developed on trunk and extremities, fexofenadine was discontinued. On 16-Feb-06, cough again severe, patient took fexofenadine again and rash appeared again. Steroid administered, event resolved. No underlying disease,	Probable
200611412JP	51	m	urticaria	po	anaphylactoid reaction, nausea, dizziness	On 14-Feb-2006, a 14-day course of Allegra was prescribed for urticaria. On an unknown date of Apr-2006, another 14-day course of Allegra was prescribed for urticaria. On (b) (6), the patient felt poorly on waking up, and experienced dizziness in a car. Diagnosis anaphylactoid reaction at hospital.	Possible
200612143JP	36	f	urticaria	60 bid	anaphylactic reaction	05-Jul-2006: started fexofenadine for urticaria. Immediately after taking 1 tablet, felt tight larynx, wheeze, cough, choking. After a while, symptoms disappeared. Same symptoms after taking fexofenadine in the evening. 06-Jul-2006: Queasy and abdominal pain in addition	Probable
200612575GDDC		f	itch	180 qd	anaphylaxis, respiratory disorder hypotension	Forty-five minutes after taking one fexofenadine tablet experienced widespread urticaria, developed respiratory compromise and hypotension. Required treatment with adrenaline. The patient recovered	Probable
200613212DE	52	f	urticaria	180 qd	urticaris, angioedema	acute generalized urticaria and angioedema occurred one hour after first intake of fexofenadine. Fexofenadine was withdrawn. Treated with cortisone and recovered within one to two hours. Concomitant medication was not given. Reporter states same event(s) occurred during treatment with levocetirizine and clemastine.	Probable
200613537FR	38	f	urticaria	180 once	angioedema, urticaria	took two tables prednisone in the morning and one table fexofenadine in the afternoon; and immediately urticaria aggravated and dyspnea. fexofenadine discontinued and steroid dose increased. Recovered	Probable

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200614561FR	70	m	contact dermatitis	po	angioedema, rash	history of diabetes mellitus, hyperlipemia, atrial fibrillation and flutter. Concomitant treatment for years included fluindione for atrial fibrillation and flutter, metformin for diabetes mellitus, amiodarone for atrial flutter fibrillation and fenofibrate for hyperlipemia. On (b) (6), experienced angioedema with hypereosinophilia at 1,600/mm3. On admission, fexofenadine was stopped. Blood workup, ultrasound, pelvic CT, myelogram. Infection serologies negative. On (b) (6) he was discharged on a treatment including prednisone, pantoprazole, calcium, repaglidine, propylthiouracil, coumadine, hemigoxine, fenofibrate and finasteride.	Possible
200615146GDDC	48	f	rash	180 bid	anaphylactic reaction	on 24-Apr-06, first day of treatment, analphylactic reaction with tongue and cheek swelling, rash all over body. fexofenadine discontinued. Treated with adrenaline, steroids and chlorpheniramine. The patient is recovering	Probable
200710053JP	39	f	allergic rhinitis	120 qd	Stevens Johnson Syndrome	started fexofenadine in Nov-2006 for rhinitis allergic. In the beginning of Dec-2006, she used suppository and enema for constipation for two to three days. In the middle of Dec-2006, she took Yutan-en (oral Chinese herbal medicine) for constipation prn. On 30-Dec-2006, erythema developed on the thoracoabdominal region and the back. Betamethasone was prescribed. On 1-Jan-2007, erosion and ulcer developed on the lip. On 3-Jan-2007 prednisolone was prescribed. The symptom did not improve, hospitalized on (b) (6). fexofenadine discontinued. Stevens-Johnson syndrome was diagnosed. ESR-30:2, ESR-60:6, ESR-120:21, CRP:0.08, WBC:104. Betamethasone (Rinderon) 8 mg/day was intravenously administered from (b) (6). Thereafter, the symptom gradually improved and she was discharged	Possible
200716428GDDC	29	f	urticaria	po	angioedema, swelling face	took fexofenadine for the first time, 3 tablets in Apr-07, for treatment of urticaria from use of a sunscreen on body and face. Had swelling in face and eyes which lasted for 5 days with a severe reaction for the first three days. Then after using the sunscreen just on body, again urticaria, and took 1 tablet fexofenadine on 10-Jul-07, within 3 hours of fexofenadine had same reaction, diagnosed as angioedema by physician. Treated with steroid and aminocaproic acid. Fexofenadine hydrochloride was discontinued on 11-Jul-07 and the outcome is reported as recovering.	Probable
200811466JP	30	f	atopic dermatitis	60 bid	Stevens Johnson Syndrome	On 22-Nov-2005, minocycline and fexofenadine for atopic dermatitis prescribed. About a week later, developed cough. On 12-Dec-2005, cefditoren pivoxil and loxoprofen sodium given for cold-like symptoms. On 17-Dec-2005, lip and oral erosions and erythema developed on trunk and limbs. On (b) (6), hospitalized with lip, oral, and ocular erosions and erythema on the trunk and the limbs. Treated with infusion of prednisolone. On (b) (6) the patient was discharged	Possible

Mfr Number	Age	Sex	Indication	Dose	AE	Comments	Causality
200811598JP	42	f	urticaria	120 qd	anaphylactic shock, loss of consciousness	on (b) (6) given fexofenadine and betamethasone/d-chlorpheniramine maleate for urticaria after eating seafood salad previous evening. Both meds taken 18:00, and 10-15 min later nausea and vomiting. Fainted, taken to hospital. Referred to another hospital because BP dropped to 80's. On (b) (6) : recurrence of exanthema and administration of steroid pulse therapy as symptoms persisted. Discharged.	Possible
200911084JP	51	f		60 po	anaphylactoid shock, lip swelling, choking	On (b) (6), fexofenadine, loxoprofen and teprenone prescribed. It was the first time fexofenadine prescribed, although the patient had taken other two drugs before. Three drugs taken at the same time, experienced discomfort around the lips immediately. Lip and face swelling, was obvious to the patient's daughter. Also difficulty breathing. In ER treated with IV steroids. A few hours later the patient's breathing condition became stable; recovered. The patient had been prescribed loxoprofen and teprenone more than 10 times without adverse reactions.	Probable
200915735GDDC	5	f	urticaria	5 ml bid	tachycardia, angioedema	after 3 days on fexofenadine for urticaria on whole body, hospitalized (b) (6) for worsening of urticaria and angioedema. Given promethazine intramuscular, adrenaline and ranitidine. After that, developed psychosomatic disorders with hallucination (unspecified), abdominal pain, and psychomotor agiatation. Recovered next day.	Possible

MO Comment *The proposed labeling already includes an allergy warning, "Do not use if you have an allergy to this product or any of its ingredients". It would be helpful to the consumer if the label could list symptoms to watch for, like "difficulty breathing" as in the Netherlands label (see Appendix 9.2), and state what to do if such symptoms arise (stop use and ask your doctor).*

Drug Interaction

The sponsor identified 168 reports with a suspected drug interaction, including non-serious events, from the total postmarketing database of 14572 reports. The most commonly reported drugs suspected of interaction are given in Table 44. There were 17 reports of interactions with macrolides. The macrolides are known to increase the bioavailablity of fexofenadine as is stated on the prescription label (also see Section 9.1). Erythromycin, for example, increased steady-state fexofenadine peak concentrations by 82% and increased AUC by 109%. Fexofenadine had no effect on the pharmacokinetics of erythromycin.

Twelve postmarketing spontaneous reports described drug interactions with anticonvulsants. Of these cases, 6 reported convulsions (1 each with phenytoin, carbamazepine, valproate, phenytoin/ phenobarbital, levetiracetam, and barbexaclone), 3 reported *increased* anticonvulsant levels (one report each for increased phenytoin, carbamazepine and valproate levels), 2 reported *decreased* anticonvulsant levels (phenytoin and valproate), and 1 reported palpitations due to phenytoin toxicity.

Eleven reports describe interactions with estrogen/ progesterone hormonal therapies, either oral contraceptives or female hormone replacement therapy. The most frequently reported events associated with suspected interaction were drug interaction, and drug ineffective, and pregnancy Eleven reports describe drug interaction with alcohol. The events reported in these cases included drug/alcohol interaction, balance and coordination difficulties, blood alcohol increased, breath alcohol test positive, dizziness, dysarthria, impaired driving ability, and road traffic accident.

Table 44 Most Frequently Reported Drug Interactions by Class (Sanofi-aventis database)

Drug Class in Suspected Interaction	Number (%) of reports
Total Interaction Reports	168
Macrolides	17 (10%)
Anticonvulsant	12 (7.1%)
Oral contraceptives/hormone replacement	11 (6.5%)
Alcohol	10 (5.9%)

MO Comment *The database of 953 SAEs was examined to search for serious cases involving fexofenadine interaction with a macrolide or an anticonvulsant. There are 20 such cases in* Table 45. *Of the 15 cases involving a macrolide, 13 cases reported a cardiac SAE. The anticonvulsants cases all reported seizures. Five cardiac SAE cases with a possible contribution of fexofenadine interaction with macrolides are:*

> *199911526HMRI 45 yo M experienced rapid heart rate (150 bpm) and a dazed state after taking one or two doses of clarithromycin. He had been taking fexofenadine for some time (not specified). Events*

lasted for one hour and resolved. The patient had no cardiac history and had taken clarithromycin two previous occasions without any problems, while not taking fexofenadine. Hence each drug had been taken separately without any adverse reaction, but SAE occurred on the first or seond dose of clarithromycin when the two drugs were taken together.

199710046HMRI a 37 yo F experienced cardiac dysrhythmia in February, 1997. Relevant tests/laboratory data were negative. No relevant history or preexisting medical conditions. The patient took two doses of Biaxin (clarithromycin) and Allegra,and began having an irregular pulse and chest tightness. Allegra was stopped and symptoms abated. She continued with Biaxin with no recurrence.

199812436HMRI 43 yo F was started on Allegra 60 mg bid for SAR and erythromycin for infection on May 14, 1998 At (b) (6)*, patient developed retrosternal pain radiating across shoulders and into the left arm with shortness of breath. In ER, BP was 97/64, RR32 and heart rate of 220 with a supraventricular tachycardia. Treated with adenosine and then tenormin and ASA. No concomitant diseases, but a positive family history of heart disease and no history of alcohol abuse or drugs. Smokes ½ ppd. No concomitant medications.*

200520584GDDC *A healthy 14 year old male with no history of cardiac disease started azithromycin after therapy with fexofenadine 120 mg. Eight days after initiating a 3-day treatment with azithromycin, he was hospitalized with a ventricular arrhythmia. The following month he took another 3-day course of azithromycin and was admitted to the hospital 10 days later for a ventricular arrhythmia (positive rechallenge). Patient had an AV node reentrant tachycardia of the fastslow type. He required cardioversion and was discharged on sotalol. Fexofenadine was discontinued, and 4 days later a third episode occurred. Concomitant long- term medications included fluticasone with salmeterol. The reporting pharmacist was not sure whether QT prolongation occurred. Concomitant seretide (fluticasone/salmeterol).*

199912441HMRI 63 yo male physician was on Allegra for the past 9 months and discontinued it at some point, subsequently developed a URI and treated it with 5 days of Azithromycin and Sudafed. He then restarted Allegra and after one day developed atrial fibrillation.

The case 199911526HMRI is especially suggestive of drug interaction between fexofenadine and clarithromycin, because the subject had no cardiac history and had a cardiac SAE with the two drugs together, but had recently taken both drugs separately without adverse event. Likewise the case 199710046HMRI is suggestive of drug interaction, because the subject continued clarithromycin without recurrence after the cardiac SAE involving that same drug with fexofenadine.

The death cases in Table 45 *are included in* Table 39. *ISR6745141-9 is a literature case (Del Rosario et al. Mo Med 2010:107(1):53-58); it was assessed as possible and involved numerous concomitant drugs (including azithromycin) that could also have caused the arrhythmia.*

In summary, the postmarket database contains over 10 cardiac SAE cases with possible contribution from fexofenadine interaction with macrolide, including two deaths. However, if the label has appropriate information about cardiac adverse events, a separate drug interaction warning may not be needed.

Table 45 SAEs with Fexofenadine and Macrolide or Anticonvulsant

Concomitant	Case Number	Age	Type of Reaction	Principal AE
Azithromycin	199912441HMRI	63	Cardiac	Atrial fibrillation
	200113319GDDC	55	Cardiac	Atrial tachycardia
	200520584GDDC	14	Cardiac	Supraventricular tachycardia

Concomitant	Case Number	Age	Type of Reaction	Principal AE
	200214859US	16	Cardiac	Syncope
	ISR6745141-9	27	Death	Prolonged QT, torsade
Erythromycin	199812436HMRI	43	Cardiac	Supraventricular tachycardia
	200113787GB	22	Cardiac	Collapse, palpitations
	200113832EU	42	Cardiac	Tachycardia
	200011299HMRI	56	Death	Seizure, ventricular fibrillation
Clarithromycin	199911526HMRI	45	Cardiac	Tachycardia
	200124328GDDC	23	Cardiac	Tachycardia
	200810968JP	9	Cardiac	Loss of consciousness
	97001126	74	Cardiac	Cardiac arrest, ventricular fibrillation
	199710046HMRI	37	Cardiac	Cardiac dysrhythmia
	200413431JP	67	Hypersensitivity	Hypersensitivity reaction, dyspnea
	199710610HMRI	26	Seizure	Convulsion
Carbamazepine	199810897HMRI		Seizure	Breakthrough seizure
Valproate	199813394HMRI		Seizure	Seizure
Valproic acid	97001296		Seizure	Stupor
Phenytoin	200216323US	30	Seizure	Convulsion
Phenytoin and phenobarbitol	200717933GDDC		Seizure	Drug Interaction

Seizure

The Sponsor identified 38 reports of convulsions in patients with prior history of seizure disorder, plus another 17 cases in subjects without an underlying seizure disorder. The Sponsor noted that causality of seizure reports with fexofenadine can be difficult to assess in subjects with a history of seizures, as the underlying disease can provide an explanation. In addition, recurrent seizure can result from sub-therapeutic levels of anticonvulsant medication, which may result from drug interactions between anticonvulsants and fexofenadine.

MO Comment *Although there is a literature report that carbamazepine lowers fexofenadine levels (Yamada et al. 2009), there does not appear to be any known interaction whereby fexofenadine affects levels of carbamazepine or any other anticonvulsant. The prescription labels of phenytion and carbamazepine, for example, do not list any interactions with fexofenadine, although chlorpheniramine increases risk of phenytoin toxicity.*

The seizure cases in Table 45 *with fexofenadine and an anticonvulsant do not have a clear explanation and are not associated with any particular anticonvulsant. There does not appear to be a clear signal of drug interaction.*

In the reports of convulsions in subjects with an underlying seizure disorder, there are cases where the subject was not on anticonvulsants or there was a history of many years without a seizure when the SAE occurred:

- *199910449HMRI, 50Y F after 3 days on fexofenadine, convulsion seizure free on no anticonvulsants for 25 yrs (but concomitant doxycycline)*
- *200011970HMR, 25 Y F convulsion after 180 mg one dose; seizure free for ~ 2 ½ yrs on no anticonvulsants.*

200020480US 11Y F Grand mal convulsion after 7 weeks on fexofenadine; seizure-free for several yrs on no anticonvulsants.

200115278US,22Y F convulsion after taking 180 mg once; seizure free for 12 yr on no medication.

Among the 17 seizure reports identified by the Sponsor where the subject had no prior history of seizure, there were five cases with a causality assessment of possible. Two examples are:

200011484HMRI, 28Y F had a seizure after one dose (60 mg) fexofenadine, concomitant ibuprofen and doxycycline.

200511160JP, 40Y M had a seizure 10 days after fexofenadine was replaced by loratadine, and after fexofenadine was taken in addition to loratadine because of lack of effect.

The review of the postmarket database did not find clear evidence of seizures caused by fexofenadine.

Somnolence

The Sponsor analyzed serious and non-serious spontaneous reports with somnolence and related terms. There were 751 such cases, of which 724 (96%) were nonserious.

