CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201373Orig1s000

OTHER REVIEW(S)

Labeling Review for Allegra Allergy, Children's Allegra Allergy, Allegra Hives and Children's Allegra Hives *2nd Addendum - Draft Labeling*

SUBMISSION DATES:	January 11 and 12, 2011
NDA/SUBMISSION TYPE:	201-613 (Tablet) 201-373 (Oral Suspension) 21-909/S-003 (Orally Disintegrating Tablet)
ACTIVE INGREDIENTS:	30 mg, 60 mg and 180 mg fexofenadine (201-613) 30 mg/5ml fexofenadine (201-373) 30 mg fexofenadine (21-909/S-003)
DOSAGE FORMS:	Tablet, Oral suspension and Orally disintegrating tablets
SPONSOR:	Sanofi-aventis, LLC Inc Judith Plon (610) 889-6947
REVIEWER:	Ayana K. Rowley, Pharm.D.
TEAM LEADER:	Marina Y. Chang, R.Ph

I. BACKGROUND

This is an amendment to the draft labeling review completed on December 14, 2010, by this reviewer. On Thursday January 6, 2011 the agency provided additional draft labeling comments to the sponsor. The sponsor has resubmitted revised labeling as a response to the agency's comments. Labels for NDA 201-373 and s21-909/S003 were submitted on January 11, 2011. Labels for NDA 201-613 were submitted on January 12, 2011

Submitted Labeling	Representative of
[redacted] (b) (4)	

(b) (4)

[redacted]

NDA 21-909 (S-003) Orally Disintegrating Tablets	
30 mg Allergy immediate container (blister front) - 6 count	N/A
30 mg Allergy immediate container (blister back) – 6 count	N/A
30 mg Allergy outer carton -12 count	N/A
30 mg Hives immediate container (blister front) – 6 count	N/A
30 mg Hives immediate container (blister back) – 6 count	N/A
30 mg Hives outer carton- 12 count	N/A
NDA 201-373 Allegra Oral Suspension	
30 mg/5mL Allergy outer carton 4 fl. oz.	N/A
30 mg/5mL Allergy immediate container (bottle) 4 fl. oz.	N/A
30 mg/5mL Hives outer carton 4 fl. oz.	N/A
30 mg/5mL Hivers immediate container (bottle) 4 fl. oz.	N/A

REVIEWER'S COMMENTS

A. Outer Carton labels for fexofenadine tablets, oral suspension and orally disintegrating products.

i. Outer Carton Label Outside Drug Facts

a. Principal Display Panel

(a) The sponsor added the phrase "Indoor and Outdoor Allergies" on the Allergy indicated products. This is acceptable *(Please see prior reviews by this reviewer for further discussion).*

b. Drug Facts Panel

(a) The sponsor revised the drug facts section as requested. No further revisions have been noted. This is acceptable.

(b) The annotated font specifications are in accordance with 21 CFR 201.66(d). This is acceptable.

ii. Immediate Container Labels for fexofenadine tablets, oral suspension and orally disintegrating products.

a. For all products. The above-mentioned "Drug Facts" label revisions were applied to the immediate container (bottle) labels, respectively. No further revisions have been noted. This is acceptable.

b. As noted in the previous review.

(a) For NDA's 201-613 and 21-909 (S-003). The submitted immediate container (blister card) labels are acceptable.

(b) The sponsor did not include the draft "dosing cup" graphic design in the December 8, 2010 labeling submission. However, these draft "dosing cup" design graphics (Allergy and Hives) were submitted in previous labeling submission and have been reviewed and found to be acceptable by CMC. We will request that the sponsor include the dosing cup as a part of the final printed labeling submission, in order to keep a current record of the dosing device that accompanies the product.

iii. Consumer Information Leaflet or Package Insert

There is no consumer information leaflet or package insert associated with this application. This is acceptable.

II. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Allegra Allergy, Children's Allegra, Allergy, Allegra Hives and Children's Allegra Hives labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to:

(b) (4)

NDA 21-909 (S-003) Orally Disintegrating Tablets (Submitted January 11, 2011)
30 mg "Allergy" immediate container (blister front and blister back) - 6 count, 30 mg "Allergy" outer carton -12 count; 30 mg "Hives" immediate container (blister front and blister back) – 6 count; and 30 mg "Hives" outer carton- 12 count.

NDA 201-373 Allegra Oral Suspension (Submitted January 11, 2011)
30 mg/5mL "Allergy" outer carton and immediate container (bottle) 4 fl. oz., 30 mg/5mL "Hives" outer carton and immediate container (bottle) 4 fl. oz., and 30 mg/5mL; as well as the graphic layout of the Allergy dosing cup and Hives dosing cup (submitted on December 8, 2010).

III. SUBMITTED LABELING

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

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


NON-DROWSY
Children's Allegra® Allergy
Ages 2 Years and Older
12 HOUR
NON-DROWSY
Children's Allegra® Allergy
Ages 2 Years and Older
12 HOUR
Drug Facts (continued)
Other information
■ each 5 mL teaspoon contains: sodium 18 mg
■ safety sealed: do not use if carton is opened or if printed foil inner seal on bottle is torn or missing
■ store between 20° and 25°C (68° and 77°F)
Inactive ingredients
butylparaben, edetate disodium, flavor, poloxamer 407, propylene glycol, propylparaben, purified water, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sucrose, titanium dioxide, xanthan gum, xylitol
Questions or comments?
call toll-free 1-800-633-1610 or www.allegra.com
The makers of Allegra® do not make store brand products.
The trade dress of this Allegra® package is subject to trademark protection.
Dist. By: Chattem, Inc. (part of the sanofi-aventis Group), Chattanooga, TN 37409-0219 ©2010 50094566
NON-DROWSY
NDC 41167-4244-4
Children's Allegra® Allergy
fexofenadine HCl oral suspension 30 mg/5 ml antihistamine
Indoor and Outdoor Allergies
Ages 2 Years and Older
alcohol free
dye free
12 HOUR
RELIEF OF:
✔ Sneezing
✔ Runny Nose
✔ Itchy, Watery Eyes
✔ Itchy Nose or Throat
berry flavor
Oral Suspension/4 fl. oz. (120 ml)
0 41167 42444 5
LOT
EXP
NON-DROWSY
Children's Allegra® Allergy
Ages 2 Years and Older
Read Label Directions
CHILDREN'S Allegra ALLERGY
2 tsp 10 mL
1 tsp 5 mL
Dosing Cup Included
Wash and let air dry after each use
alcohol free
dye free
berry flavor
995760
Drug Facts
Active ingredient (in each 5 mL teaspoonful) Purpose
Fexofenadine HCl 30 mg..... Antihistamine
Uses
temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ runny nose ■ itchy, watery eyes
■ sneezing ■ itching of the nose or throat
Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients.
Ask a doctor before use if you have kidney disease. Your doctor should determine if you need a different dose.
When using this product
■ do not take more than directed
■ do not take at the same time as aluminum or magnesium antacids
■ do not take with fruit juices (see Directions)
Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions ■ shake well before using
■ use only with enclosed dosing cup
adults and children 12 years of age and over: take 2 teaspoonfuls (10 mL) every 12 hours; do not take more than 4 teaspoonfuls (20 mL) in 24 hours
children 2 to under 12 years of age: take 1 teaspoonful (5 mL) every 12 hours; do not take more than 2 teaspoonfuls (10 mL) in 24 hours
children under 2 years of age: ask a doctor
adults 65 years of age and older: ask a doctor
consumers with kidney disease: ask a doctor
Note: teaspoonful = tsp
094566


NON-DROWSY
Children's Allegra® Hives
Ages 6 Years and Older
12 HOUR
NON-DROWSY
NDC 41167-4244-5
Children's Allegra® Hives
fexofenadine HCl oral suspension 30 mg/5 ml antihistamine
Ages 6 Years and Older
alcohol free
dye free
12 HOUR
RELIEF OF ITCHING DUE TO HIVES
berry flavor
Oral Suspension/4 fl. oz. (120 ml)
0 41167 XXXXX X
NON-DROWSY
Children's Allegra® Hives
Ages 6 Years and Older
Dosing Cup Included
Wash and let air dry after each use
alcohol free
dye free
berry flavor
FPO
XXXX60
Drug Facts (continued)
When using this product
■ do not take more than directed
■ do not take at the same time as aluminum or magnesium antacids
■ do not take with fruit juices (see Directions)
Stop use and ask a doctor if
■ an allergic reaction to this product occurs. Seek medical help right away.
■ symptoms do not improve after 3 days of treatment
■ the hives have lasted more than 6 weeks
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions ■ shake well before using ■ use only with enclosed dosing cup
adults and children 12 years of age and over: take 2 teaspoonfuls (10 mL) every 12 hours; do not take more than 4 teaspoonfuls (20 mL) in 24 hours
children 6 to under 12 years of age: take 1 teaspoonful (5 mL) every 12 hours; do not take more than 2 teaspoonfuls (10 mL) in 24 hours
children under 6 years of age: ask a doctor
adults 65 years of age and older: ask a doctor
consumers with kidney disease: ask a doctor
Note: teaspoonful= tsp
Other information
■ each 5 mL teaspoon contains: sodium 18 mg
■ safety sealed: do not use if carton is opened or if printed foil inner seal on bottle is torn or missing
■ store between 20° and 25°C (68° and 77°F)
Inactive ingredients
butylparaben, edetate disodium, flavor, poloxamer 407, propylene glycol, propylparaben, purified water, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sucrose, titanium dioxide, xanthan gum, xylitol
Questions or comments?
call toll-free 1-800-633-1610 or www.allegra.com
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509XXXX
Drug Facts
Active ingredient (in each 5 mL teaspoonful) — Purpose
Fexofenadine HCl 30 mg ..... Antihistamine
Uses
reduces hives and relieves itching due to hives (urticaria). This product will not prevent hives or an allergic skin reaction from occurring.
Warnings
Severe Allergy Warning: Get emergency help immediately if you have hives along with any of the following symptoms:
■ swelling of tongue ■ trouble swallowing ■ swelling in or around mouth ■ trouble speaking ■ wheezing or problems breathing ■ drooling ■ dizziness or loss of consciousness
These symptoms may be signs of anaphylactic shock. This condition can be life threatening if not treated by a health professional immediately. Symptoms of anaphylactic shock may occur when hives first appear or up to a few hours later.
Not a Substitute for Epinephrine. If your doctor has prescribed an epinephrine injector for "anaphylaxis" or severe allergy symptoms that could occur with your hives, never use this product as a substitute for the epinephrine injector. If you have been prescribed an epinephrine injector, you should carry it with you at all times.
Do not use
■ to prevent hives from any known cause such as: ■ foods ■ insect stings ■ medicines ■ latex or rubber gloves
because this product will not stop hives from occurring. Avoiding the cause of your hives is the only way to prevent them. Hives can sometimes be serious. If you do not know the cause of your hives, see your doctor for a medical exam. Your doctor may be able to help you find a cause.
■ if you have ever had an allergic reaction to this product or any of its ingredients
Ask a doctor before use if you have
■ kidney disease. Your doctor should determine if you need a different dose.
■ hives that are an unusual color, look bruised or blistered
■ hives that do not itch ▶
The makers of Allegra® do not make store brand products. The trade dress of this Allegra® package is subject to trademark protection.
09XXXX
FPO