Table 46 Reports of Somnolence and Related Adverse Events

Primary System Organ Class	Adverse Event Count (Case Count)		
Preferred Term	Serious	Non-Serious	Total
Total	30 (28)	753 (724)	783 (751)
Nervous system disorders	30 (28)	753 (724)	783 (751)
Depressed level of consciousness	4 (4)	7 (7)	11 (11)
Disturbance in attention	2 (2)	26 (25)	28 (27)
Hypersomnia	1 (1)	4 (4)	5 (5)
Lethargy	2 (2)	28 (28)	30 (30)
Sedation	3 (3)	22 (22)	25 (25)
Somnolence	17 (17)	665 (651)	682 (667)
Stupor	1 (1)	1 (1)	2 (2)

Note:
1. Adverse Events (cases) reported as diagnosis or symptom
2. Symptoms are represented with the seriousness of the diagnosis.
3. Since a case may contain both serious and non-serious events, the total number of cases may not equal the sum of the serious cases plus non-serious cases.

MO Comment. *Among the serious cases, there were four reports of somnolence with automobile accidents, and another report with a fall. As shown in* Table 35 *for the Nervous systems disorders SOC, the total numbers of AEs (cases) was 3607 AEs (2960 cases) of which somnolence and related terms accounted for 783 AEs (751 cases). In the controlled clinical trial database, somnolence was reported by 0.79% to 1.49% of subjects (total fexofenadine groups). Higher incidences of somnolence were reported in some dose groups (e.g., 2.45% in the 60 mg BID group,* Table 14*) but dose dependence was not consistently observed.*

It is acceptable for the label to claim "NONDROWSY" but consumers should be informed that a few percent of users can feel drowsy and should take care if driving or operating machinery.

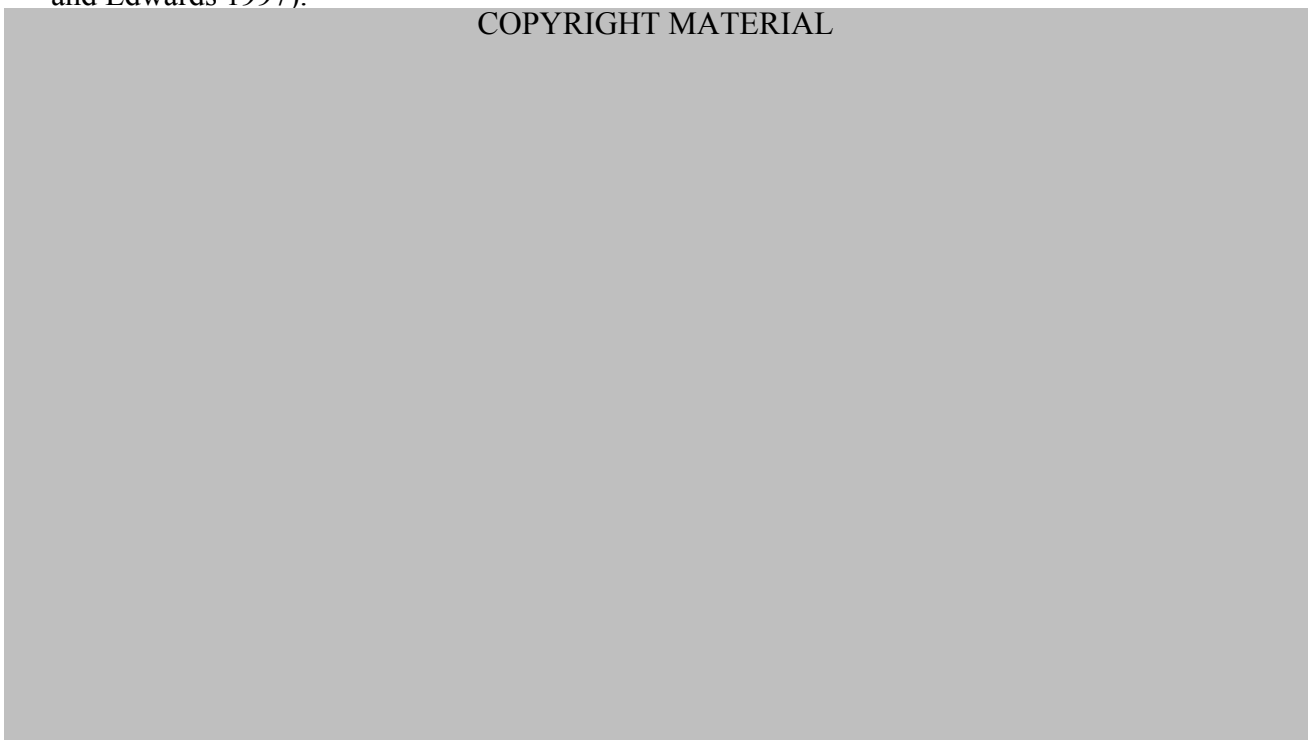
9 Appendices

9.1 Literature Review/References

Fexofenadine is a second generation, non-sedating antihistamine. It is the main active metabolite of terfenadine which is responsible for the latter drug's antihistaminic activity. Fexofenadine undergoes minimal systemic metabolism (about 5%) following oral administration. Following the oral administration of a dose of fexofenadine, 80% is recovered from the feces and 12% from urine. It does not cross the blood-brain barrier and is poorly lipid-soluble. It is a highly selective peripheral H_1-receptor antagonist. Fexofenadine is an effective antihistamine, which is largely free from the sedating and anticholinergic effects of the first generation antihistamines (Mason et al. 1999 Clin Exp Allergy).

Cardiac Events

Certain of the non-sedating antihistamines, like terfenadine and astemizole, have been linked with cardiac arrhythmias. Terfenadine is associated with QT prolongation, due to blockage of cardiac muscle potassium channels and impaired repolarization of heart muscle. This results in an increased risk of ventricular tachyarrhythmias, notably torsade de pointes (Figure 1, Lindquist and Edwards 1997).



Most cases of terfenadine cardiac toxicity involved subjects with predisposing cardiac disease or interactions with drugs (e.g., macrolide antibiotics, ketoconazole) that increased serum levels by inhibiting the hepatic CYP3A4-mediated metabolism of terfenadine (Taglialatela et al. 1999;

Paakari 2002). In addition, combined use of some blockers of hepatic CYP3A4, like erythromycin and ketoconazole, increase the plasma concentration of fexofenadine by a factor of 2 to 3 (Paakari 2002). This may be the result of inhibition of P-glycoprotein which increases bioavailability and decreases excretion of fexofenadine.

Since fexofenadine is not metabolized significantly by the cytochrome P450 system, and since it does not block the cardiac potassium current I_{Kr} (HERG), fexofenadine is not expected to have cytochrome P450 metabolic-based drug interactions or QT prolongation-associated cardiac arrhythmias (Ten Eick et al. 2002). In healthy volunteers at single doses of up to 800 mg QD and multiple doses up to 690mg BID for 28 days (above the OTC maximum dose of 180 mg), fexofenadine caused no significant prolongation of the QTc-interval (Pratt et al., 1999a and b). In controlled studies with about 6000 patients, no cases of torsade de pointes or increases in mean QTc were reported. In longer term studies, there were no statistically significant QTc increases in subjects taking fexofenadine 80 mg BID for 3 months, 60 mg BID for 6 months, of 240 mg QD for 12 months. In addition, when fexofenadine (120 mg bid) was combined with erythromycin (500 mg 4x daily; 18 subjects) or ketoconazole 400 mg qd; 23 subjects), no significant changes in the QT-interval were observed after 7 days (Pratt et al. 1999a and b).

Nevertheless, according to a case report fexofenadine has been associated with QT-prolongation and ventricular arrhythmia (Pinto et al. 1999). Pinto et al. described the case of a 67 year old man, who developed syncope and collapsed. His QTc was prolonged on admission and shortened when fexofenadine was discontinued. It increased again when fexofenadine was restarted, and polymorphic ventricular tachycardia or torsades de pointes developed which progressed to ventricular fibrillation. After cardioversion and discontinuation of fexofenadine a second time, QTc shortened but remained longer than normal even without fexofenadine. This individual had a pre-disposing condition, long QTc and left ventricular hypertrophy, in the absence of fexofenadine (this is case 199910471DDC in Table 40).

Serum from the patient in the Pinto et al. study was used in a follow-up study (Scherer et al. 2002) of the HERG channels and the sensitivity of the I_{Kr} currents to fexofenadine and terfenadine. This patient was found to have the variant HERG channel K897T which was insensitive to fexofenadine but was otherwise similar to the wild-type HERG channel. Scherer et al. concluded that the QT prolongation and cardiac arrhythmia susceptibility of this patient was not due to fexofenadine inhibition of cardiac potassium currents, but the arrhythmia susceptibility was not explained.

A post-marketing cohort study (Craig-McFeely et al. 2001) evaluated fexofenadine safety using prescription event monitoring from general practitioners in England. From 16638 questionnaires analyzed, there were 40 adverse event reports in 27 subjects. Less than 2% of patients stopped using the drug because of side effects. There were eight reports of cardiac events (palpitations, 3; chest pain, 3; arrhythmia, 1; chest tightness, 1). None was serious. None of 30 reported deaths was related to fexofenadine.

Ten Eick et al. (2001) reviewed AERS reports through July 2, 1999 to compare three nonsedating, second generation antihistamines: fexofenadine, loratadine, and cetirizine since release in the US. Results are summarized in Table 47, which gives the total numbers of reports

reviewed (duplicate case reports were removed), and the numbers (percents) of cases describing selected types of reaction.

Table 47 Distribution of AERS reports by selected reactions (Ten Eick et al. 2001)

	Fexofenadine	Loratadine	Cetirizine
Reports reviewed	547	1412	1338
Dysrhythmias	109 (19.9%)	164 (11.6%)	100 (7.6%)
Convulsions	17 (3.1%)	30 (2.1%)	34 (2.5%)

The reviewer performed a chi-square analysis of the data in Table 47 which shows that there was a significantly higher proportion (19.9%) of dysrhythmia reports for fexofenadine than for either loratadine (11.6%) or cetirizine (7.6%) (both pairwise comparisons, $p<0.0001$, chisquare). Dysrhythmias included atrial dysrhythmia, atrioventricular, bradycardia, nonspecific dysrhythmia, QT prolongation, tachycardia, ventricular dysrhythmias. However, the reporting rates of convulsions were similar for all three. The analysis of Table 47 includes less serious cardiac events as well as life-threatening events, and finds evidence of a signal associated with fexofenadine.

DRUG INTERACTION REPORTS IN THE LITERATURE

Ketoconazole is known to increase Cmax and AUC of fexofenadine (by 164% and 135%, respectively), but the interaction is not attributable to intestinal absorption of fexofenadine (Tannergren et al. 2003).

Itraconazole is a potent inhibitor of CYP3A activity in vitro and in vivo, and itraconazole coadministration with a CYP3A substrate can result in clinically significant drug interaction. Itraconazole is known to have inhibitory effect on fexofenadine clearance, so that AUC of fexofenadine is increased almost 3-fold. However, this interaction is not dose-dependent for itraconazole doses above 50 mg (Uno et al. 2006)

Coadministration with azithromycin led to fexofenadine Cmax increased by 69% and AUC increased by 67%. (Gupta et al. 2001)

Coadministration with rifampin led to significant increase of clearance of oral fexofenadine, with reduction by as much as 2-fold in Cmax or AUC. (Hamman et al. 2001)

Fexofenadine pharmacokinetic parameters were the same in cystic fibrosis patients and healthy volunteers when fexofenadine was administered with or without probenecid, although probenecid significantly increased fexofenadine AUC and decreased both urinary and total body clearance (Liu et al. 2008)

Verapamil significantly increased fexofenadine Cmax and AUC by 2.9-fold and 2.5-fold, respectively. Fexofenadine AUC was also increase by 50% with probenecid. Fexofenadine PK parameters were not affected by cimetidine. (Yasui-Furukori et al. 2005). Verapamil causes a stereo-selective increase in bioavailability of fexofenadine (Takashi et al. 2009).

Fexofenadine did not affect PK parameters of omeprazole or its two metabolites (Takahata et al. 2004)

Carbamazepine significantly decreases fexofenadine plasma concentrations, probably as a result of P-glycoprotein induction in the small intestine (Yamada et al. 2009).

Fexofenadine PK is not affected by metronidazole (Kim and Park 2010).

Single dose St. John's wort increased Cmax by 45% and reduced clearance of fexofenadine by 20%, but no fexofenadine PK changes were observed after two weeks administration. This contrasts with rifampin which reduces fexofenadine concentration by 50%. (Wang et al. 2002)

FOOD INTERACTION

Grapefruit juice reduces bioavailability of fexofenadine by reducing Cmax and AUC. Banfield et al. (2002) found a 30% reduction of fexofenadine Cmax and AUC with grapefruit juice. Dresser et al. (2005) showed that the reduction of bioavailable was more severe with larger volumes of grapefruit juice, up to 3-fold in AUC with 1.2 L grapefruit juice.

DROWSINESS

Change in reaction time from baseline with fexofenadine was not significantly different from placebo, but was significant for cetirizine (P=0.017) in a safety study (Tashiro et al. 2004). An earlier Positron Emission Tomography study (Tashiro et al. 2002) showed that during psychomotor testing, almost no H1 receptors in the cerebral cortex were occupied by fexofenadine while approximately 20% to 50% of H1 receptors were occupied by ceterizine ($p<0.01$).

In a safety study evaluating effects on cognition and psychomotor function, fexofenadine at all doses tested was not statistically different from placebo in any of the tests, and loratadine did not cause any significant impairment of cognitive function (Hindmarch et a. 1999). Fexofenadine was not distinguishable from placebo in cognitive function tests for up to 7 seven hours after dosing, although a significant impairment was seen for promethazine (Hindmarch et al. 2002).

There were no differences between fexofenadine and placebo in a battery of cognitive function tests pertinent to aircraft piloting (digit symbol substitution task, vigilance task and tracking task), whereas promethazine impaired performance and increased objective sleepiness and subjective sleepiness. (Nicholson et al. 2000). In a comparison between fexofenadine and diphenhydramine, subjects with fexofenadine performed better on measures of omission and commission errors and on variable symbol digit coding delayed recall accuracy; they also reported less drowsiness (Bower et al. 2003). Vacchiano et al. (2008) found that fexofenadine was comparable to placebo in effects on ploting skills, while cetirizine may affect piloting ability.

In tests of psychomotor performance relevant to driving, subjects performed better in a driving simulator with fexofenadine or with alcohol than with diphenhydramine. Lane keeping was impaired with both alcohol and diphenhydramine compared with fexofenadine (Weiler et al. 2000). Vermeeren et al. (2005) also found that fexofenadine did not impair driving performance. Brake reaction time with and without cellular phone usage in fexofenadine-treated subjects did

not differ significantly from placebo, but hydroxyzine-treated subjects were significantly more sedated than those administered fexofenadine (Tashiro et al. 2005).