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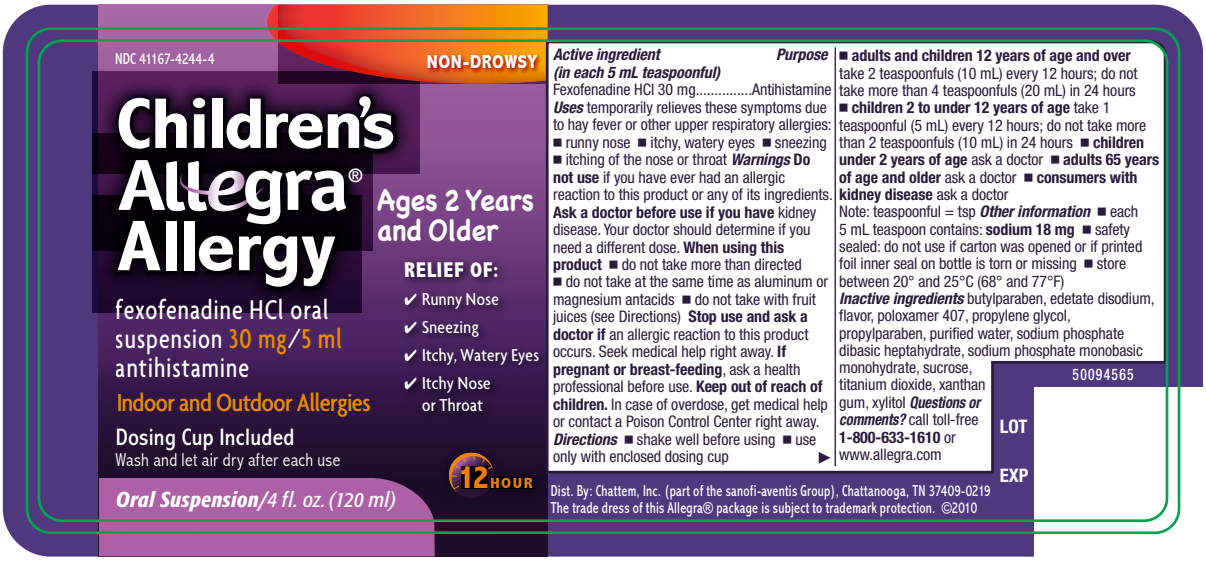

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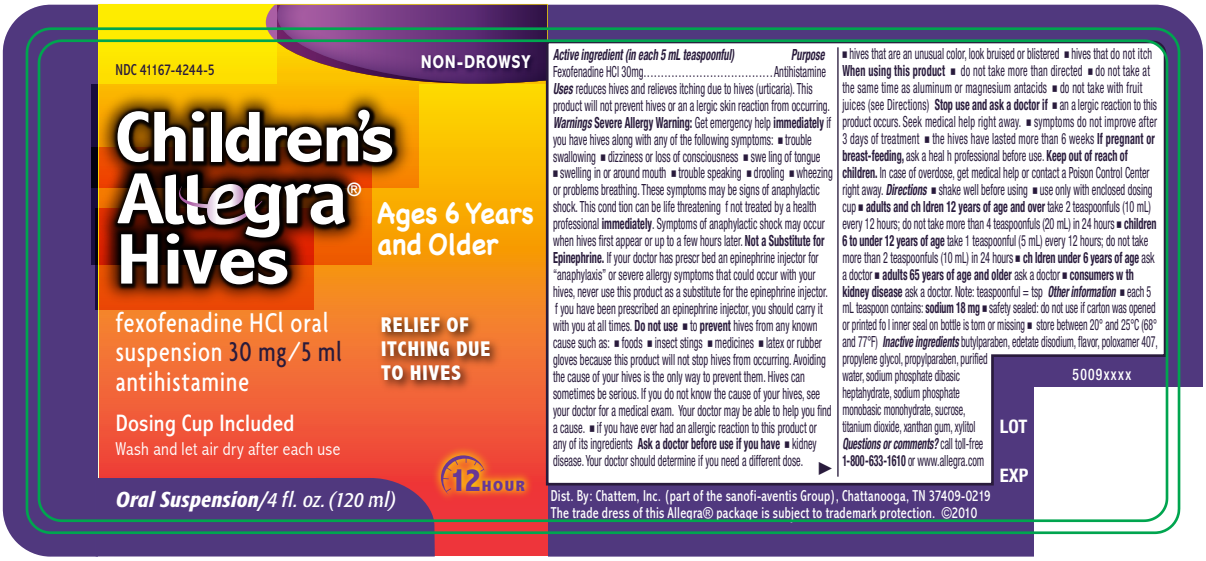

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Drug Facts

Active ingredient (in each tablet) — **Purpose**
Fexofenadine HCl 180 mg ..... Antihistamine

Uses
temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
- runny nose
- sneezing
- itchy, watery eyes
- itching of the nose or throat

Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients.

Ask a doctor before use if you have kidney disease. Your doctor should determine if you need a different dose.

When using this product
- do not take more than directed
- do not take at the same time as aluminum or magnesium antacids
- do not take with fruit juices (see Directions)

Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. ▶

Drug Facts (continued)

Directions

adults and children 12 years of age and over	take one 180 mg tablet with water once a day; do not take more than 1 tablet in 24 hours
children under 12 years of age	do not use
adults 65 years of age and older	ask a doctor
consumers with kidney disease	ask a doctor

Other information
- safety sealed: do not use if carton is opened or if printed foil inner seal on bottle is torn or missing
- store between 20° and 25°C (68° and 77°F)
- protect from excessive moisture

Inactive ingredients
colloidal silicone dioxide, croscarmellose sodium, hypromellose, iron oxide blends, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, titanium dioxide

Questions or comments?
call toll-free **1-800-633-1610** or www.allegra.com

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ORIGINAL PRESCRIPTION STRENGTH
NON-DROWSY
Children's Allegra® Allergy
Ages 6 Years and Older
12 HOUR
NDC 41167-4222-2
ORIGINAL PRESCRIPTION STRENGTH
NON-DROWSY
Children's Allegra® Allergy
fexofenadine HCl tablet
30 mg/antihistamine
Indoor and Outdoor Allergies
6 Tablets 30 mg each
Ages 6 Years and Older
RELIEF OF:
✔ Sneezing
✔ Runny Nose
✔ Itchy, Watery Eyes
✔ Itchy Nose or Throat
12 HOUR
50094531
50094531
Children's Allegra® Allergy
Ages 6 Years and Older
The makers of Allegra® do not make store brand products. The trade dress of this Allegra® package is subject to trademark protection.
0 41167 42222 9
Drug Facts
Active ingredient (in each tablet) Purpose
Fexofenadine HCl 30 mg ..... Antihistamine
Uses
temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ runny nose ■ itchy, watery eyes
■ sneezing ■ itching of the nose or throat
Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients.
Ask a doctor before use if you have kidney disease. Your doctor should determine if you need a different dose.
When using this product
■ do not take more than directed
■ do not take at the same time as aluminum or magnesium antacids
■ do not take with fruit juices (see Directions)
Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Drug Facts (continued)
Directions
adults and children 12 years of age and over: take two 30 mg tablets with water every 12 hours; do not take more than 4 tablets in 24 hours
children 6 to under 12 years of age: take one 30 mg tablet with water every 12 hours; do not take more than 2 tablets in 24 hours
children under 6 years of age: do not use
adults 65 years of age and older: ask a doctor
consumers with kidney disease: ask a doctor
Other information
■ safety sealed: do not use if carton is opened or if individual blister units are torn or opened
■ store between 20° and 25°C (68° and 77°F)
■ protect from excessive moisture
Inactive ingredients
colloidal silicone dioxide, croscarmellose sodium, hypromellose, iron oxide blends, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, titanium dioxide
Questions or comments?
call toll-free 1-800-633-1610 or www.allegra.com
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50094531
ORIGINAL PRESCRIPTION STRENGTH
NON-DROWSY
Children's Allegra® Allergy
Ages 6 Years and Older


Allegra® Allergy
ORIGINAL PRESCRIPTION STRENGTH
NON-DROWSY
12 HOUR
NDC 41167-4131-2
Allegra® Allergy
fexofenadine HCl tablet 60 mg/antihistamine
Indoor and Outdoor Allergies
12 Tablets 60 mg each
RELIEF OF:
✔ Sneezing
✔ Runny Nose
✔ Itchy, Watery Eyes
✔ Itchy Nose or Throat
Allegra® Allergy
The makers of Allegra® do not make store brand products.
The trade dress of this Allegra® package is subject to trademark protection.
0 41167 41312 8
50094533
Drug Facts
Active ingredient (in each tablet) Purpose
Fexofenadine HCl 60 mg ..... Antihistamine
Uses
temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ runny nose ■ itchy, watery eyes
■ sneezing ■ itching of the nose or throat
Warnings
Do not use if you have ever had an allergic reaction to this product or any of its ingredients.
Ask a doctor before use if you have kidney disease. Your doctor should determine if you need a different dose.
When using this product
■ do not take more than directed
■ do not take at the same time as aluminum or magnesium antacids
■ do not take with fruit juices (see Directions)
Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions
adults and children 12 years of age and over: take one 60 mg tablet with water every 12 hours; do not take more than 2 tablets in 24 hours
children under 12 years of age: do not use
adults 65 years of age and older: ask a doctor
consumers with kidney disease: ask a doctor
Other information
■ safety sealed: do not use if carton is opened or if individual blister units are torn or opened
■ store between 20° and 25°C (68° and 77°F)
■ protect from excessive moisture
Inactive ingredients
colloidal silicone dioxide, croscarmellose sodium, hypromellose, iron oxide blends, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, titanium dioxide
Questions or comments?
call toll-free 1-800-633-1610 or www.allegra.com
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50094533
ORIGINAL PRESCRIPTION STRENGTH NON-DROWSY
12 HOUR
Allegra® Allergy

Version 1.0

Reference ID: 2891137

FOR FDA SUBMISSION ONLY

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Allegra Hives
ORIGINAL PRESCRIPTION STRENGTH
NON-DROWSY
The makers of Allegra® do not make store brand products. The trade dress of this Allegra® package is subject to trademark protection. Dist. By: Chattem, Inc. (part of the sanofi-aventis Group), Chattanooga, TN 37409-0219 ©2010
Drug Facts (continued)
These symptoms may be signs of anaphylactic shock. This condition can be life threatening if not treated by a health professional immediately. Symptoms of anaphylactic shock may occur when hives first appear or up to a few hours later.
Not a Substitute for Epinephrine. If your doctor has prescribed an epinephrine injector for "anaphylaxis" or severe allergy symptoms that could occur with your hives, never use this product as a substitute for the epinephrine injector. If you have been prescribed an epinephrine injector, you should carry it with you at all times.
Do not use
■ to prevent hives from any known cause such as:
■ foods ■ insect stings ■ medicines ■ latex or rubber gloves
because this product will not stop hives from occurring. Avoiding the cause of your hives is the only way to prevent them. Hives can sometimes be serious. If you do not know the cause of your hives, see your doctor for a medical exam. Your doctor may be able to help you find a cause.
■ if you have ever had an allergic reaction to this product or any of its ingredients
Ask a doctor before use if you have
■ kidney disease. Your doctor should determine if you need a different dose.
■ hives that are an unusual color, look bruised or blistered
■ hives that do not itch
When using this product
■ do not take more than directed
■ do not take at the same time as aluminum or magnesium antacids
■ do not take with fruit juices (see Directions)
Drug Facts (continued)
Stop use and ask a doctor if
■ an allergic reaction to this product occurs. Seek medical help right away.
■ symptoms do not improve after 3 days of treatment
■ the hives have lasted more than 6 weeks
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions
adults and children 12 years of age and over: take one 60 mg tablet with water every 12 hours; do not take more than 2 tablets in 24 hours
children under 12 years of age: do not use
adults 65 years of age and older: ask a doctor
consumers with kidney disease: ask a doctor
Other information
■ safety sealed: do not use if carton is opened or if individual blister units are torn or opened
■ store between 20° and 25°C (68° and 77°F)
■ protect from excessive moisture
FPO
0 00000 00000 0
Drug Facts (continued)
Inactive ingredients
colloidal silicone dioxide, croscarmellose sodium, hypromellose, iron oxide blends, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, titanium dioxide
Questions or comments?
call toll-free 1-800-633-1610 or www.allegra.com
5009XXXXX
12 Tablets 60 mg each
12 HOUR
RELIEF OF ITCHING DUE TO HIVES
fexofenadine HCl tablet 60 mg/antihistamine
Allegra® Hives
ORIGINAL PRESCRIPTION STRENGTH
NON-DROWSY
NDC 41167-4131-3
FPO
5009XXXX
FPO
XXXX6005
Drug Facts
Active ingredient (in each tablet) — Purpose
Fexofenadine HCl 60 mg ..... Antihistamine
Uses
reduces hives and relieves itching due to hives (urticaria). This product will not prevent hives or an allergic skin reaction from occurring.
Drug Facts (continued)
Warnings
Severe Allergy Warning: Get emergency help immediately if you have hives along with any of the following symptoms:
■ trouble swallowing ■ dizziness or loss of consciousness
■ swelling of tongue ■ swelling in or around mouth
■ trouble speaking ■ drooling ■ wheezing or problems breathing

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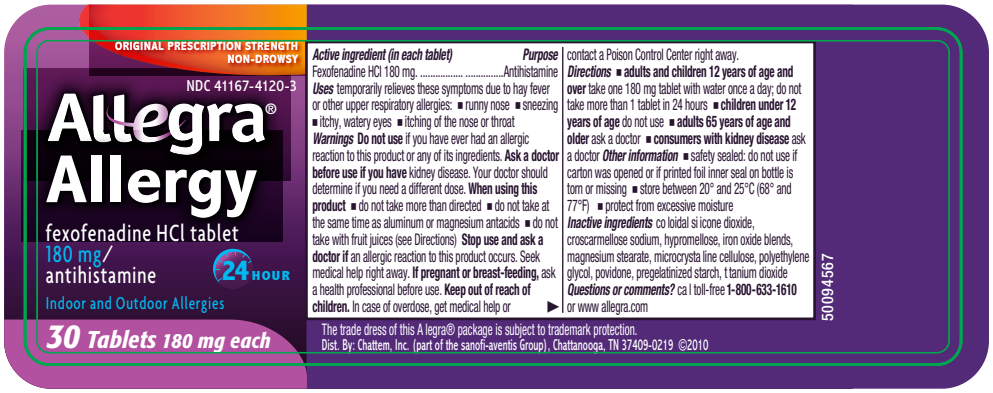

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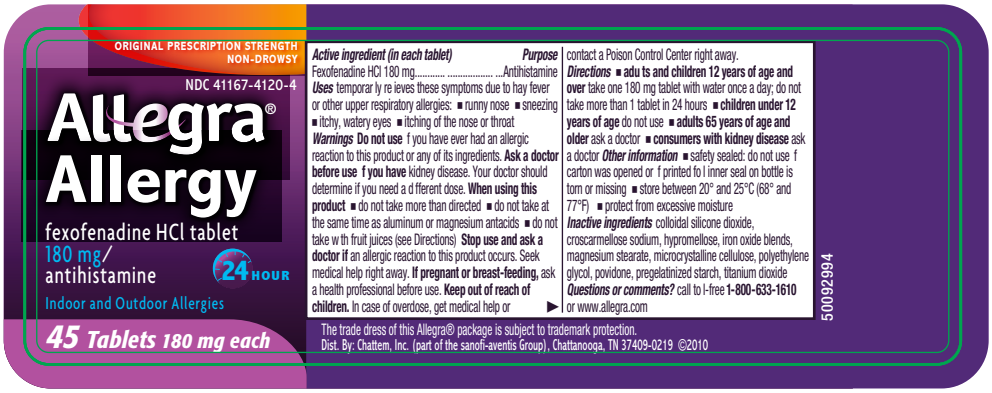

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/s/

AYANA K ROWLEY
01/13/2011

MARINA Y CHANG
01/13/2011

Labeling Review for Allegra Allergy, Children's Allegra Allergy, Allegra Hives and Children's Allegra Hives *Addendum - Draft Labeling*

SUBMISSION DATES:	March 26, June 24, August 20, August 27, September 27, and December 8, 2010
NDA/SUBMISSION TYPE:	201-613 (Tablet) 201-373 (Oral Suspension) 21-909/S-003 (Orally Disintegrating Tablet)
ACTIVE INGREDIENTS:	30 mg, 60 mg and 180 mg fexofenadine (201-613) 30 mg/5ml fexofenadine (201-373) 30 mg fexofenadine (21-909/S-003)
DOSAGE FORMS:	Tablet, Oral suspension and Orally disintegrating tablets
SPONSOR:	Sanofi-aventis, LLC Inc Judith Plon (610) 889-6947
REVIEWER:	Ayana K. Rowley, Pharm.D.
TEAM LEADER:	Marina Y. Chang, R.Ph

I. BACKGROUND

This is an amendment to the preliminary draft labeling review completed on December 2, 2010, by this reviewer. This review also incorporates the comments provided by the review team on December 7, 2010 during the first "labeling day" meeting.

The following recommendations have been revised and updated in order to provide a Complete Response action to the sponsor for initiation of labeling negotiations.

The below mentioned labeling recommendations and comments are based on the revised labels submitted by the sponsor (December 8, 2010) in response to a teleconference with the Division of Medication Errors and Prevention and Analysis (DMEPA).

Submitted Labeling	Representative of Following SKUs
NDA 201-613 Fexofenadine Tablets	
[redacted] (b) (4)	
NDA 21-909 (S-003) Orally Disintegrating Tablets	
30 mg Allergy immediate container (blister front) - 6 count	N/A
30 mg Allergy immediate container (blister back) – 6 count	N/A
30 mg Allergy outer carton -12 count	N/A
30 mg Hives immediate container (blister front) – 6 count	N/A
30 mg Hives immediate container (blister back) – 6 count	N/A
30 mg Hives outer carton- 12 count	N/A
NDA 201-373 Allegra Oral Suspension	
30 mg/5mL Allergy outer carton 4 fl. oz.	N/A
30 mg/5mL Allergy immediate container (bottle) 4 fl. oz.	N/A
30 mg/5mL Hives outer carton 4 fl. oz.	N/A

Submitted Labeling	Representative of Following SKUs
30 mg/5mL Hivers immediate container (bottle) 4 fl. oz.	N/A

REVIEWER'S COMMENTS

A. Outer Carton labels for fexofenadine tablets, oral suspension and orally disintegrating products.

During the labeling meeting held on December 7, 2010, the following recommendations were discussed based on the previously submitted carton and immediate container (bottle and blister card) labels. However, the agency spoke with the sponsor and informed them to remove the "(b) (4)" flag from the principal display panel on the oral suspension products (see the review from December 2, 2010 for a full explanation). This review is based on the carton and immediate container (bottle and blister card) labels submitted on December 8, 2010. This review and recommendation supersedes the initial review dated December 2, 2010 and recommendations to the sponsor should be based on this review.

i. Outer Carton Label Outside Drug Facts

a. Principal Display Panel

(a) For "Allergy" products only. The sponsor has submitted the required clinical studies to support the "Indoor and Outdoor Allergies claim (see the labeling review from December 2, 2010). Although currently omitted from principal display panel from the December 8, 2010 labeling submission, the statement "indoor and outdoor allergies" is acceptable. The sponsor initially proposed this statement claim on its labels. The sponsor should be notified of the acceptability of the statement claim and they may put it back to the label, if they wish.

(b) Proprietary Name. DMEPA has found the proposed proprietary names conditionally acceptable. The DMEPA notes that the name acceptability is contingent upon the fact that the indications for the products indication remain unchanged.

b. Drug Facts Panel

For this current review, the submitted "Drug Facts" labels are not acceptable and the sponsor must revise the labels as follows:

(a) Warnings
  (i) When Using this Product
    1. Add "[bullet] Do not take with fruit juices (see Directions)"

(b) Directions

1. For NDA's 201-613 and 21-909 (S-003) under the 30 mg "Allergy" and "Hives" products. Revise children under 6 years of age from (b) (4) to "do not use".

2. For NDA's 201-613 under the 60 mg and 180 mg "Allergy" and "Hives" products only. Revise children under 12 years of age from: (b) (4) to "do not use".