MO Comment *The review of literature did not reveal any new or unexpected safety issues.*

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9.2 Labeling Recommendations

The following language is recommended for the OTC label:

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

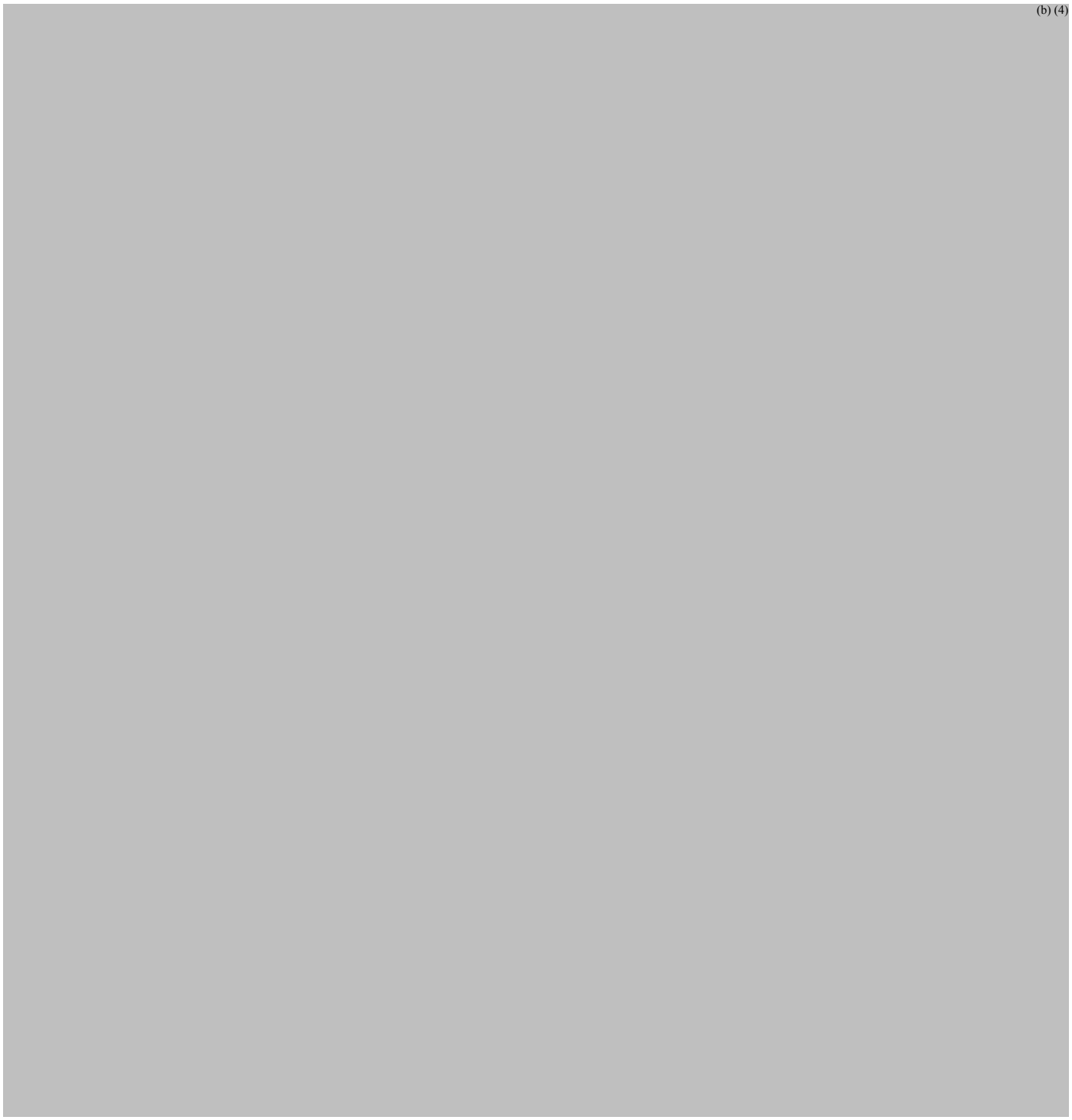
- you have or ever had heart disease, since this kind of medicine may lead to a fast or irregular heart beat
- you are taking certain antibiotics (erythromycin, azithromycin, or clarithromycin)
- you have kidney disease or if you are over 65 years old; your doctor should determine if you need a different dose.

When using this product

- do not take with fruit juice or at the same time as aluminum or magnesium antacids.

The word "NONDROWSY*"can be used on the label with a qualification, that although the medicine is unlikely to affect the ability to drive or operate machinery, a few people may be impaired and care should be taken.

7 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page



9.3 Advisory Committee Meeting

Not applicable

9.4 WHO Causality Assessment System

Causality term	*Assessment criteria**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

* All points should be reasonably complied with

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

/s/

LINDA S HU
12/02/2010

DAIVA SHETTY
12/02/2010

I concur with Dr. Hu¿s recommendation for approval of this NDA. I do not agree with some her labeling recommendations. See my CDTL review which addresses differences in our opinions.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201-613, 201-373, 21-909
Priority or Standard	Standard
Submit Date(s)	March 25, 2010
Received Date(s)	March 25, 2010
PDUFA Goal Date	January 25, 2011
Division / Office	DPARP
Reviewer Name(s)	Anya C. Harry M.D., Ph.D.
Review Completion Date	November 24, 2010
Established Name	Fexofenadine HCl
(Proposed) Trade Name	Pending
Therapeutic Class	Antihistamine
Applicant	Sanofi-Aventis US Inc.
Formulation(s)	Film coated tablets, immediate release oral suspension and immediate release oral disintegrating tablets
Dosing Regimen	30, 60, 180 mg fexofenadine HCl 30 mg oral disintegrating tablet, 6mg/ml oral suspension
Indication(s)	Symptoms of hay fever or other upper respiratory allergies, reduction of hives and relief of itching due to hives
Intended Population(s)	The tablet and oral disintegrating tablet formulations for allergic rhinitis and itching due to hives in adults and children ≥6; The oral suspension for allergic rhinitis in children ≥2 and for itching due to hives in adults and children ≥6

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended action is **approval** for NDA 201-613 S001 and sNDA 21-909 S003, which were combined submissions from Sanofi-Aventis for the proposed prescription to over-the-counter (OTC) switch of the monoproducts, Allegra® tablets (fexofenadine HCl 30, 60 and 180 mg) and Allegra® orally disintegrating tablets (30 mg). The recommended action is **approval** for NDA 201-373 S001, the partial switch of Allegra® oral suspension 6 mg/ml. Fexofenadine HCl (referred to as fexofenadine hereafter) oral suspension for pediatric patients younger than 6 years of age with CIU will remain as prescription use under NDA 21-963. These products were approved under Section 505(b) of the FD&C Act. 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 3) the relief of itching due to hives. The targeted population and dose are dependent on the specific formulation. The use of the tablet and orally disintegrating tablet (ODT) formulations in the treatment of symptoms of allergic rhinitis and itching due to hives will be in adults and children ≥ 6. The use of the oral suspension for the treatment of allergic rhinitis will be in adults and children ≥2 however, the indication for treatment of itching due to hives, will be for adults and children ≥6 years of age, hence the reason for the partial switch for the suspension formulation.
The meeting of the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products held on May 11, 2001 concluded that fexofenadine demonstrated a risk/benefit profile suitable for an OTC antihistamine. No new clinical trials were required to support the application due to the extensive pre-approval and subsequent post-approval database for fexofenadine. The Sponsor submitted 4 studies performed on patients with Perrenial Allergic Rhinitis (PAR), two pivotal and two supportive for the use of the term 'indoor and outdoor allergies' on the sell copy. In support of the fexofenadine monoproduct applications, Sanofi-Aventis references the efficacy and safety data previously reviewed in the original NDAs that supported initial approval of Allegra® Tablet, Allegra® Oral Disintegrating Tablets (ODT) and Allegra® Oral Suspension as well as post-marketing safety data. The referenced studies provide adequate support of the efficacy and safety of the proposed partial OTC switch.

1.2 Risk Benefit Assessment

The four PAR efficacy trials submitted to support the use of indoor and outdoor allergies in the sell copy were reviewed. The results of these data did not alter the favorable risk benefit profile of the fexofenadine monoproduct for OTC switch.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements and commitments are recommended at the time of this review.

2 Introduction and Regulatory Background

The public health burden of allergic rhinitis is reflected by high prevalence rates of 10-30 percent in adults and up to 40 percent in children (Long A, McFadden C, et al., Agency for Healthcare Research and Quality 2002 Evidence Reports/Technology Assessments, No. 54). The major modalities for therapy

include allergen avoidance, anti-allergic medication and immunotherapy. Amongst the anti-allergic medications, antihistamines are the most frequently prescribed for symptomatic relief of allergic rhinitis. Many of the currently available OTC products in the US have as their main drawback the tendency to cause sedation. These include some monograph products: brompheniramine, chlorpheniramine, diphenhydramine and doxylamine. The adverse central nervous system effects such as sedation from antihistamines negatively influences quality of life and is therefore a significant public health concern. California Blue Cross submitted a Citizen's Petition requesting OTC status for "non-sedating" (second generation) antihistamines, including loratadine, fexofenadine and cetirizine in 1998. In response, loratadine has been approved for OTC status [Claritin® NDA 19-658] and cetirizine has been approved for partial OTC status [Zyrtec®, Zyrtec-D® NDA 22-155 N000, 21-621 S-005, 19-835 S-022, 21-150 S-007].

Allegra was first approved for marketing in the US on 7/25/96 [NDA 20-625] as a capsule formulation (no longer available) at the dose of 60 mg BID for the treatment of symptoms of SAR in adults and adolescents ≥12 years of age. A lactose-free tablet of fexofenadine was developed as an alternative to the 60 mg capsule formulation containing the same dose and on 2/27/00 [NDA 20-872], the monoproduct was approved as a tablet formulation for doses of 30 mg BID, 60 mg BID, and 180 mg once daily (QD). The monoproduct 60 mg BID and 180 mg QD formulations were approved for the relief of symptoms associated with SAR in adults and children 12 years and older. The monoproduct 60 mg BID formulation was also approved for the relief of symptoms of chronic idiopathic urticaria (CIU) in adults and children 12 years and older. The monoproduct 30 mg BID formulation was approved for the treatment of SAR and CIU in children 6 to 11 years of age. On 10/13/05 the fexofenadine 180 mg tablet was approved as a QD treatment of symptoms of CIU in adults and adolescents ≥12 years of age [NDA 20-872 S-015]. For ease of administration in children, an oral suspension of fexofenadine 6 mg/ml was approved on 10/16/06 for the treatment of SAR and CIU in children 2 to 11 years of age and for the treatment of CIU in children 6 months to younger than 2 years of age [NDA21-963]. The suspension was to be administered at a dose of 30 mg BID and 15 mg BID to the respective age groups. On 7/26/07, under NDA 21-909, an orally disintegrating 30 mg tablet of fexofenadine was approved for the treatment of SAR and CIU in children 6 to 11 years of age. The original NDAs are listed as follows:

- 20-625 (Allegra Capsules)
- 20-872 (Allegra Tablets)
- 21-704 (Allegra-D 24 Hour)
- 20-786 (Allegra-D 12 Hour)
- 21-963 (Allegra Suspension)
- 21-909 (Allegra ODT)

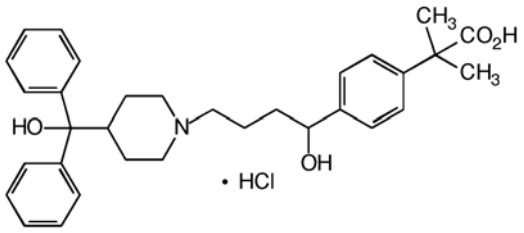
Refer to Table 1 for a summary of the available doses of Allegra ® for the SAR and CIU indications with relevant approval details.

Table 1 Fexofenadine available doses, formulation and source of efficacy data

Age for Indication	SAR	NDA, Approval Date	CIU	NDA, Approval Date
≥12	60 mg BID	20-625,7/25/96 20-872, 2/25/00	60 mg BID	20-625,7/25/96 20-872, 2/25/00
	180 mg QD	20-625,7/25/96 20-872, 2/25/00	180 mg QD	20-872 S015, 10/13/05
6-11	30 mg BID	20-782, 2/25/00	30 mg BID	20-782, 2/25/00
	30 mg BID ODT	sNDA21-909 7/26/07	30 mg BID ODT	sNDA21-909 7/26/07
2-<6	30 mg oral suspension BID	21-963, 10/16/06	30 mg oral suspension BID	21-963, 10/16/06
6 months-<2	N/A	N/A	15 mg oral suspension BID	21-963, 10/16/06

2.1 Product Information

Fexofenadine HCl (subsequently referred to as fexofenadine) is a pharmacologically active metabolite of terfenadine and as such is a selective peripheral H1-receptor antagonist. The chemical name (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-a,a-dimethyl benzeneacetic acid hydrochloride. molecular weight is 538.13 and the empirical formula is C32H39NO4•HCl. The proposed trade name for the OTC monoproducts of Allegra is still pending at the time of this review. The chemical structure is depicted below:



The indication, dosage and target population are as follows:
Seasonal Allergic Rhinitis: Allegra® is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively include sneezing; rhinorrhea; itchy nose, palate, throat; itchy, watery, red eyes. Adults and children 12 years and older: the recommended dose of Allegra® is 60 mg twice daily, or 180 mg once daily. Children 6 to 11 years: the recommended dose of Allegra® is 30 mg twice daily. Young children 2 to 5 years: the recommended dose is 30 mg twice daily
Chronic Idiopathic Urticaria: Allegra® is indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. It significantly reduces pruritis and the number of wheals**.** Adults and children 12 years and older: the recommended dose of Allegra® is 60 mg twice daily or 180 mg once daily. Children 6 to 11 years: the recommended dose of Allegra® is 30 mg twice daily. Young children 2 to 5 years of age: the recommended dose of Allegra® is 30 mg twice daily. Infants 6 months to <2 years of age: the recommended dose of Allegra® is 15 mg of the oral suspension twice daily.

2.2 Currently Available Treatments for Proposed Indications

While suppression of allergic inflammation is effectively carried out by both intranasal corticosteroids and immunotherapy to specific allergens, the standard modalities to treat the symptoms include: allergen avoidance, oral and intranasal antihistamines, decongestants, and intranasally applied anticholinergic agents. Several antihistamines are currently marketed as OTC monograph drugs in the US, including first-generation agents such as brompheniramine, chlorpheniramine, diphenhydramine and doxylamine. These products are indicated for the temporary relief of symptoms of “hay fever or other upper respiratory allergies” [21 CFR 341.12]. As first-generation antihistamines they are effective in symptom relief; however, they are characteristically limiting due to sedation as an adverse effect. There are also antihistamines marketed OTC in the US that were initially approved as NDA products, such as clemastine, and the second-generation antihistamines; loratadine, loratadine/PSE, cetirizine and cetirizine/PSE. These typically have limited penetration of the CNS and are therefore associated with less or minimal sedation. There are many antihistamines still available only by prescription in the US, including hydroxyzine, cyproheptadine, fexofenadine, and desloratadine.

2.3 Availability of Proposed Active Ingredient in the United States

The mono-products are approved and available with a prescription in approximately 85 countries for over 10 years. They have been approved and available without a prescription in 12 countries for over 10 years.

Fexofenadine HCl is also approved in the US as a generic drug in tablet formulations by various manufacturers (ANDA 76-191, Barr Laboratories, ANDA 76-502, Dr. Reddy's Laboratories, and ANDA 76-447, Teva Pharmaceutical Industries).
Based upon International Marketing Services estimates from July 1997 (first available data in International Marketing Services) through June 2009, approximately (b) (4) of fexofenadine have been sold, translating into an estimated patient exposure of 32.05 million patient-years.

2.4 Important Safety Issues With Consideration to Related Drugs

As noted above, both first and second generation antihistamines can cause sedation due to their lipophilic qualities enabling crossover of the blood brain barrier as well as dry mouth, urinary retention and reduced bronchial secretions due to the anticholinergic properties. The second generation agents were developed primarily to limit the adverse effect of sedation. Two less sedating antihistamines previously approved in the US, terfenadine and astemizole, were withdrawn from the market due to their association with fatal cardiac arrhythmias. These drugs prolonged the QTc interval and were associated with torsades de pointes. The second generation antihistamines currently available on the market: loratadine, desloratadine, fexofenadine (a metabolite of terfenadine), and cetirizine do not appear to cause significant QT prolongation and have not been associated with similar cardiac events. A consult to the QT group in the Cardio-renal division was requested by the DNCE reviewer. The QT group initially recommended the need for a through QT study to rule out small changes (< 10msecs) in QT. However, this recommendation was revisited following discussion with the office (Dr Bob Temple), both review divisions (DNCE, DPARP), and ONP and ODE office directors. The QT group re-evaluated the existing data and concluded that *"the non-clinical data and clinical information from the literature, the clinical trail data and the post-marketing experience when considered in total provides reasonable re-assurance that pro-arrhythmic liability for fexofenadine is negligible and a thorough QT assessment is not required for fexofenadine."* (*DCRP consult addendum*)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On December 14, 2009, a pre-IND meeting was held with Sanofi-Aventis, to discuss the planned Rx-to-OTC switch submission strategy for both the monoproduct, fexofenadine as well as the twice daily and once daily fixed dose combination fexofenadine/PSE products. Major points addressed during the meeting included:

- Exemption from any pediatric studies under PREA
- Concern that some consumers may mistakenly take 180 mg of fexofenadine BID. Based on this concern, the Sponsor was requested to evaluate safety data greater than 360 mg fexofenadine and compare safety profiles for greater than or equal to 360 mg and 180 mg.
- The overall format of the monoproduct and combination product submissions which were to include two separate integrated summaries of efficacy as well as two separate integrated summaries of safety
- Organization of the safety data and the global integrated database (GIDB)
- The need for consistency between the prescription and proposed drug facts labels.
- Acceptance from the Agency of the plan to submit 4 PAR studies as support for a sell copy claim (i.e., "indoor and outdoor allergies") on the principal display panel

Further contacts with the Agency concerned the electronic format of the proposed datasets as well as the required user fees.
The Applicant met with the Division of Pulmonary and Allergy Products in May 5, 2003 to discuss four Phase 3 studies (PJPR0057, M016455M/3097, M016455M/3001, and M016455M/3002, evaluating the efficacy of different doses of fexofenadine in adult patients with perennial allergic rhinitis (PAR). The Division indicated that based on their review of the pre-NDA meeting briefing package, the Applicant may have sufficient data to support the efficacy of fexofenadine 60 mg BID and 180 mg QD in patients aged

12 years and older with PAR. Fexofenadine 60 mg BID is approved for PAR in Canada and Australia. A dose response must be demonstrated to support a higher dose. It was recommended that the results of the 4 trials should be presented side by side and not pooled together.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The significant changes made to the tablet formulation were new packaging configurations for the HDPE bottle and the (b) (4) foil lid to provide the child-resistant functionality to the blister packages, otherwise there were no new changes to the previously approved CMC. The oral suspension formulation also incorporated a new bottle size as well as the inclusion of a dosing cup as an administrative device. And for the ODT formulation, there were no changes to previously approved CMC information.

4.3 Preclinical Pharmacology/Toxicology

As the monoproduct of Allegra®, fexofenadine HCl [NDAs 20-625 and 20-872] are already approved drugs with the pharmacology and toxicology well known, preclinical data was not required for approval of the OTC switch for the monoproduct.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were submitted with this application.

6 Review of Efficacy

Efficacy Summary

The application for change of status from prescription to nonprescription use of the Allegra® monoproducts: tablets (fexofenadine HCl 30, 60 and 180 mg); orally disintegrating tablets (ODT, 30 mg) and the partial switch of the oral suspension (6 mg/ml) formulation has been submitted under Section 505(b) of the FD&C Act. The fexofenadine oral suspension for pediatric patients younger than 6 years of age with CIU will remain as prescription use under NDA 21-963. The regulation permits an approval of such a switch to be based upon the Agency's previous findings of safety and efficacy for the drug(s). The Sponsor must provide adequate support for the use of the product in the OTC setting. The Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products in 2001 concluded that the second generation antihistamines, which include fexofenadine, demonstrate a risk/benefit profile suitable for an OTC antihistamine. The clinical efficacy of fexofenadine in all three formulations: tablet, oral suspension and ODT in the treatment of SAR and CIU has been established in the referenced NDAs 20-625 (Allegra® Capsules, no longer marketed) and 20-872 (Allegra® Tablets). Because of the extensive pre-approval and post-approval database for Allegra®, no new clinical trials were required to support this application for the indication of relief of symptoms associated with SAR and CIU. In addition, the Sponsor also submitted the results of 4 Phase 3 perennial allergic rhinitis (PAR) studies conducted previously but not submitted with the earlier NDAs. Furthermore, 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 display panel. These studies include two trials that studied the approved doses and two trials that studied doses higher than the approved ones. The efficacy data

submitted from the referenced NDAs as well as the 4 PAR Phase 3 studies support the partial OTC switch of the Allegra® monoproducts.

1. Summary of Efficacy for Prescription NDA

1.1. Indication: SAR and CIU 30, 60, 180 mg tablet

The data in support of approval of Allegra®, fexofenadine 30, 60, 180 mg relies on the efficacy data previously submitted to the approved prescription NDAs [NDA 20-625, 20-872]. There were 9 trials conducted: 4 were pivotal trials PJPR0009, PJPR0010, PJPR0023, and PJPR0024 included in NDA 20-625 in support of fexofenadine 60 mg BID in adults with SAR. As well, 5 were pivotal in NDA 20-872, M016455B/3081, PJPR0066/77, PJPR0039, PJPR0067 and M016455A/4121 presented in support of fexofenadine 30 mg BID in patients with SAR and CIU (pediatric dose), 60 mg BID in CIU, and 180 mg QD in SAR and CIU. The findings of these studies were reviewed. See Table 2 for details of the 9 adequate and well controlled pivotal trials previously reviewed, a summary of each will follow.

Table 2 Adequate and well-controlled studies supporting fexofenadine tablets-seasonal allergic rhinitis and chronic idiopathic urticaria

Indication	Study	Doses evaluated	Study population	NDA
SAR 60 mg BID	PJPR0009	20, 40, 60, 80 mg BID	Subjects 12–65 years, SAR	20-625, S8-V1.185-P12
	PJPR0010	20, 40, 60, 80 mg BID	Subjects 12–65 years, SAR	20-625, S8-V1.202-P1
	PJPR0023	60, 120, 240 mg BID	Subjects 12–65 years, SAR	20-625, S8-V1.219-P1
	PJPR0024	40, 60, 120 mg BID	Subjects 12–65 years, SAR	20-625, S8-V1.239-P1
SAR 180 mg QD	M016455B/3081	120, 180 mg QD	Subjects 12–65 years, SAR	20-872, S8-V1.64-P20
SAR/CIU 30 mg BID	PJPR0066/77	15, 30, 60 mg BID	Subjects 6–11 years, SAR	20-872, S8-V1.225-P2
CIU 60 mg BID	PJPR0039	20, 60, 120, 240 mg BID	Subjects 12–65 years, CIU	20-872, S8-V1.170-P1
	PJPR0067	20, 60, 120, 240 mg BID	Subjects 12–65 years, CIU	20-872, S8-V1.189-P1
CIU 180 mg QD	M016455A/4121	180 mg QD	Subjects 12 and older, CIU	20-872; S-015 clinstat

BID = twice daily; CIU = chronic idiopathic urticaria; QD = once daily; SAR = seasonal allergic rhinitis;

Source: Table 1 Integrated Summary of Efficacy NDA 201-613

PJPR0009, PJPR0010, PJPR0023, and PJPR0024

These 4 trials were adequate and well-controlled evaluating the efficacy and safety in patients with SAR. Over a double-blind 2 week period the Sponsor compared serial doses of 20, 40, 60, 80, 120 and 240 mg fexofenadine vs. placebo in multicenter, randomized, double-blind, placebo-controlled, dose-response trials. PJPR0009 and PJPR0010 were conducted in the spring where as PJPR0023 and PJPR0024, in the fall. In Studies PJPR0009 and PJPR0010, the physician's assessment of symptoms at the entry visit was used to qualify patients and subsequently, they were randomized and entered a 2-day single-blind placebo lead-in period followed by a 14-day double-blind treatment period. The placebo lead-in period was used to establish baseline scores for the patient's symptom assessment for the analyses of efficacy. In Studies PJPR0023 and PJPR0024, a 3-day single-blind placebo lead-in period was used to qualify patients based on their own assessments of symptom severity prior to randomization. In Studies PJPR0009 and PJPR0010, the primary efficacy endpoint was based on an ITT analysis of the change from baseline in the average 12-hour reflective total symptom score (rTSS) performed at bedtime (1 to 3 hours following the evening dose) while in Studies PJPR0023 and PJPR0024, the primary efficacy endpoint was also based on an ITT analysis of the change from baseline in the average 12-hour rTSS performed immediately prior to the evening dose (7:00 PM). Baseline was defined as the average of the scores recorded during the placebo lead-in period. The post baseline average TSS was calculated using the average of the scores recorded during the 2-week treatment period. If patients discontinued early, then all available scores were used to calculate this average. Patients used the same scoring methods to assess their symptom severity in the 4 SAR trials described in Table 3. Each of 5 symptoms was

assessed as absent to very severe in severity. The TSS was calculated as the sum of all symptom scores excluding nasal congestion and ranged from 0 to 16.

Table 3 Symptoms evaluated for efficacy in Studies PJPR0009, PJPR0010, PJPR0023, and PJPR0024

Symptom	Scale/description of score
1. Sneezing	0 - Absent - symptom not present.
2. Rhinorrhea	1 - Mild - symptom is present but is not annoying or troublesome/bothersome.
3. Itchy nose, palate, and/or throat	2 - Moderate - symptom is frequently troublesome/bothersome, but does not interfere with either normal daily activity or sleep.
4. Itchy, watery, red eyes	3 - Severe - symptom is sufficiently troublesome/bothersome to interfere with normal daily activity or sleep.
5. Nasal congestion	4 - Very severe - symptom is so severe as to warrant an immediate visit to the physician.

Source: Table 14, Integrated Summary of Efficacy NDA 201-613

A total of 182 (5.7%) of the safety evaluable patients in Studies PJPR0009, PJPR0010, PJPR0023, and PJPR0024 discontinued before completion of the study. The most common reasons for early discontinuation were “adverse event” and “subject elected to discontinue.” The percentages of patients discontinuing were similar between patients who received fexofenadine and placebo. There was no dose-related trend in the percentage of patients who discontinued. All baseline demographic characteristics were similar across the 4 pivotal trials. The results of these trials demonstrate the statistical significance of the 60 mg BID dose in reducing the mean PM rTSS. These 4 trials submitted for the original NDA support the efficacy for the OTC switch of fexofenadine 60 mg BID in the treatment of SAR. See Table 4 for summary of the results.

Table 4 Primary efficacy results in pivotal controlled studies, seasonal allergic rhinitis, twice-daily dosing

Treatment	PJPR0009	PJPR0010	PJPR0023	PJPR0024
	Number of subjects			
Placebo	190	198	141	137
Fexofenadine 20 mg	194	197	NA	NA
Fexofenadine 40 mg	195	201	NA	135
Fexofenadine 60 mg	191	203	141	138
Fexofenadine 80 mg	192	196	NA	NA
Fexofenadine 120 mg	NA	NA	144	135
Fexofenadine 240 mg	NA	NA	144	NA
	Change from baseline (mean ± SE)			
Placebo	-0.66 ± 0.14	-0.85 ± 0.14	-1.56 ± 0.20	-1.21 ± 0.18
Fexofenadine 20 mg	-1.03 ± 0.13	-1.26 ± 0.14	NA	NA
Fexofenadine 40 mg	-1.46 ± 0.13	-1.44 ± 0.14	NA	-1.86 ± 0.18
Fexofenadine 60 mg	-0.98 ± 0.14	-1.58 ± 0.14	-2.64 ± 0.20	-1.86 ± 0.18
Fexofenadine 80 mg	-1.32 ± 0.13	-1.36 ± 0.14	NA	NA
Fexofenadine 120 mg	NA	NA	-2.41 ± 0.20	-2.11 ± 0.18
Fexofenadine 240 mg	NA	NA	-2.58 ± 0.20	NA
	Treatment difference versus placebo (mean ± SE)			
Fexofenadine 20 mg	-0.37 ± 0.19	-0.40 ± 0.20	NA	NA
p-value	.0515	.0415		
Fexofenadine 40 mg	-0.80 ± 0.19	-0.58 ± 0.20	NA	-0.65 ± 0.25
p-value	.0001	.0030		0.0087
Fexofenadine 60 mg	-0.32 ± 0.19	-0.73 ± 0.20	-1.07 ± 0.28	-0.66 ± 0.24
p-value	.0907	.0002	.0001	.0075
Fexofenadine 80 mg	-0.66 ± 0.19	-0.51 ± 0.20	NA	NA
p-value	.0005	.0095		
Fexofenadine 120 mg	NA	NA	-0.85 ± 0.28	-0.91 ± 0.25
p-value			.0026	.0002
Fexofenadine 240 mg	NA	NA	-1.02 ± 0.28	NA
p-value			.0003	

Analyses were conducted in the ITT populations.
For PJPR0010, p-values, means, and associated standard errors (SE) from an ANCOVA model containing investigative site, baseline, treatment, treatment by baseline interaction, and treatment by site interaction. For other studies, p-values, means, and associated SEs from an ANCOVA model containing investigative site, treatment, and baseline.
NA=Not applicable.
Source: NDA 20-625, Table 8-479, S8-V1.261-P36, Table 8-480, S8-V1.261-P37, Table 8-481, S8-V1.261-P39, Table 8-482, S8-V1.261-P40,
PJPR0009, Report K-94-0780-CDS, NDA 20-625, Table 8-257, S8-V1.185-P76
PJPR0010, Report K-94-0782-CDS, NDA 20-625, Table 8-307, S8-V1.202-P66
PJPR0023, Report K-95-0005-CDS, NDA 20-625, Table 8-360, S8-V1.219-P72
PJPR0024, Report K-95-0007-CDS, NDA 20-625, Table 8-413, S8-V1.239-P74

To support the other two doses (30 mg BID and 180 mg QD) in the treatment of SAR and CIU as well as the 60 mg BID dose in the treatment of CIU, data from 5 adequate and well controlled pivotal studies included in NDA 20-872 were reviewed.

M016455B/3081

This trial was a double-blind, randomized, parallel, placebo-controlled study comparing the efficacy and safety of fexofenadine 120 mg QD, fexofenadine 180 mg QD, and placebo in the treatment of patients 12 to 65 years of age with SAR in the autumn. The primary efficacy measure was an ITT analysis of the change from baseline in the 8:00 AM instantaneous TSS (iTSS) over the 2-week double-blind treatment period. Results of this analysis show a significant improvement in symptoms with the fexofenadine 180 mg dose than with the fexofenadine 120 mg dose. The treatment difference in the AM iTSS was -0.49 ± 0.16 with a p value=0.0016.

PJPR0066 and PJPR0077

NDA 20-872 included 1 combined pivotal controlled trial, PJPR0066/77, in support of a BID dosing regimen of fexofenadine in pediatric patients 6 to 11 years of age. Study PJPR0066/77 represents the pooled data from 2 identical trials which evaluated multiple BID doses. Sample size targets were not met in either of these trials, and when the trials were concluded, the number of patients in each was insufficient to detect differences between individual fexofenadine doses as specified in the analysis plans. The Sponsor performed a pooled analysis from the combined data of these identical trials and this

provided a sufficient number of patients to achieve the required statistical power. Therefore, prior to closing the studies, the Sponsor proposed that the primary and secondary efficacy data be analyzed using the pooled datasets from these 2 trials. The FDA agreed with this approach, but requested that the primary efficacy analysis was additionally completed separately for each trial. These two trials assessed the efficacy of 15, 30, and 60 mg of fexofenadine BID compared to placebo. The pooled analysis of the results demonstrated that the efficacy of fexofenadine 30 mg in pediatric patients was not statistically significant in the combined Studies PJPR0066/77. The 30 mg BID dose was approved in the US based on the Agencies' review of the clinical data of the combined Studies PJPR0066 and PJPR0077, as well as the separate studies, and the extrapolation of efficacy for the pediatric population based on the Pediatric Rule under the supposition that the pathophysiology of SAR is similar in adults and children. As well, comparable plasma levels of fexofenadine to those of adults have been shown in children 7 to 12 years of age (Study PJPR0037) treated with a single dose of fexofenadine 30 mg.

Reviewer's Comment:
Of note, following the approval of fexofenadine 30 mg BID for the treatment of pediatric patients 6 to 11 years of age with SAR based on combined Studies PJPR0066/77 and extrapolation of data, the Sponsor conducted another trial in pediatric patients 6 to 11 years of age comparing the efficacy and safety of fexofenadine 30 mg BID in SAR for submissions in Europe. The supportive trial M016455C/3212 was included and the data was summarized in NDA 201-373 and sNDA 21-909. The primary efficacy endpoint in Study M016455C/3212 was the same as in PJPR0066/77: the change from baseline in average 7:00 PM (19:00 hours) reflective 12-hour TSS over the double-blind period. The trial demonstrated that fexofenadine 30 mg BID had a statistically significant LS mean difference of 0.73 vs. placebo in the primary efficacy analysis (p value=0.0001) for the change from baseline in mean TSS at 7:00 PM for the ITT population.