(ii) For all products. Add "Adults 65 years of age and older: ask a doctor."

(c) Questions

(i) Add the days of the week times of the day a consumer can call to speak to a representative. This recommendation is from 21 CFR 201.66 (c) (9).

(d) On December 2, 2010 the DNCE medical officer, noted in the clinical review that additional labeling warnings should be added. It was then noted during the Labeling Day (December 7, 2010) meeting that these additional warnings are pending further review and internal discussion. The sponsor should be notified that additional warnings may be required to be added to the "Drug Facts" label.

(e) The annotated font specifications are in accordance with 21 CFR 201.66(d). This is acceptable.

ii. Immediate Container Labels for fexofenadine tablets, oral suspension and orally disintegrating products.

a. For all products. The above-mentioned "Drug Facts" label revisions are also applicable to the immediate container (bottle) labels, respectively.

b. For NDA's 201-613 and 21-909 (S-003). The submitted immediate container (blister card) labels are acceptable.

c. The sponsor did not include the draft "dosing cup" graphic design in the December 8, 2010 labeling submission. However, these draft "dosing cup" design graphics (Allergy and Hives) were submitted in previous labeling submission and have been reviewed and found to be acceptable by CMC. We will request that the sponsor include the dosing cup as a part of the final printed labeling submission, in order to keep a current record of the dosing device that accompanies the product.

iii. Consumer Information Leaflet or Package Insert

There is no consumer information leaflet or package insert associated with this application. This is acceptable.

II. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies. Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations. Also, inform the sponsor that these are preliminary comments, further labeling revisions, especially warnings in the "Drug Facts" panel may be necessary.

1. Required labeling changes to all NDAs Outer Carton "Drug Facts" Panel and immediate Container (bottles) labels, where applicable:

    a. Under the Heading "Warnings". Add under the subheading "When Using this Product" [bullet] "Do not take with fruit juices (see Directions)"

    b. Under the Heading "Directions"
        i. For NDA's 201-613 and 21-909 (S-003) for the 30 mg "Allergy" and "Hives" products only. Revise children under 6 years of age from: "ask a doctor" to "do not use".

        ii. For NDA's 201-613 under the 60 mg and 180 mg "Allergy" and "Hives" products only. Revise children under 12 years of age from: "ask a doctor" to "do not use".

        iii. Add "Adults 65 years of age and older: ask a doctor."

2. Recommended Labeling Changes but not required to the approvability of the application.

    Under the Heading "Questions"- Add the days of the week times of the day a consumer can call to speak to a representative as stated in 21 CFR 201.66 (c) (9).

3. Inform the sponsor of the following remarks

    Although currently omitted from principal display panel from the December 8, 2010 labeling submission, the claim "indoor and outdoor allergies" is acceptable.

III. SUBMITTED LABELING

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

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

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	December 13, 2010
To:	Andrea Leonard-Segal, M.D., M.S., Director Division of Nonprescription Clinical Evaluation
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s) and Application Type/Number:	**Allegra Allergy** (Fexofenadine HCl) Tablets 60 mg, 180 mg **Children's Allegra Allergy** (Fexofenadine HCl) Tablets 30 mg **Allegra Hives** (Fexofenadine HCl) Tablets)60 mg, 180 mg **Children's Allegra Hives** (Fexofenadine HCl) Tablets 30 mg NDA 201613 **Children's Allegra Allergy** (Fexofenadine HCl) Orally Disintegrating Tablets 30 mg **Children's Allegra Hives** (Fexofenadine HCl) Tablets Orally Disintegrating Tablets 30 mg NDA 021909/S-003 **Children's Allegra Allergy** (Fexofenadine HCl) Suspension 30 mg/5 mL **Children's Allegra Hives** (Fexofenadine HCl) Suspension 30 mg/5 mL NDA 201373 **Allegra-D 12 Hour Allergy & Congestion** (Fexofenadine HCl and Pseudoephedrine HCl) Tablets 60 mg/120 mg NDA 020786/S-027 **Allegra-D 24 Hour Allergy & Congestion** (Fexofenadine HCl and Pseudoephedrine HCl) Tablets 180 mg/240 mg NDA 021704/S-008
Applicant:	Sanofi-Aventis US, Inc
OSE RCM #:	2010-1112, 2010-1115, 2010-1116, 2010-1117, 2010-1120, 2010-1121

CONTENTS

EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis (DMEPA) evaluation of the labels and labeling for the Allegra product line due to the proposed switch from the prescription status to over-the-counter status.

We noted that the Applicant addressed all our concerns from the November 29, 2010 teleconference and we have no further comments.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from the Division of Nonprescription Clinical Evaluation dated May 20, 2010 for DMEPA for evaluation of the container label and carton labeling for Sanofi-Aventis's over-the-counter Allegra product line for potential to contribute to medication errors. The proposed Allegra product line will include the following products: Allegra Allergy, Allegra Hives, Children's Allegra Allergy, Children's Allegra Hives, Allegra-D 12 Hour Allergy and Congestion, and Allegra-D 24 Hour Allergy and Congestion.

1.2 REGULATORY HISTORY

On March 25, 2010 Sanofi-Aventis submitted applications for the switch of Allegra product line from a prescription status to a non-prescription status. DMEPA found the names Allegra-D 12 Hour Allergy and Congestion and Allegra-D 24 Hour Allergy and Congestion acceptable on October 29, 2010 in OSE RCM Review #2010-1056 and 2010-1057. Additionally, DMEPA found the remaining four names, Allegra Allergy, Children's Allegra Allergy, Allegra Hives, and Children's Allegra Hives acceptable on December 8, 2010 in OSE RCM Review #2010-1058, 2010-1059, 2010-1060, and 2010-1061. The applicant submitted container labels and carton labeling on August 20, 2010 for a total of ten products listed in the Table 1 below.

Table 1: Proposed Non-prescription Allegra Product Line

NDA#	Proposed Allegra Drug Product	Strength
201613	(b) (4)	
021909/S-003	Children's Allegra Allergy Orally Disintegrating tablets Children's Allegra Hives Orally Disintegrating Tablets	30 mg 30 mg
201373	Children's Allegra Allergy Suspension Children's Allegra Hives Suspension	30 mg/5 mL 30 mg/ 5 mL
020786/S-027	Allegra-D 12 Hour Allergy and Congestion Tablets	60 mg/120 mg
0210704/S-008	Allegra-D 24 Hour Allergy and Congestion Tablets	180 mg/240 mg

During DMEPA's initial evaluation of the container labels and carton labeling, we noted that the carton labeling for Allegra Hives and Allegra Allergy as well as those for Children's Allegra Hives and Children's Allegra Allergy were extremely similar and would lead to selection errors. DMEPA discussed these concerns with DNCE at a meeting held on November 23, 2010. DMEPA also discussed our additional labeling recommendations including presentation of the proprietary name in a contiguous manner as well as relocating the graphic of the clock (See Appendix A).

DMEPA and DNCE agreed that DMEPA could discuss our concerns with the Applicant during a teleconference that was scheduled for the following week.

During the teleconference on November 29, 2010, DMEPA advised the Applicant of our concerns of possible confusion and our labeling recommendations to ensure sufficient differentiation between Allegra Allergy and Allegra Hives products in order to minimize the potential for medication errors (See Appendix A).

2 METHODS AND MATERIALS

Since the Allegra product line is currently marketed in the United States, DMEPA conducted a search of the AERS database to evaluate if confusion has occurred with any of the Allegra products related to the labels and labeling. To determine if labeling confusion may occur when the Allegra product line enters the over the counter market, we expanded our search to include Claritin and Zyrtec products lines.

The non-prescription Claritin product line is marketed with a labeling strategy similar to Allegra product line. Claritin is also an OTC non-sedating antihistamine that was originally marketed only as a prescription product. Thus, any medication errors associated with Claritin's labels and labeling may be indicative of the medication errors that may occur with the Allegra product line once marketed.

The non-prescription Zyrtec product line also is marketed with a labeling strategy similar to the proposed over-the-counter Allegra product line. Zyrtec is also an OTC non-sedating antihistamine that was originally marketed only as a prescription product. Thus, any medication errors associated with the use of Zyrtec's labels and labeling may be indicative of the medication errors that may occur with the non-prescription Allegra line once marketed.

The reports identified through the FDA Adverse Event Reporting System (AERS) database were manually reviewed to group duplicate reports into cases and to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. For cases describing a medication error, we reviewed the cases to identify factors that contributed to the errors, and to ascertain if these risks might apply to the proposed labels and labeling of the OTC Allegra product line.

DMEPA also requested that Schering-Plough and McNeil submit data from the Safety Database and the Consumer Call Center regarding medication errors involving Claritin Hives Relief and Claritin Allergy products as well as Zyrtec Hives Relief and Zyrtec Allergy products.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The following sections detail the criteria for medication error searches.

2.1.1 Allegra Product Line Medication Error Search Criteria

The Adverse Event Reporting System (AERS) database search conducted on May 24, 2010 used the following criteria: MedDRA high level group term (HLGT) "Medication Errors" and "Product Quality Issues" as well as high level terms (HLT) "Maladministrations", "Medication Errors NEC", and "Product Quality Issues NEC" along with the trade name Allegra and verbatim "Allegr%". The search was limited to the timeframe of May 12, 2003 to May 24, 2010 because DMEPA had conducted an AERS search previously through May 12, 2003 identifying medication errors associated with existing Allegra products for OSE RCM review #05-0179 completed on August 23, 2005.

2.1.2 Claritin Product Line Medication Error Search Criteria

The AERS database search conducted on May 24, 2010 used the following criteria: MedDRA high level group terms (HLGT) "Medication Errors" and "Product Quality Issues" as well as high level terms (HLT) "Maladministrations", "Medication Errors NEC", and "Product Quality Issues

NEC" along with a trade name Claritin and verbatim "Clari%". The search was limited to the dates of May 1, 2006 to May 24, 2010 because DMEPA conducted a medication error search involving Claritin product line previously in OSE RCM review #06-0013 completed on May 23, 2006.

2.1.3 Zyrtec Product Line Medication Error Search Criteria

The AERS database search conducted on May 24, 2010 used the following criteria: MedDRA high level group terms (HLGT) "Medication Errors" and "Product Quality Issues" as well as high level terms (HLT) "Maladministrations", "Medication Errors NEC", and "Product Quality Issues NEC" along with a trade name Zyrtec and verbatim "Zyrt%". The search was limited to the dates of June 12, 2007 to May 24, 2010 because a medication error search for the Zyrtec product line was conducted previously in OSE RCM Review # 007-400, 2007-402, 2007-403, 2007-404, 2007-405, 2007-406, and 2007-407 completed on November 7, 2007.

2.2 LABELS AND LABELING RISK ASSESSMENT

DMEPA evaluated the labels and labeling of the over-the-counter Allegra product line submitted to the FDA on December 8, 2010 (See Appendix B container labels and carton labeling images):

Table 3: Proposed Labeling for OTC Allegra Product Line

Name	Dosage Form and Strength	Carton Labeling	Container Label
Allegra Allergy Tablets (Fexofenadine HCl)	Tablets 60 mg	12 count carton	6 count blister pack (identical to Allegra Hives 60 mg)
	Tablets 180 mg	5 count carton 15 count carton 30 count carton 45 count carton 90 count carton	5 count blister pack (identical to Allegra Hives 180 mg) 30 count bottle 45 count bottle
Allegra Hives Tablets (Fexofenadine HCl)	Tablets 60 mg	12 count carton	6 count blister pack (identical to Allegra Allergy 60 mg)
	Tablets 180 mg	5 count carton	5 count blister pack (identical to Allegra Allergy 180 mg)
Children's Allegra Allergy (Fexofenadine HCl)	Tablets 30 mg	6 count carton	6 count blister pack (identical to Allegra Hives 30 mg)
	Orally Disintegrating Tablets 30 mg	12 count carton	6 count blister pack (identical to Allegra Hives 30 mg)
	Suspension 30 mg/5 mL	120 mL carton	120 mL bottle 10 mL Dosing Cup

Children's Allegra Hives (Fexofenadine HCl)	Tablets 30 mg	6 count carton	6 count blister pack (identical to Allegra Allergy 30 mg)
	Orally Disintegrating Tablets 30 mg	12 count carton	6 count blister pack (identical to Allegra Allergy30 mg)
	Suspension 30 mg/5 mL	120 mL carton	120 mL bottle 10 mL Dosing Cup
Allegra-D 12 Hour Allergy & Congestion (Fexofenadine HCl and Pseudoephedrine HCl)	Tablets 60 mg/120 mg	10 count carton 20 count carton	5 count blister pack
Allegra-D 24 Hour Allergy & Congestion (Fexofenadine HCl and Pseudoephedrine HCl)	Tablets 180 mg/240 mg	5 count carton 10 count carton	5 count blister pack

3 RESULTS AND DISCUSSION

The following sections describe the findings of our Adverse Event Reporting System (AERS) database searches and labels and labeling review.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

3.1.1 Allegra Product Line Medication Error Cases

DMEPA retrieved a total of thirty nine reports (n=39) from the FDA Adverse Event Reporting System (AERS) database associated with the currently marketed Allegra product line. After eliminating reports not relevant to medication errors occurring with Allegra (e.g., adverse events and allergic reactions) and grouping duplicate reports into cases, two cases remained. Both cases were associated with the placement of the wrong drug product (Glucovance or Atenolol) into Allegra prescription bottles during the dispensing process due to similarity in tablets' size, shape, and color. In the Glucovance case (ISR #5210269-1), the reporter (pharmacist) stated that error occurred due to the similarity in tablets' size, shape, and color. Thus, this error does not appear to be related to the container label of Allegra.

In the Atenolol case (ISR #5295918-4), the reporter (also pharmacist) was not able to identify the source of the confusion between Atenolol and Allegra. Although the case lacks details to determine the root cause for the occurrence of this error, we can not exclude that label confusion contributed to this error. (See Appendix D for the narrative summary of cases).

3.1.2 Claritin Medication Error Cases

DMEPA retrieved a total of forty eight reports (n=48) from the AERS database involving the Claritin product line. However, after grouping duplicate reports into cases and eliminating cases not pertaining to confusion with Claritin's labels and labeling, no relevant cases remained.

However, Schering-Plough submitted the requested information from Pharmacovigilance and Consumer Information Databases regarding medication errors involving confusion between Claritin Allergy and Claritin Hives Relief products to the FDA on August 12, 2010. The Sponsor reported three cases (n=3) of confusion between April, 2006 and November, 2008. All three cases

reported purchasing of Claritin Hives Relief instead of Claritin Allergy product. Patient outcome was not reported. Although not enough details in cases were provided to identify the root cause of the error, we suspect that this error occurred due to the due to the confusing nomenclature and insufficient differentiation in the labeling. (See Appendices G for narrative summary of cases).

3.1.3 Zyrtec Medication Error Cases

DMEPA retrieved a total of two hundred and forty one reports (n=241) from the AERS database associated with the Zyrtec product line. After grouping duplicate reports into cases and eliminating cases not pertaining to confusion with the Zyrtec's labels and labeling, one relevant case remained (n=1, ISR #5798449-8). This medication error case involved mix-up of two Zyrtec products due to confusion of the modifiers. The reporter stated that her pediatrician instructed her to buy Zyrtec Allergy for a 20-month-old child. However, the consumer became confused and bought Zyrtec Hives instead. Although the consumer acknowledged that the error may not have "mattered" given that both "Hives Relief" and "Allergy" products had the same active ingredient and concentration, the consumer was upset and anxious when she later discovered that the labeling for Zyrtec Hives states the product is inappropriate for children under 6 years of age (See Appendix I for the complete narrative of the case). It appears from this case that both nomenclature and labeling contributed to this medication error.

Additionally, McNeil submitted requested information from the Pharmacovigilance and Consumer Information Databases regarding medication errors involving confusion between Zyrtec Hives Relief and Zyrtec Allergy products to the FDA on August 5, 2010. The Sponsor reported that during the time period between January 1, 2008 and July 30, 2010 fifty four medication error cases (n=54) involving confusion between Children's Zyrtec Hives Relief and Children's Zyrtec Allergy have occurred. Two cases (n=2, AER #2008054103 and AER #2009000760) reported administration of Children's Zyrtec Hives Relief instead of Children's Zyrtec Allergy to a 19 month old and a 15 month old children respectively. The doses were not specified in the reports. The remaining fifty-two cases (n=52) reported confusion between Children's Zyrtec Hives Relief and Children's Zyrtec Allergy. These cases stated that the product was not administered at the time of reporting. Forty three case (n=43) reported purchase of Children's Zyrtec Hives Relief instead of Children's Zyrtec Allergy. Two cases (n=2) reported purchase of Children's Zyrtec Allergy instead of Children's Zyrtec Hives Relief. Four cases (n=4) described customers that were in a process of purchasing one of the Children's Zyrtec product, but were confused due to the different modifiers, but identical active ingredients. The remaining three cases (n=3) did not specify which product they had, just stated the confusion. McNeil reported that none of the fifty-four cases (n=54) resulted in patient harm.

Although no specific details in cases were provided to identify the precise root cause of the error, we suspect that this error occurred due to the confusing nomenclature (i.e. shared root names and presence of the modifiers) and insufficient differentiation in the labeling of the products. Thus, since all of the OTC Allegra product will share the root name and contain similar modifiers to Claritin's product line (e.g., Allergy and Hives), it is important to achieve sufficient differentiation among the products through labeling.

We also note that McNeil has since discontinued marketing products containing the modifier "Hives relief" such as Children's Zyrtec Hives Relief from the market. No additional cases of confusion between the labeling of Zyrtec products containing various modifiers were reported. (See Appendices F for narrative summary of cases).

4 CONCLUSSIONS AND RECOMMENDATIONS

The Applicant implemented all DMEPA's recommendations in the labeling revisions submitted to the FDA on December 8, 2010. Our evaluation of the revised labeling did not note any areas of needed improvement at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Janet Anderson at 301-796-0675.

4.1 COMMENTS TO THE APPLICANT

We have evaluated the container labels and carton labeling for the proposed OTC Allegra product line: Allegra Allergy, Children's Allegra Allergy, Allegra Hives, Children's Allegra Hives, Allegra-D 12 Hour Allergy and Congestion, and Allegra-D 24 Hour Allergy and Congestion and we have no further comments at this time.

Additionally, we have evaluated the dosing cup labeling. The evaluation of this labeling noted that dosing cup is labeled in accordance with recommendations found in FDA's Guidance for Industry "Dosage Delivery Devices for OTC Liquid Drug Products." Thus, we have no comments regarding the dosing cup labeling at this time.

REFERENCES

1. ***FDA Adverse Event Reporting System (AERS) Database***

   AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. ***Maslov, Yelena OSE Review #2010-1056, 2010-1057 Allegra-D 12 Hour Allergy and Congestion and Allegra-D 24 Hour Allergy and Congestion Proprietary Name Review***

3. ***Maslov Yelena OSE Review # 2010-1058, 2010-1059, 2010-1060, 2010-1061 Allegra Allergy, Allegra Hives, Children's Allegra Allergy and Children's Allegra Hives Proprietary Name Review.***

<u>Appendix A</u>: DMEPA's recommendations for the OTC Allegra product line labels and labeling submitted to the FDA on September 28, 2010 and September 30, 2010 discussed with the Applicant during teleconference on November 29, 2010.

A. All Container and Carton Labeling

Revise the presentation of the proprietary name to appear in the in the same font size, type style, and color type. This presentation will emphasize the full name of the product. As currently presented, the name modifiers may be overlooked leading to confusion.

B. All Carton Labeling

Consider relocating the graphic featuring the clock that states "12 Hour" and "24 Hour" away from the proprietary name (e.g., lower right corner). As currently presented, the dosing frequency statement may be misinterpreted as a part of the proprietary name.

C. Allegra Hives Caron Labeling

Revise the background coloring scheme for Allegra Hives products to differentiate between Allegra Allergy and Allegra Hives products. As currently presented, the products appear very similar to each other and difficult to tell apart; thus, increasing the potential for confusion. Additionally, DMEPA has postmarking evidences of the products containing similar modifiers being confused.

D. Children's Allegra Container Labels and Carton Labeling

Consider increasing the prominence of the statement identifying the acceptable age for administration of the product without physician's supervision on the principle display panel (e.g., 'Ages 2 Years and Older' and 'Ages 6 Years and Older') by printing it in a larger font and/or bolding. As currently presented, this statement is not prominent, which may result in incorrect product selection for the wrong patient population.