PJPR0039 and PJPR0067
NDA 20-872 included these 2 controlled trials in support of a BID dosing of fexofenadine for the treatment of Chronic Idiopathic Urticaria (CIU). The design of the 2 Studies PJPR0039 and PJPR0067 was identical. They were both multicenter, randomized, double-blind, placebo-controlled, dose-response studies in patients with CIU. The fexofenadine doses evaluated were 20, 60, 120, and 240 mg BID for 4 weeks. To be eligible, patients had to have a TSS of 3 or more based on the sum of the scoring for pruritis (itching) and wheals (hives) in Table 5:

- Number of wheals in the previous 12 hours were to have been ≥1
- Number of wheals had to be confirmed by the Investigator
- The score for pruritis (itching) had to be ≥2

Table 5 Symptoms evaluated for efficacy in chronic idiopathic urticaria

Symptom	Scale/description of score
Pruritus (Itching)	0 - None (no itching present)
	1 - Mild (minor irritation; hardly noticeable; not annoying or troublesome)
	2 - Moderate (annoying and troublesome; may have interfered somewhat with normal daily activity and/or sleep)
	3 - Severe (very annoying and troublesome; substantially interfered with normal daily activity and/or sleep)
	4 - Very severe (warranted a visit to the physician)
Number of wheals (hives)	0 - None
	1 - 1 to 5 wheals (hives)
	2 - 6 to 15 wheals (hives)
	3 - 16 to 25 wheals (hives)
	4 - >25 wheals (hives)

Source: Table 66 in Integrated Summary of Efficacy, NDA 201-613

Efficacy of fexofenadine in treatment of CIU was evaluated on the basis of the daily symptom scoring by the patients, and evaluations by investigators at office visits, throughout the trial. Pruritis was assessed using the symptom scale described previously (Table 5) twice a day, immediately prior to the morning (approximately 7:00 AM) and evening (approximately 7:00 PM) doses of study medication. The score was to be based on the severity of pruritis over the preceding 12-hour period. A daily Mean Pruritis Score (MPS) was calculated as the mean of the 2 pruritis scores for each study day. Scores on the day following Visit 1 or 1A (i.e., the symptom assessments covering the 24 hours before the first dose of double-blind study medication) served as a baseline. The primary measure of efficacy was the mean change from baseline in MPS over the 4-week treatment period. Primary efficacy analyses were based on the ITT populations. In Study PJPR0039, 93.1% (418 of 449) of exposed patients were included in the ITT population. In Study PJPR0067, 95.2% (439 of 461) of exposed patients were included in the ITT population. Based on the randomized populations, 29.1% (136 of 468) of the patients from Study PJPR0039 and 21.6% (103 of 476) of the patients from Study PJPR0067 discontinued treatment before completion of the trial. The most frequent reason for early discontinuation was “treatment failure” in both studies, followed by “other reason” and “adverse event.” In both trials, treatment with fexofenadine led to improvement in itching compared to treatment with placebo outlined in Table 6. In each of the trials, there was a greater decrease in MPS for the fexofenadine 60 mg BID group than for the fexofenadine 20 mg BID group. Doses above 60 mg BID produced little or no additional average improvement beyond that observed in the 60 mg BID group.

Table 6 Primary efficacy results (Mean Pruritis Score) in pivotal controlled Studies PJPR0039 and PJPR0067 in chronic idiopathic urticaria

Treatment (BID)	PJPR0039	PJPR0067
	Number of subjects	
Placebo	79	90
Fexofenadine 20 mg	90	91
Fexofenadine 60 mg	90	86
Fexofenadine 120 mg	77	89
Fexofenadine 240 mg	82	83
	Change from baseline (mean ± SE)	
Placebo	-0.40 ± 0.082	-0.47 ± 0.068
Fexofenadine 20 mg	-0.68 ± 0.076	-0.88 ± 0.068
Fexofenadine 60 mg	-1.00 ± 0.075	-1.07 ± 0.070
Fexofenadine 120 mg	-0.84 ± 0.081	-1.07 ± 0.069
Fexofenadine 240 mg	-1.08 ± 0.079	-1.18 ± 0.071
	Treatment difference versus placebo (mean ± SE)	
Fexofenadine 20 mg	-0.286 ± 0.1101	-0.407 ± 0.0954
p-value	.0098	.0001
Fexofenadine 60 mg	-0.601 ± 0.1100	-0.596 ± 0.0971
p-value	.0001	.0001
Fexofenadine 120 mg	-0.441 ± 0.1141	-0.595 ± 0.0956
p-value	.0001	.0001
Fexofenadine 240 mg	-0.684 ± 0.1123	-0.709 ± 0.0975
p-value	.0001	.0001

Note: Analyses were conducted in the ITT populations.
PJPR0039: Adjusted means (least squares means), adjusted standard errors, and p-values from the final ANCOVA model containing site, treatment, baseline, and treatment-by-baseline interaction. Treatment comparisons are performed at the average baseline score.
PJPR0067: Adjusted means (least squares means), adjusted standard errors, and p-values from the final ANCOVA model containing site, treatment, and baseline.
ANCOVA = analysis of covariance; ITT = intent-to-treat; SE = standard error
Source:
NDA 20-872, Table 8-134, S8-V1.296-P87 (PJPR0039)
NDA 20-872, Table 8-135, S8-V1.296-P88 (PJPR0067)

M016455A/4121

This trial evaluated the efficacy of fexofenadine 180 mg QD in patients 12 years of age and older with a diagnosis of CIU and those with a history of urticaria wheals (hives) for at least 3 days per week for the 6 consecutive weeks. This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled

trial. A single-blind placebo run-in period of 2 to 5 days beginning at Visit 1 was followed by a 28-day double-blind treatment period. Each lesion score (i.e., total number of lesions and average size of lesion) must be ≥1 and the pruritis score must have been ≥2 in order to qualify for enrollment into the placebo run-in phase of the study, see Table 7.

Table 7 Symptoms assessed to meet criteria for single-blind study medication

Total symptom score					
Score	**Total number of lesions**	**Score[a]**	**Number of separate episodes[a] (>1 hr apart) (frequency)**	**Score**	**Average size of lesion (inches)**
0	0	0	0	0	0"
1	1 – 10	1	1	1	<1/2"
2	11 – 20	2	2 or 3	2	1/2" – 1"
3	>20	3	>3	3	>1"
Score	**Average duration of lesions (hr)**	**Score**	**Severity of pruritus**		
0	None	0	None (no itching present)		
1	Up to 4	1	Mild (minor irritation; hardly noticeable; not annoying or troublesome)		
2	>4 – 12	2	Moderate (annoying and troublesome; may have interfered with normal daily activity and/or sleep)		
3	>12 – 24	3	Severe (very annoying and troublesome; substantially interfered with normal daily activities and/or sleep)		
4	>24	4	Very severe (warrants a visit to the physician)		

[a] Symptoms were not assessed at this visit

Source: Table 75 Integrated Summary of Efficacy

A total of 25 (25 of 259, 9.7%) randomized patients withdrew before the planned end-of-study. The overall incidence of patients withdrawn was greater in the placebo group (14.1%, 13 of 92 patients) vs. the fexofenadine group (7.2%, 12 of 167 patients). The most common reasons for withdrawal were "lack of efficacy" (fexofenadine: 0.6%; placebo: 6.5%) and "withdrew consent" (fexofenadine: 1.8%; placebo: 4.3%). The coprimary efficacy variables were change from baseline in the subject's mean daily wheal score (MNW) and the mean daily pruritis score (MPS) over the 28-day double-blind treatment period. During the double-blind treatment period overall, patients treated with fexofenadine 180 mg QD demonstrated a greater adjusted mean decrease in the MNW score than did patients treated with placebo. The treatment difference between the 2 groups was statistically significant in favor of fexofenadine; the difference in LS means was -0.39 with a p-value of <.0001. The MNW and severity of pruritis were significantly reduced for patients treated with fexofenadine 180 mg QD over the 28-day treatment period vs. placebo. Furthermore, AM and PM reflective scores for total number of lesions, number of separate episodes, average size of lesions, severity of pruritis, as well as the AM, PM, and daily mean TSS were significantly reduced in fexofenadine-treated patients compared with placebo. In conclusion, the studies submitted to NDA 20-872 support the efficacy of 60 mg BID for SAR; 30 mg BID for SAR and CIU and 180 mg QD for SAR and CIU and will be acceptable in support of the OTC switch.

1. Summary of Efficacy for Prescription NDA

1.2. **Indication: SAR and CIU oral suspension (6 mg/ml) and ODT (30 mg)**

Both the oral suspension and ODT formulations were approved on the basis of bioequivalence of the fexofenadine oral suspension and the ODT with the fexofenadine 30 mg tablet. Efficacy for the two formulations can be concluded from the efficacy demonstrated for the fexofenadine 30 and 60 mg tablets and capsules. Reference was made to NDA 20-625 and NDA 20-872 which presented the efficacy and safety data for fexofenadine 30 and 60 mg BID in SAR and CIU, reviewed above.

Reviewer's Comment: This reviewer referred to the MO review by Dr Charles Lee for NDA 21-963 dated 12/15/05 for the oral suspension and NDA 21-909 dated 5/11/07 for the ODT formulation. Fexofenadine oral suspension 30 mg (6 mg/ml) and the 30 mg ODT formulation are bioequivalent to the fexofenadine

30 mg tablet in that the CI for the ratio of both the C_{max} and the AUC $_{(0-\infty)}$ fell within the 80 -125% limits. There was a food effect for both with a 30% reduction in AUC $_{(0-\infty)}$ and 47% reduction in C_{max} seen for the oral suspension and a 40% reduction in $AUC_{(0-\infty)}$ and 59% reduction in C_{max} for the ODT relative to the fasted state. Also of note, as reviewed by the Clinical Pharmacology reviewer, Arun Agrawal, the bioavailability of 180 mg fexofenadine is decreased mean AUC by 56% and Cmax by 58% if administered within 15 minutes of aluminum and magnesium containing antacids. As well, co-administration of fexofenadine with either ketoconazole or erythromycin results in increased plasma concentrations of fexofenadine in healthy adult subjects. Based on the current submission, fruit juices such as grapefruit, orange, and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine was administered with either grapefruit or orange juices compared to water. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. A comment regarding the antacids will be recommended for the label revisions.

2. Summary of Efficacy for Prescription NDA

2.1. Indication: PAR-Pivotal Trials

The following four trials were conducted previously but not included in the prescription NDA. They were submitted in support of the use of the term 'indoor and outdoor allergies' in the display panel, but not included in the proposed label. These were not required to support the OTC switch. PJPR0057 and M016455M/3097 were the pivotal trials and will be reviewed in detail below. The two supportive trials M016455M/3001 and 3002 which assessed higher doses not approved will only briefly be summarized in Section 2.2 Indication: PAR-Supportive Trials. See Table 9 for summary.

Table 9- Adequate and well-controlled studies supporting fexofenadine tablets-perennial allergic rhinitis

Study	Doses evaluated	Study population
PJPR0057	60 mg BID, 120 mg QD	12 to 78 years of age, PAR
M016455M/3097	120, 180 mg QD	12 to 78 years of age, PAR
M016455M/3001	120 mg BID, 240 mg QD	12 to 78 years of age, PAR
M016455M/3002	120 mg BID, 240 mg QD	12 to 78 years of age, PAR

PJPR0057

A Double Blind, Randomized, Parallel Study Comparing the Efficacy and Safety of Fexofenadine 60 mg BID, 120 mg QD and Placebo in the Treatment of Perennial Allergic Rhinitis.

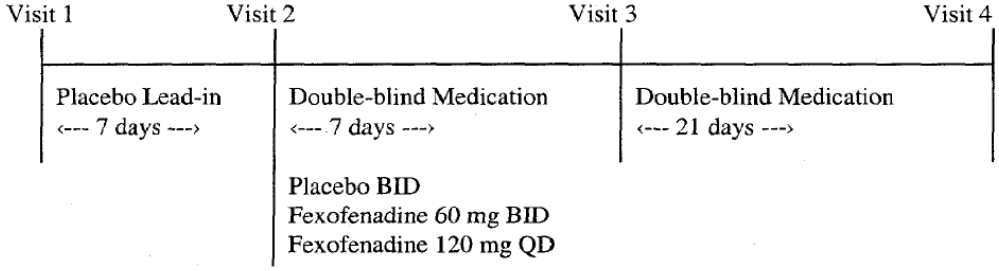
Design

This trial was a double-blind, randomized, placebo-controlled, parallel trial to compare the efficacy of fexofenadine 60 mg BID, fexofenadine 120 mg QD, and placebo in the treatment of PAR. The duration of the trial was approximately 5 weeks, during which the patient was seen on 4 occasions:

- screening visit (Week 1),
- baseline visit (Week 2) and
- 2 treatment visits (Weeks 3 and 5).

Patients first entered into a 7-day, single-blind placebo lead-in period to qualify for the trial and establish their baseline allergy symptoms. Patients, who met study criteria were then randomized to double-blind study medication (placebo, fexofenadine 60 mg BID, or fexofenadine 120 mg QD) and treated for 4 weeks, refer to the figure below representing the design. Fexofenadine 120 mg was administered as 2 fexofenadine 60 mg capsules in the morning; an additional placebo capsule was administered in the evening for the fexofenadine 120 mg QD treatment group or in the morning for the fexofenadine 60 mg BID treatment group to maintain the study blind.

Figure 1 Study Design Schematic



Source: Section III Investigational Plan; Full Integrated Clinical Study Report, Protocol No. 016455PR0057

Study population

To qualify for the trial the patients had to be ≥ 12 years of age, have a history of PAR for the previous 2 years, and exposure to a relevant allergen (i.e., house dust mites, molds, and pets). The diagnosis was confirmed by a positive epicutaneous skin test response (wheal diameter ≥5 mm greater than diluent within 15 minutes after beginning of test) to relevant allergen at Visit 1 or during the previous 15 month period. The patient had to have a history of a positive response to antihistamines for symptoms of PAR. Patients suffering from both PAR and springtime SAR could not be enrolled later than 30 days prior to the local spring pollen season. At Visit 1 the patient's rTSS for the previous 12 hours had to include 2 or more symptoms, excluding nasal congestion, rated as “moderate” or “severe” and no symptom, including nasal congestion, rated as “very severe.” At Visit 2, all PM and AM reflective PAR assessments from the Visit 1 Daily Symptom Diary had to be completed and the reflective PAR assessments from the placebo lead-in had to show 2 or more symptoms (excluding nasal congestion) rated as “moderate” or “severe” for 3 of the 4 most recent PM assessments, and 2 or more symptoms (excluding nasal congestion) rated as “moderate” or “severe” for 3 of the 4 most recent AM assessments. No symptom, including nasal congestion, was to be rated as “very severe” at any PM or AM assessment at Visits 1 or 2.

Efficacy evaluations and parameters

Efficacy variables were based on the patient’s assessment of symptom severity as well as the physician evaluation of the overall effectiveness of study medication at Visit 4. The symptom score was the same as that used for SAR seen in Table 3.

Reviewer’s Comment:
Nasal congestion was assessed, but its severity rating was not included in the TSS as relief of nasal congestion is not expected using an H1-antagonist.

Throughout the trial, patients assessed their PAR symptoms daily at 7:00 AM (± 1 hour) and 7:00 PM (± 1 hour) immediately prior to taking study medication. Symptoms were assessed reflectively (for the previous 12-hour period) and instantaneously (for the previous 1 hour period).
The primary efficacy endpoint:

- Change in average daily 7:00 PM reflective TSS (during the double-blind medication period) from average baseline 7:00 PM rTSS (during the placebo lead-in period)

The primary analyses were performed on the ITT population using the analysis of variance (ANOVA) model. There was no statistical related change in a single amendment (dated December 13, 1995). However, in the statistical analysis plan (dated September 16, 1996), an analysis of covariance (ANCOVA) procedure was proposed rather than the ANOVA described in the protocol. As well, the approach to adjust for multiplicity was also revised.

Reviewer’s Comment:
These changes in the statistical analysis were reviewed by the Statistics team and were considered acceptable.

The secondary efficacy parameters:

- Change from baseline in average daily 7:00 PM rTSS for the first week of double-blind medication
- Change from baseline in average daily 7:00 PM rTSS for the second to fourth week of double-blind medication
- Change from baseline in average daily 7:00 AM and PM iTSS
- Change from baseline in average daily 7:00 AM rTSS
- Physician's assessment of overall effectiveness of study medication

Secondary efficacy parameters and subgroups were analyzed only for the ITT population using similar methods used for the primary efficacy endpoint. For the physician's assessment of the overall effectiveness of study medication the three treatment groups were compared wit a Cochran-Mantel-Haenszel procedure controlling for site.

Safety Parameters

Safety was evaluated by adverse event (AE) reporting, clinical laboratory data, ECG, vitals, physical exam and concomitant medications.

Disposition

A total of 906 patients were screened at 25 sites. Six hundred and seventy six (676) were randomized with 673 patients exposed (identified as safety evaluable -exposed to double-blind medication with post-baseline AE assessment) and were assessed in all safety analyses. Six hundred and seventy-one (671) patients were included in the ITT population (patients with baseline and on-treatment 7:00 PM reflective symptom assessments) and were included in all ITT analyses. Of the 671 ITT patients, 617 did not have major protocol violations and were classified as protocol-correct. A total of 48 (7.1%) of the patients exposed to double-blind study medication withdrew prior to completing the trial. Nineteen (19) were in the placebo group and 13 in the 60 mg BID group and 16 in the 120 mg QD group. The most common reasons for early discontinuation were patient/investigator decision to discontinue (3.3%) and AEs (1.6%). The proportion of patients who discontinued prematurely was similar across treatment groups.

Table 10 Patient's Accountability N (%)

	Study 0057		
	Placebo	**60mg BID**	**120mg QD**
Randomized	220	228	228
Completed study treatment	201 (91)	215 (94)	212 (93)
Discontinued treatment	19 (9)	13 (6)	16 (7)
Reason of early discontinuation of study treatment			
Adverse event	6 (2.8)	2 (0.9)	3 (1.3)
Patient/investigator decision to discontinue	8 (3.7)	7 (3.1)	7 (3.1)
Lost to follow-up	2 (0.9)	2 (0.9)	0
Use of prohibited medication	1 (0.5)	0	1 (0.4)
Other	2 (0.9)	2 (0.9)	5 (2.2)
ITT	217	227	227
Safety	218	228	227
PP	199	208	210

Source: Biostatistician, Feng Zhou review 10/26/10

Demographic

There were no significant differences among the treatment groups with respect to gender, race, age, weight, height, and years since first episode of PAR occurred. Among 671 patients in the ITT population,

34% were male, 92% were caucasian, and the mean age was 34 years (range 12 to 78 years of age). Patients' mean weight and height were 72 kg and 167 cm, respectively. The number of years since the first episode of PAR occurred ranged between 1.3 and 66. The most common allergen responsible for the patient's PAR symptoms was dust (89%). About 5 percent of patients failed one of the inclusion criteria (i.e. baseline TSS ≥4), and they were considered protocol violators.

Results and Conclusions

Efficacy

The 60 mg BID dose group demonstrated a statistically significant reduction in the 7PM rTSS, with a LS mean value of -2.18 (±0.14) and a -0.66 difference from placebo (p value<0.001). The 120 mg QD dose group did not reach statistical significance with a mean difference of -0.25 (p value=0.197), refer to Table 11 below.

Table 11 Analysis Results of TSS

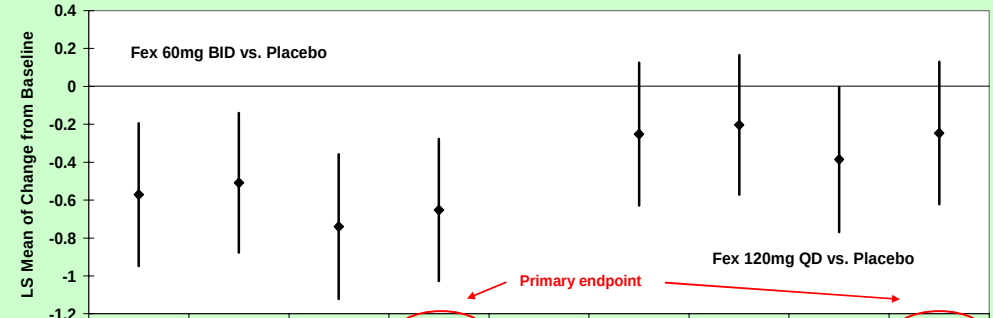
Study/Treatment	***Baseline***	***Change from Baseline over 4-weeks***		
	Mean (SE)	***Mean (SE)***	***Median (Range)***	***LS Mean (SE)[a]***
7PM reflective TSS (Primary)				
60mg BID (227)	6.80 (0.13)	-2.27 (0.14)	-2.32 (-7.72, 4.23)	-2.18 (0.14)
120mg QD (227)	6.84 (0.12)	-1.90 (0.15)	-1.60 (-9.28, 3.03)	-1.77 (0.14)
Placebo (217)	6.74 (0.13)	-1.58 (0.15)	-1.61 (-8.70, 5.17)	-1.53 (0.14)
7PM instantaneous TSS				
60mg BID (227)	6.21 (0.15)	-1.85 (0.15)	-1.74 (-7.34, 5.70)	-1.76 (0.14)
120mg QD (227)	6.37 (0.15)	-1.59 (0.16)	-1.32 (-7.97, 4.83)	-1.41 (0.14)
Placebo (217)	6.13 (0.15)	-1.06 (0.17)	-1.02 (-10.04, 7.52)	-1.02 (0.14)
7AM reflective TSS				
60mg BID (227)	6.11 (0.16)	-1.47 (0.15)	-1.30 (-7.10, 6.07)	-1.41 (0.14)
120mg QD (227)	6.12 (0.16)	-1.18 (0.16)	-1.14 (-8.0, 5.04)	-1.11 (0.14)
Placebo (217)	6.16 (0.16)	-0.97 (0.15)	-0.91 (-8.67, 7.43)	-0.90 (0.14)
7AM instantaneous TSS				
60mg BID (227)	6.18 (0.17)	-1.44 (0.15)	-1.22 (-8.67, 5.69)	-1.44 (0.14)
120mg QD (227)	6.35 (0.17)	-1.22 (0.16)	-1.00 (-10.17, 5.21)	-1.12 (0.14)
Placebo (217)	6.38 (0.16)	-0.95 (0.17)	-0.84 (-9.37, 8.26)	-0.87 (0.14)

LS Mean and SE were from an ANCOVA model with treatment, baseline value and center effects.
Source: Table 5 Biostatistician, Feng Zhou review 10/26/10

When the data points are plotted graphically as in Figure 2, the fexofenadine 60 mg BID dose for all endpoints are clearly do not cross the line of unity as opposed to the 120 mg QD dose (not an approved

dose in the US), with the exception of the 7 PM iTSS which was a secondary endpoint with a p value of 0.048.

Figure 2 LS Mean Change from Baseline of TSS over 4 weeks



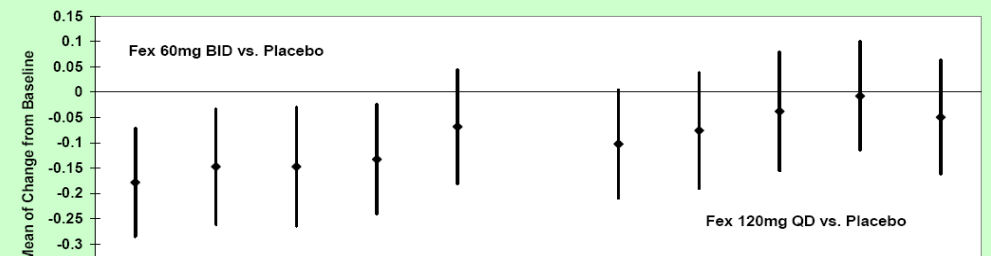
	7AM iTSS (p=0.003)	7AM rTSS (p=0.007)	7PM iTSS (p<0.001)	7PM rTSS (p<0.001)		7AM iTSS (p=0.189)	7AM rTSS (p=0.277)	7PM iTSS (p=0.048)	7PM rTSS (p=0.197)
95%CI-L	-0.95	-0.88	-1.12	-1.03		-0.63	-0.57	-0.77	-0.62
95%CI-U	-0.19	-0.14	-0.36	-0.28		0.12	0.16	0.00	0.13
◆ Fex-Plb	-0.57	-0.51	-0.74	-0.65		-0.25	-0.20	-0.39	-0.25

Observed Time

[a]: LS Mean, 95%CI, and p- value were from an ANCOVA model with treatment, baseline value, and center effects.
Source: Figure 4 Biostatistician, Feng Zhou review 10/26/10

Analysis of the individual symptom scores: sneezing; rhinorrhea; itchy nose, palate, throat; watery, red eyes demonstrated consistent results with the exception of nasal congestion which is not unexpected. The plot for the individual symptom scores is depicted in Figure 3 below. The results of the physician's assessment of overall effectiveness of study drug are also consistent with the primary analysis results.

Figure 3 LS Mean Change from Baseline of 7 PM Reflective Symptoms over 4 weeks



	Sneezing	Rhinorrhea	Itchiness	Itchy watery eyes	Nasal congestion		Sneezing	Rhinorrhea	Itchiness	Itchy watery eyes	Nasal congestion
95%CI-L	-0.29	-0.26	-0.26	-0.24	-0.18		-0.21	-0.19	-0.16	-0.12	-0.16
95%CI-U	-0.07	-0.03	-0.03	-0.03	0.04		0.00	0.04	0.08	0.10	0.06
◆ Fex-Plb	-0.18	-0.15	-0.15	-0.13	-0.07		-0.10	-0.08	-0.04	-0.01	-0.05

7PM Reflective Individual Symptoms

LS Mean, 95% CI, and p value were from an ANCOVA model with treatment, baseline value and center effects
Source: Figure 6 Biostatistician, Feng Zhou review 10/26/10

The results of this trial demonstrate the fexofenadine 60 mg BID treatment group was statistically significant in reducing 7:00 PM rTSS as well as the other time points and thus the effect was maintained throughout the dosing interval in the treatment of PAR.

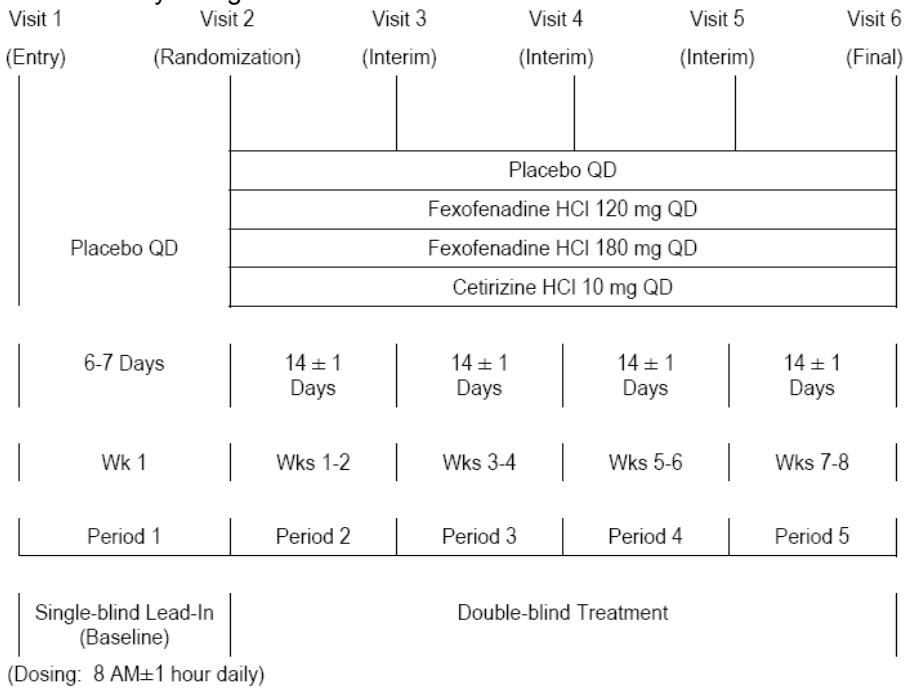
Safety

The investigator's description of each AE was coded to an Included Term which automatically mapped to a Preferred Term and System Organ Class (SOC) according t the Hoechst Marion Roussel version of the World Health Organization Reaction Terminology Dictionary. When looking at TEAE 10% of the patients receiving fexofenadine and 11.5% of the patients receiving placebo experienced one or more AE, There was no obvious difference in the occurrence of rate of AE between the two active dose groups (i.e., 11.4% for 60 mg BID vs. 8.4% for 120 mg QD). The SOC with the highest number of patients reporting TEAE was the Neurologic System with the most common AE in patients treated with fexofenadine was headache (4.0%). Of note, drowsiness was reported in 1.1% of patients receiving fexofenadine and 0.5% of patients receiving placebo.
There were no serious TEAE and no deaths. Evaluation of the laboratory data revealed two laboratory parameters, sodium in the two active dose groups and total cholesterol in the 60 mg BID dose group had a statistically significant mean change from baseline to the study end, but not considered clinically significant. Review of vitals revealed no statistically significant change in diastolic or systolic blood pressure or heart rate as well as ECG changes from baseline to the final visit in patients treated with fexofenadine compared to placebo.

M016455M/3097
A Double-Blind, Randomized, Parallel Study Comparing the Efficacy and Safety of Fexofenadine HCl 120 mg QD, 180 mg QD, Cetirizine HCl 10 mg QD, and Placebo QD in the Treatment of Perennial Allergic Rhinitis.

Design
Study M016455M/3097 was a prospective, double-blind, randomized, placebo-controlled, 4-arm trial with a 1-week placebo lead-in period followed by an 8-week double-blind treatment period. The trial was conducted at 65 sites in the US and Canada designed to assess the clinical efficacy and safety of fexofenadine administered QD at 120 mg and 180 mg compared to placebo in patients ≥ 12 years of age in the treatment of PAR. Cetirizine 10 mg QD which is the highest marketed dose for the treatment of PAR in both the US and Canada, was included as an active comparator. The trial was carried out from November 1998 to May 1999. The patients were randomized to 1 of 4 treatment groups, see Figure 4. Prior to randomization to double-blind medication, patients were treated for 1 week with single-blind placebo QD. Patients who met the randomization criteria were treated with double-blind medication (placebo QD, fexofenadine 120 mg QD, fexofenadine 180 mg QD, or cetirizine 10 mg QD) for 8 weeks. The trial duration was a total of 9 weeks which included 6 visits. To establish a similar baseline TSS across the treatment groups, a stratified randomization was performed (high or low TSS based upon the number of 8 AM instantaneous assessments, with iTSS>6, low = 1-4, high = 5-7). A placebo control was incorporated as a comparator for the active treatments. A single blind placebo lead-in was used to reduce the number of placebo responders in the double blind portion of the study where patients who did not meet symptom criteria were discontinued. An 8-week treatment period was used to facilitate an extensive evaluation of the effectiveness of the doses tested. Doses of 120 mg QD and 180 mg QD fexofenadine were selected because previous SAR and PAR studies have shown 120 mg QD to be effective or marginally effective in reducing severity of symptoms, and 180 mg QD was shown to be effective.

Figure 4 Study Design



Source: Section 3 Case Study Report M016455M/3097

Throughout the trial, patients assessed their PAR symptoms daily at 8 AM (±1 hour) immediately prior to taking study medication and again at 8 PM (±1 hour). Patients recorded these assessments in Daily Symptom Diaries. The diaries captured the patient's PAR symptoms reflectively (for the previous 12-hour period, 8 AM and 8 PM) and instantaneously (for the previous 1 hour period, at the end of the dosing interval, 8 AM).

Study Population

Patients were considered for enrollment if ≥12 years of age with a history of PAR for the previous 2 years and the presence of house dust mites in the subject's environment. The diagnosis was to be confirmed by a positive epicutaneous skin test response (wheal diameter ≥3 mm greater than diluent within 15 minutes after beginning test) to house dust mites at Visit 1 or during the previous 15-month period. At Visit 1 (entry visit), the subject's 12-hour reflective symptom assessment must have included 2 or more symptoms, excluding nasal congestion, rated as "moderate" or "severe" and no symptom, including nasal congestion, rated as "very severe." To qualify for randomization to double-blind study medication, the PAR assessments from Period 1 Daily Symptom Diary must have met the following criteria:

- All 8:00 AM, reflective and instantaneous, and all 8:00 PM assessments must have been completed
- No symptom (instantaneous or reflective), including nasal congestion, was to be rated as "very severe" at any 8:00 AM or 8:00 PM assessment
- Two or more symptoms (excluding nasal congestion) had to be rated as "moderate" or "severe" for 4 of the 6 most recent 8:00 AM instantaneous symptom assessments

The symptoms assessed by the subject and the rating of each symptom were the same as in the studies for SAR and in Study PJPR0057.

Efficacy Evaluation and Parameters

The primary efficacy endpoint was:

- Change from baseline in average 8 AM instantaneous TSS (iTSS) over the two month double-blind treatment period. The symptom scale was the same as in Study PJPR0057. The change in

the TSS assessment was defined as: average double-blind 8 AM iTSS – average baseline 8 AM iTSS.