E. Children's Allegra Allergy Suspension Carton Labeling

(b) (4)

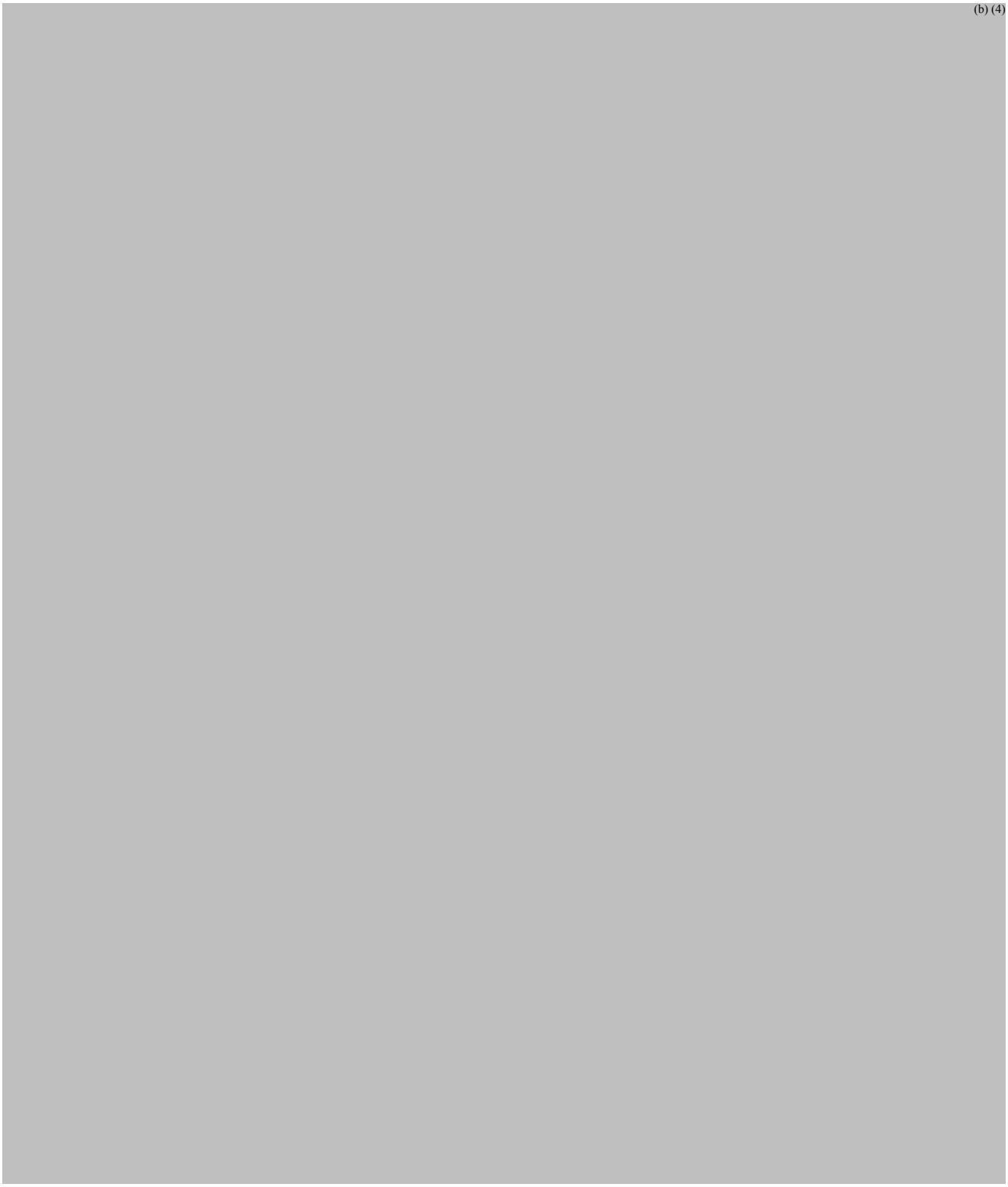
F. Dosing Cup

DMEPA does not have any additional comments regarding dosing cup at this time.

<u>Appendix B:</u> Current Labels and Labeling of OTC Allegra Product Line submitted to the FDA on December 8, 2010

Allegra Allergy 60 mg Carton Labeling 12 tablets

(b) (4)



Appendix D: Narratives of medication error cases involving confusion with currently marketed Allegra product line from AERS database searched from May 12, 2003 to May 24, 2010.

FDA Receipt Date/ ISR #	Type of Medication Error	Narrative	Patient Outcome
01/16/2007 5210269-1	Wrong drug was found in the prescription bottle-Glucovance	41 yo female patient was dispensed Glucovance tablets in pharmacy prescription bottle with the correctly affixed label for Allegra. Patient took the wrong medication from July 2006 until September 2006. Patient felt weak and dizzy the entire time. Lab tests at MD office showed severe hypoglycemia. When patient brought the bottle to the pharmacy, pharmacist explained that Allegra tablets and Glucovance tablets are stored together on the shelf and look very much alike (similar size, shape and color).	Patient experienced severe hypoglycemia for 2 months while taking the wrong medication.
04/10/2007 5295918-4	Wrong drug was found in the prescription bottle-Atenolol	A prescription was written for Allegra 60 mg, but the refill bottle contained Atenolol 25 mg instead of generic Fexofenadine. Pharmacist reporting the medication error stated that tablets do not look similar at all. He said he did not have explanation to why this error occurred.	Patient caught the error before administering a tablet and brought the bottle to the pharmacy

Appendix E Narrative of pertinent medication error case with Zyrtec brand product line from AERS database from June 12, 2007 to May 26, 2010

FDA Receipt Date/ ISR #	Type of Medication Error	Narrative	Patient Outcome
07/01/2008 5798449-8	Wrong drug-names and labeling confusion between Children's Zyrtec Allergy and Children's Zyrtec Hives	Has anyone seen the new Zyrtec OTC products? Very confusing. Not sure what the real diff is between "hives" formulation and "allergy" but they are labeled differently. Could be confusing for consumers. I was given written instructions from pediatrician to give my 20 month old "1/2 tsp at bedtime." At first I grabbed the "hives" bottle but then saw it said for age 6 and up. For some reason, the age 2 "allergy" bottles were behind the pharmacy counter and not on the shelf. I think they are the same concentration so it may not have mattered. But it freaked me out. I contacted the manufacturer and asked if I bought hives by mistake (and commented that the boxes look so similar) could I still give it to my 2 year old if I gave the correct dose from the allergy box. Look-alike name confusion (both products being named Children's Zyrtec). Look-alike packaging. Two Childrens' Zyrtec products that contain the same ingredient in the same concentration and volume. The possibility of purchasing the wrong product (e.g., hives) that would have inappropriate instructions for a different indication (e.g., allergy).	Not reported

Appendix F McNeil's Pharmacovigilance and Consumer Information Databases[***]

Medication Errors from McNeil's Pharmacovigilance Database

AERS Number	Medication Error Description
2008054103	Consumer stated that she accidentally gave her 19 month old child the Hives liquid instead of the Allergy liquid; wants to know is there any harm; doctor did recommend that she give the product to her child.
2009000760	Initial call: Accidentally gave Hives product to 15 month old child. Follow-up call: What is the difference between the hives product and the regular allergy product?

Medication Errors from Consumer Information Database

I wanted Zyrtec Allergy and accidentally purchased Zyrtec Hives for my daughter who has been on Zyrtec for 3 years now. Do I need to exchange my purchase or can I just go ahead and use this one?
gender is female, bought product, asked pharmacist, but still needed verification if the product has the same ingredients as the children's allergy
I accidentally bought this is this the same as regular zyrtec
What is the difference between the Zyrtec Hives Liquid and the Regular Zrytec Liquid for Children. I think I bought the wrong one.
The doctor recommended that we give our child Zyrtec for his allergies, and I bought this Zyrtec which says for hives from the drugstore. Is that any different from the Zyrtec for allergies?
I have been giving my 6 year old the Children's Zyrtec and when i bought this at the store it says hives on it but the pharmacits says its the same ingredient and I was calling to ask if that is true?
I have been using the Children's Zyrtec because thats all I need, but I bought this Zyrtec and it says on it its for hives, but the ingredients appear to be the same. Can I use this?
I purchased this children's hives instead of regular Zyrtec is it the same?
Children's Zyrtec Hives Syrup: My 8 year old son takes this product. He usually take the regular zyrtec but I bought this by mistake. The pharmacist said it was fine, it was the same exact product. Is it the same.
I was suppose had bought the zyrtec allergy instead I accidentally bought the zyrtec hives, my question is what is the difference between the two?
I bought the hives formula for children and it looks as if the ingredients are the same as the regular Zyrtec

*** This document contains proprietary and confidential information that should not be released to the public

syrup are they the same?
has son who uses is 2 1/2 bought hives syrup by accident can i give this to him?
husband bought hives and not the allergy relief can my son still take this? did not have the box with her
Is there a difference between the Children's Zyrtec and the Children's Zyrtec HIVES formula? I bought the Hives formula on accident and returned it to Walgreen's. One of the clerks told me it had the exact same ingredients.
What is the difference between the allergy and this - I picked it up by mistake
I purchased the hive product instead of this product, will this still have work for my 11 year old daughter? Is it the same.
Consumer's grandson takes Zyrtec for allergies and this bottle says "Hives" and it looks different.
7 yr old normally takes Zyrtec for Children Allergy. My mom purchased Children's Zyrtec for Hives. Are they similar?
I purchased this product accidentally. I meant to purchase the Allergy syrup. Is there a difference between the two?
my 6 yr old uses Zyrtec, I just noticed I got the Hives Zyrtec for children, is it the same as the regular Zyrtec syrup?
is this the same as the other children's syrup because I bought this by accident but I see they have a common ingredient?
Consumer wanted to know if the product her daughter bought for grandson is there a difference between this product and the regular Zyrtec?
I have two products. One say for "hives" and the other is for "allergies" Why is that? Are they the same product
she wanted to double check with us, she was given zyrtec for hives at the store, what is the difference between the hives and zyrtec allergy syrup?
I purchased the Zyrtec hives by mistake but when I checked the ingredients they seem to be the same thing , is it?
I bought this by mistake-- look like the same as the childrens zyrtec
She has bought the wrong product and wants to know the difference between the regular syrup and the hives syrup
consumer bought and inquiring if there was a difference between this and hives relief
she bought children zyrtec with allergy on it, is there a difference between the hives and allergies syrup?
What is the difference between the two Zyrtec Syrup products? I purchased the Hives product to give to my 15 month old. Caller has not given the product to her child
Consumer picked up product for hives instead of regular one, can I use the product for hives and does it have the same ingredients?