Secondary analysis variables were as follows:

- Change from baseline in average 24-hour rTSS over the 2-month double-blind treatment period; a 24-hour reflective assessment was calculated as the average of the two 12 hour reflective assessments following each dose;
- Change from baseline in average 8 AM 12-hour rTSS over the 2-month double-blind treatment period;
- Change from baseline in average 8 PM 12-hour rTSS over the 2-month double-blind treatment period;
- Weekly change from baseline in average 8 AM iTSS;
- Daily change (up through 14 days of the double-blind treatment) from baseline in average 8 AM iTSS;
- Monthly change from baseline in average 8 AM iTSS;
- Monthly change from baseline in average 24-hour rTSS;
- Change from baseline in average individual 8 AM instantaneous symptom scores over the 2 month double-blind treatment period;
- Change from baseline in average individual 24-hour reflective symptom scores over the 2 month double-blind treatment period;
- Physician's assessment of overall effectiveness of study medication at the Final Visit/Early Termination

An analysis of covariance (ANCOVA) model with terms for investigative sites, treatment groups, average baseline 8 AM iTSS, and treatment-by-baseline interaction was used to analyze the primary efficacy parameter, change from baseline in average 8 AM iTSS. The primary analysis was performed using the ITT population. Similar statistical models and the ITT population were used for all secondary variable analyses.

Safety Parameters

Safety was evaluated by AE reporting, clinical laboratory data, urine pregnancy tests for all females, ECG, vitals, physical exam and concomitant medications. Also evaluated was somnolence using the excessive daytime sleepiness component of the Sleep-Wake Activity Inventory questionnaire. Somnolence was assessed during the 1-week single-blind baseline and the 8-week double-blind treatment periods.

Reviewer's Comment:
Other than a reference submitted, data in support of the validation of this questionnaire has not been provided.

Disposition

A total of 2430 patients were screened with 1311 randomized to the four treatment groups. A total of 192 (15%) of the patients exposed to double-blind study medication discontinued prior to completion of the study. The most common primary reasons for discontinuation were AE (5%) and election to discontinue (2%). The frequency of discontinuation was similar across treatment groups. As well, the demographic and baseline disease characteristics were generally balanced.

Results and Conclusions

The primary efficacy analysis of change in 8:00 AM instantaneous TSS was based on the ITT population. No statistical significant difference was observed between fexofenadine 180 mg and placebo for the primary or secondary endpoints (p value= 0.505) while the active comparator, cetirizine 10 mg QD showed statistically significantly improvement over placebo with a mean difference of -0.35 ± 0.16 p value=0.026 for the AM iTSS score. See Figure 5 below for summary.

Figure 5 Analysis Results of Mean Change from Baseline of TSS over 2 Month

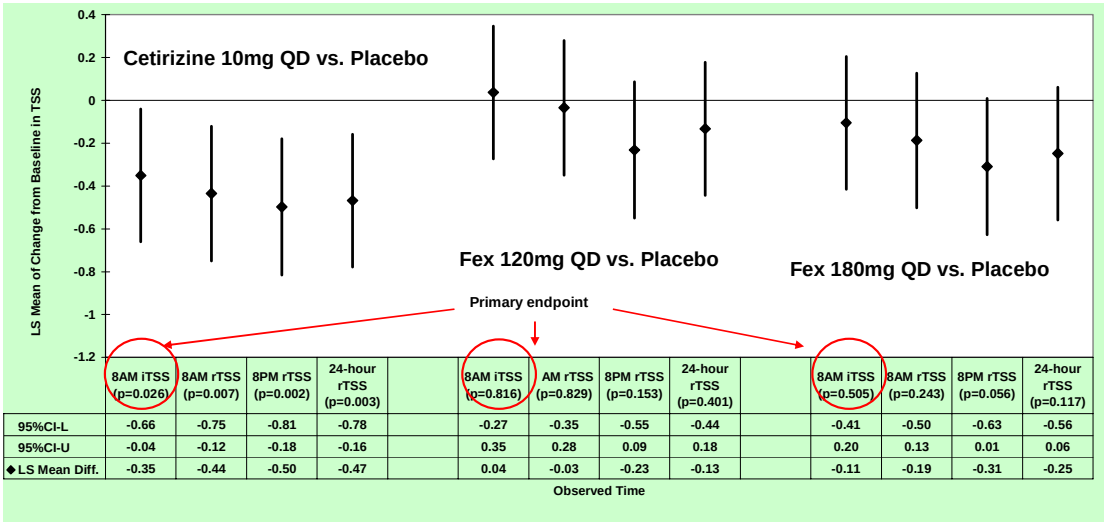
Study/Treatment	Baseline	Change from Baseline over 2-months		
	Mean (SE)	Mean (SE)	Median (Range)	LS Mean (SE)[a]
8AM instantaneous TSS (Primary)				
180mg QD (325)	7.19 (0.11)	-1.48 (0.12)	-1.3 (-9.6, 5.4)	-1.48 (0.12)
120mg QD (325)	7.23 (0.11)	-1.25 (0.12)	-1.3 (-8.9, 4.5)	-1.34 (0.12)
Cetirizine10mg QD (324)	7.31 (0.10)	-1.76 (0.12)	-1.6 (-10.3, 4.9)	-1.72 (0.12)
Placebo (319)	7.15 (0.11)	-1.35 (0.11)	-1.1 (-6.9, 4.9)	-1.37 (0.12)
8AM reflective TSS				
180mg QD (325)	7.00 (0.11)	-1.36 (0.13)	-1.1 (-10.4, 5.6)	-1.39 (0.12)
120mg QD (325)	7.16 (0.11)	-1.26 (0.12)	-1.0 (-9.0, 5.6)	-1.24 (0.12)
Cetirizine10mg QD (324)	7.21 (0.11)	-1.69 (0.12)	-1.5 (-10.3, 4.8)	-1.64 (0.12)
Placebo (319)	6.98 (0.12)	-1.15 (0.12)	-0.9 (-7.3, 5.4)	-1.20 (0.12)
8PM reflective TSS				
180mg QD (325)	6.74 (0.14)	-1.46 (0.13)	-1.2 (-9.3, 6.8)	-1.50 (0.12)
120mg QD (325)	6.89 (0.12)	-1.44 (0.13)	-1.3 (-7.7, 4.4)	-1.42 (0.12)
Cetirizine10mg QD (324)	6.95 (0.12)	-1.74 (0.13)	-1.4 (-9.6, 4.8)	-1.69 (0.12)
Placebo (319)	6.70 (0.13)	-1.14 (0.12)	-1.1 (-7.7, 5.5)	-1.20 (0.12)
24-hour reflective TSS				
180mg QD (325)	6.88 (0.13)	-1.42 (0.13)	-1.2 (-9.7, 6.2)	-1.44 (0.12)
120mg QD (325)	7.03 (0.11)	-1.36 (0.12)	-1.3 (-8.4, 4.1)	-1.32 (0.12)
Cetirizine10mg QD (324)	7.09 (0.11)	-1.72 (0.12)	-1.4 (-10.0, 4.0)	-1.66 (0.12)
Placebo (319)	6.86 (0.12)	-1.16 (0.12)	-1.0 (-7.4, 5.4)	-1.19 (0.12)

LS Mean and SE were from an ANCOVA model with treatment, baseline value, and center effects.

Source: Figure 8, Biostatistician, Feng Zhou review 10/26/10

Again, when the data points for the difference in mean change of TSS from placebo are plotted with the 95% CI as done in Figure 6, the CIs for cetirizine 10 mg QD do not cross the line of unity however, both fexofenadine 120 mg and 180 mg QD do.

Figure 6 LS Mean Change from Baseline of TSS over 2 Months



	8AM iTSS (p=0.026)	8AM rTSS (p=0.007)	8PM rTSS (p=0.002)	24-hour rTSS (p=0.003)		8AM iTSS (p=0.816)	AM rTSS (p=0.829)	8PM rTSS (p=0.153)	24-hour rTSS (p=0.401)		8AM iTSS (p=0.505)	8AM rTSS (p=0.243)	8PM rTSS (p=0.056)	24-hour rTSS (p=0.117)
95%CI-L	-0.66	-0.75	-0.81	-0.78		-0.27	-0.35	-0.55	-0.44		-0.41	-0.50	-0.63	-0.56
95%CI-U	-0.04	-0.12	-0.18	-0.16		0.35	0.28	0.09	0.18		0.20	0.13	0.01	0.06
◆LS Mean Diff.	-0.35	-0.44	-0.50	-0.47		0.04	-0.03	-0.23	-0.13		-0.11	-0.19	-0.31	-0.25

LS Mean, 95% CI and p-value were from an ANCOVA model with treatment, baseline values and center effects.

Source: Figure 10 Biostatistician, Feng Zhou review 10/26/10

The Sponsor conducted a post hoc analysis of the data based on their assessment that 1/3 of the patients with mild or less PAR symptom severity were included for randomization. Using a more restrictive randomization criteria of a mean baseline TSS score >6 for entry during the three days prior to study medication in the ITT population and looked at the difference between fexofenadine 120 mg and 180 mg QD as well as cetirizine 10 mg QD and placebo in the 24 hour rTSS. The fexofenadine 180 mg dose group showed a statistically significant improvement (p value=0.014) in the 24-hour rTSS compared to placebo for subjects who had baseline TSS ≥6. The difference between fexofenadine 120 mg and placebo was not statistically significant (p value=0.164). The cetirizine group showed statistically significant improvement compared with the placebo group (p value=0.009) See Table 12 below. The mean decrease from baseline in 24 hour rTSS was greater for the cetirizine group (-1.78) and the fexofenadine 180 mg dose group (-1.77) compared with the fexofenadine 120 mg dose group (-1.56) and the placebo (-1.31) group.

Table 12 Modified Baseline- 24 Hour Reflective Total Symptom Score (Intent to Treat Population, 4 Weeks)

		Mean ± SE		
Treatment	N	Baseline	Double Blind Period	Change from Baseline[a]
Placebo	317	6.88±0.12	6.01±0.13	-0.89±0.10
Fex HCl 120 mg	325	6.93±0.12	5.90±0.13	-1.03±0.10
Fex HCl 180 mg	323	6.89±0.13	5.69±0.13	-1.20±0.10
Cetirizine	324	6.99±0.12	5.60±0.13	-1.36±0.10
Treatment Comparison		Mean Difference ± SE[a]		P-value[a]
Fex HCl 120 mg vs Placebo		-0.14±0.14		0.333
Fex HCl 180 mg vs Placebo		-0.31±0.14		0.028
Cetirizine vs Placebo		-0.47±0.14		0.001
Fex HCl 120 mg vs 180 mg		0.17±0.14		0.215
Fex HCl 120 mg vs Cetirizine		0.34±0.14		0.017
Fex HCl 180 mg vs Cetirizine		0.16±0.14		0.253
Model Effects[a]:				
Baseline		P-value=<0.001		
Treatment		P-value=0.005		
Site		P-value=<0.001		
Interaction				
Treatment-by-baseline Interaction [b]		P-value=0.500		
Treatment-by-site [c]		P-value=0.336		

Baseline = the average value of the TSS score for the last 3 days prior to study medication.

[a] P-values, means, and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.

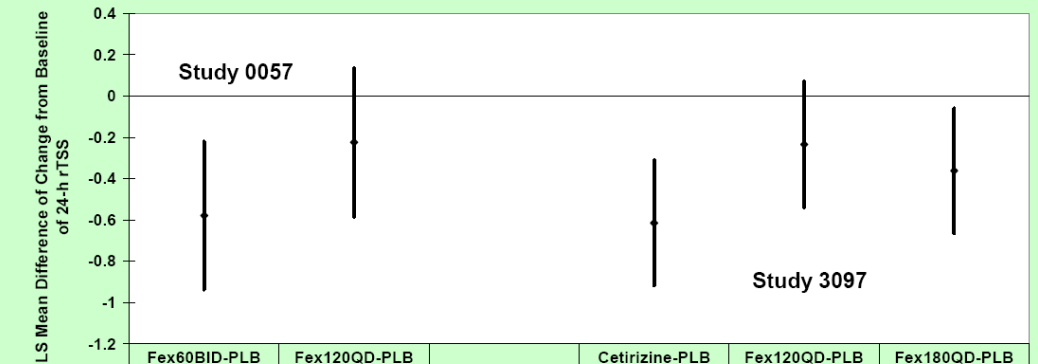
[b] P-value from ANCOVA model with investigative site, treatment, baseline, and treatment-by-baseline interaction.

[c] P-value from ANCOVA model with investigative site, treatment, baseline, and treatment-by-site interaction.

Source: Table 24 CSR M016455M/3097

The biostatistician, Feng Zhou carried out an exploratory analysis looking at the 24 hour rTSS at the 4 week timepoint, instead of 8 week in the initial analysis and looked at the two studies PJPR0057 and M016455M/3097 and also demonstrated statistical significance for change in mean baseline of the rTSS for the 180 mg QD dose as well as the 60 mg BID and cetirizine 10 mg QD, as demonstrated in Figure 7 below.

Figure 7 Treatment Comparison of Mean Change from Baseline of 24 Hour rTSS Over 4 Weeks



Source: Figure 17 Biostatistician, Feng Zhou review 10/26/10.

In summary, the two pivotal trials of fexofenadine 180 mg QD as well as 60 mg BID in the treatment of PAR provide evidence in support of the use of the term indoor and outdoor allergies for the sell copy.

Safety

The listing of the AEs in this report was updated to provide coding to the respective preferred terms using Medical Dictionary for Regulatory Activities (MedDRA) version 5.1. A total of 1,299 patients were evaluable for safety. The frequency of patients experiencing 1 or more adverse events was similar between treatment groups: 53.9% (173 of 321) of the patients receiving placebo, 52.4% (172 of 328) of the patients receiving fexofenadine HCl 120 mg, 56.9% (185 of 325) of the patients receiving fexofenadine HCl 180 mg, and 55.4% (180 of 325) of the patients receiving cetirizine. The most frequently reported AE was headache, occurring in 9.7% (31 of 321) of placebo patients, 9.5% (31 of 328) of fexofenadine HCl 120 mg patients, 8.0% (26 of 325) of fexofenadine HCl 180 mg patients, and 8.3% (27 of 325) of cetirizine patients. There was no obvious relationship between dose of fexofenadine and number of patients with reported AEs.

There were no deaths in this study. Seven patients treated with study medication experienced serious adverse events (SAEs):

- 1 subject on placebo, #1064011 experienced endometriosis;
- 2 patients on fexofenadine HCl 120 mg: patient #1062010 experienced cardiomegaly NOS, chest discomfort, chest pain, dyspnea, pulmonary congestion and hypertension and patient #1065016 experienced a meniscus lesion;
- 1 subject on fexofenadine HCl 180 mg #1080028 experienced a retinal detachment;
- 3 patients on cetirizine (1064024- monoarthritis, 1080003-food poisoning, and 1160024-anaphylactic reaction).

The incidence of patients who discontinued from the study was comparable among treatment groups: 5.3% (17 of 321) for placebo, 4.9% (16 of 328) for fexofenadine HCl 120 mg, 5.8% (19 of 325) for fexofenadine HCl 180 mg, and 4.6% (15 of 325) for cetirizine. These included: muscle twitching, chest pain and hypertension, upper abdominal pain and diarrhea, headache, insomnia, hypersensitivity, influenza like illness and dizziness. None of the patients on placebo discontinued from the study because of treatment-related adverse events compared with 1.2% of patients on fexofenadine HCl 120 mg, 1.2% of patients on fexofenadine HCl 180 mg, and 0.9% of patients on cetirizine.

A total of 48 patients reported 53 laboratory outlier values, 4 of which were considered to be clinically significant, but not adverse events, by the Investigators. Of these outlier values, only 4 were considered to be clinically significant by the Investigator: #1078019 (male/age 42) had an elevated triglyceride level (651 mg/dL); #1082012 (female/age 47) had an elevated triglyceride level (889 mg/dL); #1083001

(male/age 26) had an elevated ALT level (115 U/L); and #1083021 (male/age 18) had an elevated total bilirubin (2.2 mg/dL). No patient was reported to have medication discontinued or interrupted because of an abnormal or outlier laboratory value.
There were no statistically significant changes from baseline in vital signs among the 4 treatment groups, and only 2 patients on fexofenadine HCl 120 mg and 1 subject on fexofenadine HCl 180 mg had a blood pressure value that met the outlier criteria compared with 4 patients on placebo and 3 patients on cetirizine.

2. Summary of Efficacy for Prescription NDA

2.2. **Indication: PAR- supportive studies**

M016455M/3001
M016455M/ 3002

Two supportive controlled trials conducted in the US and Europe M016455M/3001 and M016455M/3002, evaluated the effectiveness of fexofenadine of 240 mg QD and 120 mg BID versus placebo in the treatment of PAR. The primary objective of the two trials was to assess the efficacy and safety of possible higher doses of fexofenadine (120 mg BID and 240 mg QD) compared with placebo in the treatment of PAR. Both studies were identical multinational, double-blind, randomized, parallel-group, placebo-controlled trials in patients with PAR. Patients first entered into a 7-day single-blind lead-in period to qualify for the study and establish their baseline allergy symptoms. Patients who met study criteria were then randomized to double-blind study medication and treated for 4 weeks. Male or female patients at least 12 years of age were eligible and they had a documented history of PAR for the previous 2 years confirmed by a positive skin prick test response (wheal diameter at least 3 mm greater than diluent within 15 minutes after beginning the test). For Studies M016455M/3001 and M016455M/3002, the primary analysis results were of the average daily 24-hour PM reflective TSS over the 4-week double-blind treatment period (ITT population for the primary efficacy endpoint). The symptoms and the rating of the symptoms were the same as in the previous studies for SAR and PAR. The ITT primary analyses of the primary endpoint in Study M016455M/3001 suggested a significant advantage for fexofenadine 120 mg BID over placebo (2-sided p-value=.0363 unadjusted for multiple comparisons), but not for fexofenadine 240 mg QD (2-sided p value=.2195). However, when adjustments were made for the multiple comparisons, fexofenadine 120 mg was no longer statistically significant. However, The ITT primary efficacy analyses in Study M016455M/3002 showed statistically significant decreases in the adjusted mean 24-hour PM reflective TSS over the 4-week treatment period for both fexofenadine treatment groups when compared to placebo (fexofenadine 120 mg BID – placebo: p=.0098; fexofenadine 240 mg QD – placebo: p=<.0001).

7 Review of Safety

Safety Summary

The safety of fexofenadine for OTC switch is supported by the referenced studies from the original NDA and an extensive post-marketing safety database. No new safety studies were required for this application. The CDER OTC Switch Review Team's review of safety information for fexofenadine support the safety of OTC use of fexofenadine. A review was conducted of worldwide safety information to determine whether there were safety concerns that would prevent the use of fexofenadine (as well as cetirizine and loratadine) in the OTC setting. Results of this review were presented at a joint meeting of the Nonprescription and Pulmonary-Allergy Drug Products Advisory Committees on May 11, 2001. The Advisory Committee determined that fexofenadine has a safety profile acceptable for OTC marketing [www.fda.gov/ohrms/dockets/ac/cder01.htm, Pulmonary Allergy Drugs Advisory Committee]. The Sponsor's integrated summary of safety supports the OTC switch for the proposed indications of fexofenadine for treatment of symptoms of SAR and CIU and corroborates indoor and outdoor allergies for the sell copy.

Safety data from clinical trials

The Integrated Summary of Safety (ISS) is primarily based on analyses of safety data captured in a GIDB which included data from 136 clinical studies using various mono-products and fixed dose combination products. The results included in the GIDB include studies that have previously been submitted in the 4 main NDAs and in supplements to these NDAs and the 2 NDAs for the fixed-dose combination products. The GIDB also includes safety data from additional studies, conducted under Investigational New Drug application (IND) 43,573, IND 51,709, and IND 48,486, that evaluated formulations related to the capsule or tablet or that evaluated the efficacy and safety of fexofenadine in the approved indications of SAR or CIU. Also provided are safety data from postmarketing studies conducted in the United States even if they were not conducted under the INDs, and from studies that have been submitted in Europe and Japan to gain marketing approval. In addition to the GIDB, the Integrated Summary of Safety also contains analyses of spontaneously reported safety data from the pharmacovigilance database, data from searches in external databases [World Health Organization Uppsala Monitoring Centre (WHO UMC) database and Food and Drug Administration's Adverse Event Reporting System (FDA AERS)], and a search of the literature. The clinical studies in the GIDB were organized by the type of study as follows: biopharmaceutics, pharmacokinetic, pharmacodynamic, and efficacy and safety. For this assessment of safety, all AEs in the GIDB were recoded to MedDRA version 12.0. A brief review will be included here; however, for the detailed review of safety see the DNCE clinical review by Dr. Linda Hu.

In the controlled studies in adult patients, a total of 3874 patients were exposed to fexofenadine for a mean of 16.62 days. The mean exposure in the fexofenadine 60 mg BID treatment group was similar (16.51 days), while the mean exposure in the fexofenadine 180 mg QD treatment group was higher (18.52 days). In the other controlled studies in adult patients, a total of 8263 patients were exposed to fexofenadine for a mean of 28.79 days. The dose groups of interest, fexofenadine 60 mg BID and 180 mg QD were exposed for means of 16.64 and 27.9 days, respectively. A total of 1323 patients were exposed to other treatments which included cetirizine, loratadine, and ketotifen for a mean of 24.57 days. Pivotal studies in pediatrics: A total of 646 patients were exposed to fexofenadine for a mean of 15.51 days in combined studies PJPR0066/77 in pediatric patients. The studies also included a fexofenadine 60 mg BID dose group, which is higher than the recommended total daily dose of fexofenadine in the pediatric population. In the long term studies of safety in adult patients, a total of 1109 patients were exposed to fexofenadine for a mean of 259.63 days. The majority, a total of 901 patients, were exposed to a total daily dose of 240 mg fexofenadine, which is higher than the recommended total daily dose for fexofenadine in adult patients.

TEAEs:
The ISS provides safety information from 124 clinical studies with fexofenadine as a mono-product in the adult and pediatric populations. The AE profile derived from the analyses of these pooled studies of the mono-products was similar to the known AEs for fexofenadine. Summary of the results of the most frequent in the biopharmaceutics, pharmacokinetic, and pharmacodynamic studies in pediatric patients with an incidence of at least 1% using the MedDRA preferred term include: abdominal pain (3.27%); somnolence (2.80%); viral infection (2.34%); lymphadenopathy (1.87%); nausea (1.87%); rhinorrhoea (1.87%); cough (1.40%); headache (1.40%) and venous insufficiency (1.40%). In the analysis of biopharmaceutics and pharmacokinetic studies in adult patients, the most common reported TEAEs include: headache (5.11%); nausea (1.36%) and decreased hematocrit (1.02%). In the analysis of pharmacodynamic studies in adult patients, headache was the most frequently reported TEAE (3.67%). An analysis of TEAEs, in which all biopharmaceutics, pharmacokinetic, and pharmacodynamic studies in the adult population were pooled, which revealed the 3 most frequently cited TEAEs, in decreasing order, were headache, nausea, and somnolence, for healthy patients and for patients with an illness. No obvious dose relationship was observed for these TEAEs, except perhaps for headache which was more common at doses of fexofenadine of 180 mg BID or higher.

An analysis of TEAEs in the adult population, in which all pivotal controlled and other controlled studies were pooled, was performed. The analysis revealed that the 3 most frequently cited TEAEs, in decreasing order, were headache, nasopharyngitis, and oropharyngeal pain. Doses of fexofenadine greater than 180 mg to less than 360 mg daily and over 360 mg daily suggested that there was a dose relationship, based on the number of patients reporting TEAEs. In the analysis of the pivotal controlled study in pediatric patients, the percentage of patients who reported at least 1 TEAE was similar between the total fexofenadine treatment group (34.67%) and placebo treatment group (35.37%). Similar to the studies in adult patients, the percentages of TEAEs across the 3 dose groups did not indicate that the incidences of TEAEs were dose dependent.

Death or other SAEs:
There were no deaths reported from the biopharmaceutics and pharmacokinetic, pharmacodynamic studies and the pivotal controlled trials in adult patients. However, in the other controlled studies in adult patients, 1 subject in the fexofenadine 60 mg BID group died due to respiratory failure caused by bacterial pneumonia and in the long-term safety studies in adult patients, 2 patients in the placebo group died. One subject had serious adverse events of cerebrovascular accident and cardiac arrest which resulted in death and the other completed suicide. In the pivotal controlled Studies PJPR0066/77 and in the other controlled studies in pediatric patients, there were no deaths.
A brief sampling of the SAE described in the ISS will follow: A listing of the SAEs in adult patients include: ectopic pregnancy, thermal burn and respiratory fume inhalation disorder, abdominal pain, pyloric stenosis. A listing of the SAEs in pediatric patients include: bronchial hyperactivity. In the pivotal controlled Studies PJPR0066/77, one subject had SAE of status asthmaticus, nausea, vomiting, and tachycardia.
In the other controlled studies in pediatric patients, the SAE included neutropenia. In the analysis of studies which were not previously submitted, 1 patient had a SAE of gastroenteritis.

Safety data from postmarketing reports
No new safety signals have been identified which would preclude OTC use of the fexofenadine monoproducts as directed in the proposed labeling. Refer to the DNCE review by Dr Linda Hu for further details.

9 Overall Assessment

9.1 Conclusions

The Sponsor's proposal for a prescription to OTC switch of Allegra® tablets, oral suspension and ODT is supported by the efficacy and safety data for the following indications:

- Temporary relief of symptoms due to hay fever or other upper respiratory allergies, in adults and children ≥12 years of age the doses are 60 mg BID and 180 mg QD and in children 6 to 11 years of age the dose is 30 mg BID, in young children 2 to <6 years of age the dose is 30 mg BID
- Reduce hives and relief of itching due to hives, in adults and children ≥12 years of age the doses are 60 mg BID and 180 mg QD, in children 6 to 12 years of age the dose is 30 mg BID

No new efficacy and safety studies were conducted for the proposed OTC switch for the allergic rhinitis and hives and urticaria indications however for the use of the claim 'indoor and outdoor allergies', 4 trials in patients with PAR conducted earlier were submitted. 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. Brief review of safety data from the GIDB does not identify any new safety signals. The proposed indications and dosing regimens are acceptable for OTC use, and the recommended regulatory action is approval.

9.2 Labeling Recommendations

The labels for the OTC products are primarily under the purview of the Division of Nonprescription Products. The proposed labels were briefly reviewed and are consistent with monograph labeling for other OTC antihistamines. However, based on the findings in the original NDAs, I recommend including a comment advising of drug interactions with aluminum and magnesium-containing antacids.

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/s/

ANYA C HARRY
11/23/2010

LYDIA I GILBERT MCCLAIN
11/23/2010
I concur

MEDICAL OFFICER REVIEW
Division of Pulmonary, Allergy and Rheumatology Products

Application #:	NDA# 201,373	**Application Type:**	NDA
Sponsor:	Sanofi Aventis	**Proprietary Name:**	Allegra
Investigator:		**USAN Name:**	Fexofenadine
Category:	Antihistamine	**Route of Administration:**	oral
Reviewer:	Lynne H. Wu, MD	**Review Date:**	June 4, 2010

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Submission Type	Comments
March 26, 2010	NDA	Allegra oral suspension non-prescription

REVIEW SUMMARY: This is a medical officer filing review of a NDA submitted for the proposed switch of Allegra oral suspension from prescription to nonprescription use for the treatment of seasonal allergic rhinitis (SAR) in adults and children ≥ 2 years of age; and for the proposed partial switch of Allegra oral suspension for the treatment of chronic idiopathic urticaria (CIU) in adults and children ≥ 6 years of age. The Sponsor will maintain NDA 21-963 for the prescription use of Allegra oral suspension for CIU in pediatric patients 6 months to less than 6 years of age. The proposed uses for respiratory allergies are- temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: runny nose, itchy, watery eyes, sneezing, and itching of the nose or throat; The proposed uses for urticaria are- reduces hives and relieves itching due to hives (urticaria). This product will not prevent hives or an allergic skin reaction from occurring. The proposed labeling is consistent with the OTC monograph for antihistamines. The sponsor is proposing no changes to the dose or dosing regimen.

Fexofenadine HCl has been approved under the trade name Allegra® as a mono-product (capsule [60 mg], tablet [30, 60, and 180 mg], oral suspension [6 mg/mL], and an oral disintegrating tablet [30 mg]) and under the trade names Allegra-D 12 Hour and Allegra-D 24 Hour in fixed-dose combinations with pseudoephedrine (fexofenadine 60 mg and pseudoephedrine 120 mg and fexofenadine 180 mg and pseudoephedrine 240 mg, respectively).

Allegra is marketed in more than 100 countries and was first approved in the US in July 1996 as a 60 mg capsule formulation, not currently marketed in the US. In the subsequent submissions, a tablet formulation of 3 different dose strengths (30 mg, 60 mg, and 180 mg) was approved in 2000 and 2005 for SAR and chronic idiopathic urticaria (CIU) or hives (NDA 20-872). Allegra suspension was approved in October 2006 for the treatment of SAR and CIU in pediatric patients ≥2 to <12 years of age at a dose of 30 mg twice daily, and for the treatment of CIU in patients ≥6 months to <2 years of age at a dose of 15 mg twice daily.

The oral suspension formulation was approved on the basis of bioequivalence of the fexofenadine (6mg/ mL) suspension and the fexofenadine 30 mg tablet. Efficacy of the fexofenadine suspension can be concluded from the efficacy demonstrated for the fexofenadine 30 and 60 mg tablets and capsules in SAR and CIU (NDA 20-625 and NDA 20-872). The clinical efficacy of Allegra suspension in the treatment of SAR and CIU has been previously reviewed and established in NDA 21-963. No new efficacy data is submitted at this time to support the switch application.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION: Fileable

Medical Reviewer: Lynne H. Wu, MD

Medical Team Leader: Theresa Michele, MD

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201373	ORIG-1	SANOFI AVENTIS US LLC	FEXOFENADINE HCL

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/s/

LYNNE H WU
06/04/2010

THERESA M MICHELE
06/04/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201613, 201373, 21909 **Applicant: Sanofi Aventis** **Stamp Date: March 26, 2010**

Drug Name: Allegra (fexofenadine) **NDA/BLA Type: 505(b)(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			.
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.,* Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	Applicant relies on the efficacy data from the original prescription NDAs.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			NA	4 PAR studies are submitted and are being reviewed by pulmonary for label claims
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	4 PAR studies are submitted and are being reviewed by pulmonary for label claims
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Cardiology consult to assess these data.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested	X			For the clinical studies.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				Sponsor needs to provide a literature discussion.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?				See asterisked comment below.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			NA	Already approved in the U.S. for prescription use.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				Sponsor did not wait for division reply regarding adequacy of the datasets before submitting the NDAs
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				Per pulmonary for PAR studies.
34.	Are all datasets to support the critical safety analyses available and complete?				Per cardiology for QT analyses.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				See above.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	These CRFs should have been provided for the original approvals for prescription use.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			NA	

***The Sponsor was previously told that the Agency had concerns that some consumers may mistakenly take 180 mg of fexofenadine twice a day since many consumers are accustomed to taking the 60 mg dose twice daily. If the Sponsor does not provide adequate data to demonstrate the safety of fexofenadine doses $\geq$ to 360mg per day vs 180 mg per day they may have to conduct consumer studies to demonstrate that consumers will not mistakenly dose the180 mg twice a day.**

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Information requests for the Sponsor follow:
1. Create a dataset from the DEMOG Dataset with a record for each study and the fields GROUP, STUDYID, TITLE and hyperlink to study synopsis.

2. Provide a narrative discussion and analysis of the literature pertaining to the *Adverse Events Of Special Interest* that you have previously identified in your submission (including cardiac and ventricular arrhythmic events, interactions, etc.).

3. For the section *Adverse Events Of Special Interest,* provide case numbers and hyperlinks to the serious case reports being referenced.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Linda Hu	5/24/10
Reviewing Medical Officer	Date
Daiva Shetty	5/24/10
Clinical Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201373	ORIG-1	SANOFI AVENTIS US LLC	FEXOFENADINE HCL

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/s/

LINDA S HU
05/25/2010

DAIVA SHETTY
05/25/2010