I purchased the Zyrtec Hives product instead of the Zyrtec Allergy Syrup. How different are the two products?
she usually purchases children allergies and mistakenly purchased children's hives, what is the difference between the two? they both have the same ingredient.
my son has been on regular children's Zyrtec but I accidentally picked up the Zyrtec hive, what is the difference between the children's syrup and hives?
Consumer usually buys the product and bought the Hives formula, what is the difference between the two?
I have a bottle that reads 6yrs and older and has hives relief and there is the bottle that reads 2yrs and older and has allergy relief. The ingredients are the same, what is the difference?
I have two different products here and from what I'm reading they look like its the same thing Can you tell me what's different?
I have two of your Children's Liquids and these ingredients and mg's are the same, what is the difference?
I bought Children's Zytrec Hives relief from store, can I use this product for itchy eyes and runny nose for my child? I want to know the difference in the two products and the children's syrup. Pharmacy told me I could use this product.
my doctor gave me a sample of the CHILDREN'S ZYRTEC ALLERGY SYRUP. I went to the store and pick up the CHILDREN'S ZYRTEC HIVES SYRUP. they have the same ingredients so what is the difference in the products.
I bought this zyrtec hives syrup by mistake, is this the same as other
I bought this product by mistake is it a different type of product compared to the regular children's Zyrtec?
I've been giving this product to my child thinking it was the indoor/outdoor syrup. but then I reading the ingredients and it's the same as that product. Is there a difference between this and the other zyrtec syrup for kids grape flavor?
I just purchased this one and it says hives relief on the label, I normally get the one that has allergy written on the label, are these two products the same.
I purchased this product in error and I wanted to know if I'll still be able to use it for my son? I use the syrup for allergies and everything looks the same in the ingredients.
My children take this product for there allergies, This bottle I bought here says "Hives on it, are they the same thing?
I just purchased this product and it states "Hives" is this the same as the other Zyrtec liquid products?
I accidentally bought the hives one I see the indgredriedtents are the same.
My 6 year old takes this, one teaspoon a day, I sent my husband to the store and he got the children hives, is this the same as the allergy one.
She usually buys children's Zyrtec allergy and accidentally grabbed the children's hives, what is the difference between them?
She purchased a new bottle and the ingredients are different from the old one, she had Zyrtec hives.
the allergy and hives are both still the same but is so confusing everything is same still labeled differently

Appendix G: Schering-Plough Pharmacovigilance and Consumer Information Databases[***]

	Claritin Hives - Verbatims	
		Feb 1, 2004 - Aug 12, 2010
Date	**Case Number**	**Verbatim and Notes Text**
April 3, 2006	1,261,321	Caller is very unhappy that pharmacist sold her Claritin for Hives instead of Claritin Allergy. Caller disconnected.
April 23, 2007	1,334,836	Caller wanted to know if there was a difference between Regular Claritin and the Claritin Hives Relief. Her husband inadvertently bought the Claritin Hives Relief.
June 1, 2007	1,344,617	Would the Claritin Hives Relief be the same as the Claritin Allergy? My husband inadvertently purchased the Claritin Hives Relief. How do I take it-once a day? What is the ingredient?

*** This document contains proprietary and confidential information that should not be released to the public

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

/s/

YELENA L MASLOV
12/13/2010

ZACHARY A OLESZCZUK
12/13/2010

CAROL A HOLQUIST
12/13/2010

Preliminary Labeling Review for Fexofenadine Tablets, Oral Suspension and Orally Disintegrating Tablets (Proprietary Names Pending) *Draft Labeling*

SUBMISSION DATES:	March 26, June 24, August 20, August 27 and September 27, 2010
NDA/SUBMISSION TYPE:	201-613 (Tablet) 201-373 (Oral Suspension) 21-909/S-003 (Orally Disintegrating Tablet)
ACTIVE INGREDIENTS:	30 mg, 60 mg and 180 mg fexofenadine (201-613) 30 mg/5ml fexofenadine (201-373) 30 mg fexofenadine (21-909/S-003)
DOSAGE FORMS:	Tablet, Oral suspension and Orally disintegrating tablets
SPONSOR:	Sanofi-aventis, LLC Inc Judith Plon (610) 889-6947
REVIEWER:	Ayana K. Rowley, Pharm.D.
TEAM LEADER:	Marina Y. Chang, R.Ph

I. BACKGROUND

The sponsor has submitted a NDA supplement for a prescription (Rx) to over-the-counter (OTC) switch for the 30, 60 and 180 mg fexofenadine HCl tablets, the 30 mg/5 ml fexofenadine oral suspension and the 30 mg orally disintegrating tablets single ingredient drug product with labels for separate allergy and hives indications.

Proposed draft carton and container labels were submitted in the initial submission (March 26, 2010). However, on June 24, 2010, the sponsor submitted a second set of revised labeling. Preliminary draft labeling comments concerning the principal display panel based on the June 24th submission were sent to the sponsor on June 30th (via email). No "Drug Facts" labeling comments were conveyed to the sponsor at that time because the review team had yet to

complete the division specific reviews. On August 11, 2010, a teleconference was held between the Division of Nonprescription Regulation Development (DNRD), the Division of Nonprescription Clinical Evaluation (DNCE), and the sponsor to further discuss the labels submitted on June 24, 2010. The sponsor re-submitted revised labels on August 20th, August 27th and September 27th (see table below). This review is based on the August 20th, 27th, and September 27th submission dates.

This review only provides preliminary labeling comments. At the time of this review, this reviewer was notified via e-mail (December 1, 2010) that a set of new revised labeling will be submitted based on the sponsor's discussion with the Division of Medication Errors Prevention and Analysis (DMEPA). The recommendations provided by DMEPA to the sponsor were not relayed to DNRD at the time of this review. Therefore, this labeling review will be amended based on the following pending actions: resubmission of the labeling by the sponsor based on the recommendations from the Division of Medication Errors Prevention and Analysis, the labeling day meeting (December 7, 2010) and the completion of all clinical reviews for the fexofenadine single and combination active ingredient products.

Submitted Labeling	Representative of Following SKUs	Submission Date (Submission Number)
(b) (4)		

(b) (4)

[redacted]

NDA 21-909 (S-003) Orally Disintegrating Tablets		
30 mg Allergy immediate container (blister front) - 6 count	N/A	8/20/10 (S-0016)
30 mg Allergy immediate container (blister back) – 6 count	N/A	8/27/10 (S-0017)
30 mg Allergy outer carton -12 count	N/A	8/27/10 (S-0017)
30 mg Hives immediate container (blister front) – 6 count	N/A	8/20/10 (S-0016)
30 mg Hives immediate container (blister back) – 6 count	N/A	8/27/10 (S-0017)
30 mg Hives outer carton- 12 count	N/A	8/27/10 (S-0017)
NDA 201-373 Allegra Oral Suspension		
30 mg/mL Allergy outer carton	N/A	8/27/10 (S-0017)
30 mg/mL Allergy immediate container (bottle)	N/A	8/27/10 (S-0017)
30 mg/mL Allergy dosing cup	N/A	8/27/10 (S-0017)
30 mg/mL Allergy inner seal (bottle)	N/A	8/27/10 (S-0017)
30 mg/mL Hives outer carton	N/A	8/27/10 (S-0017)
30 mg/mL Hivers immediate container (bottle)	N/A	8/27/10 (S-0017)
30 mg/mL Hives dosing cup	N/A	8/27/10 (S-0017)
30 mg/mL Hives inner seal (bottle)	N/A	8/27/10 (S-0017)

REVIEWER'S COMMENTS

A. Outer Carton labels for fexofenadine tablets, oral suspension and orally disintegrating products.

i. Outer Carton Label Outside Drug Facts

a. (b) (4) The Office of Drug Evaluation IV has concurred with this recommendation.

b. Proprietary Name- The sponsor has proposed that the proprietary name for 30 mg strength tablets, orally disintegrating tablets and oral suspension products as "Children's Allegra Allergy" and "Children's Allegra Hives". The sponsor has proposed that the proprietary name for the 60 mg and 180 mg strength tablets as "Allegra Allergy" and "Allegra Hives". The Division of Medication Errors Prevention and Analysis/proprietary name review team recommendations on the proposed proprietary names are pending. Historically antihistamine products with the "hives" indication have consistently used the modifier "hives relief" as opposed to "hives". DNRD recommends that the proposed proprietary name Allegra Hives Relief and Children's Allegra Hives Relief to maintain consistency.

c. Non-Drowsy Flag- The sponsor has included a non-drowsy flag on the principal display panel. The flag indicates to consumers that these second-generation antihistamine-containing drug products do not cause drowsiness and are consistent with the prescription labeling. These will be the first second-generation antihistamine-containing drug products that do not have a crossed reference sedation warning included in the drug facts label. Previously approved second-generation antihistamine-containing drug products either do not have a "non drowsy" flag and include a sedation warning or have a "non-drowsy" flag and crossed reference a sedation statement (see examples below). DNRD has no objections; this is acceptable.

	Principal Display Panel	Drug Facts Panel
Antihistamine 1 (first Rx to OTC switch)	N/A (no flag)	*When using this product* [bullet] drowsiness may occur [bullet] avoid alcoholic drinks[bullet] alcohol, sedatives, and tranquilizers may increase drowsiness [bullet] be careful when driving a motor vehicle or operation machinery

Antihistamine 2 (second Rx to OTC switch)	Non-Drowsy* (*when taken as directed. See Drug Facts Panel.)	*When using this product* do not take more than directed. Taking more than directed may cause drowsiness.
Fexofenadine	Non-Drowsy	N/A (no warning)

d. Indoor and Outdoor Allergies Statement- The sponsor's current labeling submissions do not include an "indoor and outdoor allergies" claim on the principal display panel. However, the sponsor submitted 4 trials of patients with perennial allergic rhinitis to support an "indoor and outdoor allergies" claim (under the fexofenadine application (201-613)). The medical reviewer from Division of Pulmonary, Allergy, and Rheumatology Products found these studies to be acceptable to support this claim. If in the future the sponsor wishes to add these claims DNRD has no objections at this time, but this may be subject to future review.

ii. Outer Carton Drug Facts Label

The proposed "Drug Facts" labeling is consistent with the OTC class labeling for these second-generation antihistamine drug products. The following are the preliminary comments that can be related to the sponsor for these specific single-ingredient products:

a. ***Active ingredient/Purpose***

(a) The active ingredient/purpose sections are acceptable.

b. ***Uses***

[bullet]Reduces Hives
[bullet] Relieves Itching Due to Hives

Reviewer's Comments: The sponsor has proposed the following indications for the "hives" labeled products: reduce hives and relieves itching to due hives (urticaria). Historically, OTC antihistamine "hives" product carry only one indication "relieves itching to due hives." DNRD will defer to the clinical review staff of DNCE to determine if the product should be labeled for both indications.

c. ***Warnings***

(a) Under the subheading -When Using this Product
  (i) [bullet] "do not take at the same time as aluminum or magnesium antacids."

Reviewer's Comments: The sponsor has included an antacid drug interaction warning, which is consistent with the prescription labeling. The Office of Clinical Pharmacology (OCP) recommends that this is an appropriate warning to be carried over to the drug facts label. It is not

known how the consumer will interpret the phrase "at the same time" however, the prescription label does not provide further information on how the product should be taken otherwise, therefore the decision was made to keep the same language provided. DNRD concurs with this recommendation, this is acceptable. The exact wording of this statement may be revised following the team-labeling meeting.

(ii) Add: [bullet] "Do not take with fruit juices (see Directions) "

Reviewer's Comments: The sponsor has not included a fruit juice drug interaction warning, which is inconsistent with the prescription labeling. The prescription label warns consumers not to take with fruit juices; the direction section also advocates that the drug product be taken with water. The OCP recommends to add a fruit juice warning. This would be the FIRST fruit juice warning for an OTC drug product, which does not specify one or several fruit juices, but suggest that the consumer avoid ALL fruit juices while taking this product. DNRD concurs with this recommendation; this is acceptable.

d. ***Directions***

(a) For the 60 and 180 mg Allergy and Hives products only: Revise (b) (4) to "children under 12 years of age: do not use"

Reviewer's Comments
Currently, these products are not recommended in the pediatric population under the age of 12 years.

(b) Add the subpopulation: "Adult 65 years of age and older: ask a doctor."

Reviewer's Comments
The current prescription labeling indicates that adults 65 years of age and older may have underlying renal disease. This statement has been recommended to be included in the Fexofenadine combination products. Therefore, the same statement should be included for the single ingredient products as well.

e. Other Sections/Issues

(a) The sponsor has included a pregnancy/breast feeding warning as in accordance with 21 CFR 201.63. The DNCE Pharmacology/Toxicology reviewer concurs with this warning statement. DNRD has no objections; this is acceptable.

(b) The labels meet the format specifications, as in accordance with 21 CFR 201.66, therefore, the submitted labeling is acceptable.

iii. Immediate Container Labels for fexofenadine tablets, oral suspension and orally disintegrating products.

a. The final review of these immediate container labels will be deferred pending the acceptability of the proposed propriety name as well as the final language for the drug facts panels.

iv. Consumer Information Leaflet or Package Insert

There is no consumer information leaflet or package insert associated with this application. This is acceptable.

II. RECOMMENDATIONS

This is a preliminary draft labeling review and will be amended to provide recommendations on a Complete Response so that a communication can be issued to the sponsor that includes the below mentioned deficiencies in order to initiate labeling negotiations. This labeling review will be amended based on the following pending actions: resubmission of the labeling by the sponsor based on the recommendations from the Division of Medication Errors Prevention and Analysis on November 30, 2100, the labeling day meeting (December 7, 2010) and the completion of all clinical reviews for the fexofenadine single and combination active ingredient products.

a. Principal Display Panel

(a) (b) (4)

(b) The proposed proprietary names are pending approval from the Division of Medication Errors Prevention and Analysis

b. Drug Facts Panel

(a) The proposed hives indications for the "hives" product: reduces hives and relieves itching due to hives is pending acceptability from the Division of Nonprescription Clinical Evaluation

(b) Warnings

(i) Add under the subheading -When Using this Product
1. "do not take with fruit juices (see Directions)"

(c) Directions

(i) For the 60 mg and 180 mg "Allergy" and "Hives" products only. Revise children under 12 years of age from: (b) (4) to "do not use".

(ii) Add "Adults 65 years of age and older: ask a doctor."

III. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review. These labels are only a sample of the labels (not all labels were included in this preliminary review):

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

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

/s/

AYANA K ROWLEY
12/02/2010

MARINA Y CHANG
12/02/2010

NDA/BLA RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201373 BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type SE
Proprietary Name: ALLEGRA Established/Proper Name: fexofenadine hydrochloride Dosage Form: Oral Suspension Strengths: 30 mg/5mL		
Applicant: sanofi aventis Agent for Applicant (if applicable): Mary-Beth Wigley		
Date of Application: March 25, 2010 Date of Receipt: March 25, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: JANUARY 25, 2011	Action Goal Date (if different): N/A	
Filing Date: June 7, 2010	Date of Filing Meeting: May 11, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): temporary relief of symptoms due to hay fever and other upper respiratory allergies (allergic rhinitis) for adults and children 2 years of age and over and itching due to hives in adults and children 6 years of age and over.		

Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted

Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☒ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☒ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)

Other:	☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): Division of Pulmonary, Allergy and Rheumatology Products (DPARP)	
List referenced IND Number(s):	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***			X	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small*	

business waiver, orphan exemption).

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			X	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			X	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		PREA not triggered and PeRC will review the Pediatric Plan.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?			X	
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?			X	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?			X	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☒ Blister card ☒ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			DCRP Sent 4-8-2010 OSE Sent 6-21-2010

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** December 14, 2009 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			X	

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 11, 2010

BLA/NDA/Supp #: 201373

PROPRIETARY NAME: Allegra

ESTABLISHED/PROPER NAME: fexofenadine hydrochloride

DOSAGE FORM/STRENGTH: Oral Suspension/ 30mg/5mL

APPLICANT: sanofi-aventis

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): temporary relief of symptoms due to hay fever and other upper respiratory allergies (allergic rhinitis) for adults and children 2 years of age and over and itching due to hives in adults and children 6 years of age and over.

BACKGROUND: The application is for a prescription to non-prescription partial switch.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Janice Adams-King and Jessica Diaz	Y
	CPMS/TL:	Melissa Furness	Y
Cross-Discipline Team Leader (CDTL)	Daiva Shetty		Y
Clinical	Reviewer:	Linda Hu	Y
	TL:	Daiva Shetty	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	Ayana Rowley	Y
	TL:	Marina Chang	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Arun Agrawal	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	N/A	
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Cindy Li	Y
	TL:	Paul Brown	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Minerva Hughs	Y
	TL:	Shulin Ding	Y
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	N/A	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	N/A	
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:		

Other reviewers DPARP	Lynne Wu/ Theresa Michele	Y
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Andrea Leonard-Segal, Director, Division of Nonprescription Clinical Evaluation **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

JESSICA M DIAZ
11/26/2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: November 17, 2010

From: Suchitra Balakrishnan, M.D., Ph.D. &
Hao Zhu, Ph.D.

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Jessica Diaz
Regulatory Project Manager
Division of Non-prescription Clinical Evaluation

Subject: QT-IRT Consult to NDA 201613/NDA 201373/NDA 21909- *follow-up to joint meeting between DCRP, DNCE and DPARP on October 25, 2010*

This memo responds to your consult to us dated March 25, 2010 regarding evaluation of ECG data and cardiac adverse event data for fexofenadine, as part of the prescription to OTC switch of fexofenadine (Allegra) tablets, oral disintegrating tablets and oral suspension (NDA 201613/NDA 201373/NDA 21909). We referenced the following materials

- QT-IRT review under NDA 201613 / NDA 201373 / sNDA 21909 dated August 9, 2010

BACKGROUND

Fexofenadine is a selective H1-receptor antagonist that has been marketed under the trade name ALLEGRA ®, as a mono-product since 1996 for the treatment of seasonal rhinitis (SAR) and chronic idiopathic urticaria (CIU) or hives.

The QT-IRT completed a consult for fexofenadine, as part of the prescription to OTC switch of fexofenadine (Allegra) tablets, oral disintegrating tablets and oral suspension (NDA 201613/NDA 201373/NDA 21909) on August 9, 2010. The consult was initiated since the DNCE medical reviewer expressed concern regarding a few cases of sudden death and arrhythmias reported post-marketing. Input from OSE was also requested. The QT-IRT concluded that while a significant cardiac disease burden or concomitant QT-prolonging medication use was reported in most cases, a contributory role for fexofenadine is possible in a

few of the cases, although incomplete information limited assessments (refer to QT-IRT review for details).
The main reason for the TQT recommendation was that although the available clinical trial data suggested that fexofenadine is unlikely to be associated with large changes in QTc interval, the data were inadequate to rule out small effects on QTc interval (<10 ms) as defined by ICH E14 guidance.

There was a joint meeting between the QT-IRT, DNCE and DPARP and Office of the Center Director on October 25, 2010 to discuss the potential implications of the QT-IRT's consult recommendation to request a TQT study from Sanofi-Aventis for fexofenadine. The division has expressed concern since the recommendations also affect the OTC switch NDAs for Allegra-D - 12 hour and -24 hour products, both currently under review. It also impacts the other second generation antihistamines that are OTC (loratadine and cetirizine) as well as the second generation antihistamines that are prescription. The QT-IRT was asked to re-assess their recommendations following the meeting considering all data available.

QT-IRT Comments for DNCE

Clinical Pharmacology Reviewer's Opinion:

Fexofenadine is an active metabolite of terfenadine with similar chemical structure (Figure 1). Terfenadine is a potent hERG channel blocker and was withdrawn from the market because of QTc interval prolongation and TdP. Fexofenadine is a less potent hERG channel blocker than is terfenadine (Table 1), with the IC_{50} value 400-fold larger than terfenadine [1]. However, with the therapeutic dose of fexofenadine of 180 mg once daily, the steady state maximum concentration is 609 ng/mL. Thus, the steady state maximum concentration is only about 20-fold lower than the IC_{50} value, which is not a wide safety margin.

The sponsor performed intensive ECG assessment in several clinical pharmacology studies (i.e., drug-drug interaction studies). QT-IRT has requested study reports for Protocol PJPR0018 (drug interaction study with erythromycin) and Protocol PJPR0028 (drug interaction study with ketoconazole). The reported study results are difficult to interpret because of the following limitations. 1.) The sponsor only analyzed data using Bazett's correction method (i.e., QTcB). It is known that Bazett's correction method overcorrects the heart rate effect. Therefore, it is not an appropriate correction method for most cases. 2.) The primary analyses were based on time-averaged QTc interval change which would tend to minimize peak effects. 3.) The mean QTc interval change reported in ketoconazole arm demonstrated a negative value (please refer to QT-IRT review dated on August 9, 2010). This is inconsistent with our experience in the thorough QT study where ketoconazole demonstrated a significant concentration-dependent QTc interval increase. 4.) The sponsor also reported the QTc interval changes following the administration of terfenadine in the similar drug-drug interaction studies with ketoconazole and erythromycin. The mean values are either close to zero (~ 0.5 ms) or negative (Table 2).

The existing data from clinical trials and post-marketing experience do not suggest large changes in QTc interval following the treatment of fexofenadine. However, the information for cardiac-related risk is not definitive in the following high-risk scenarios, including: 1.) significant

overdose (e.g., >10-fold of the therapeutic dose), 2.) co-administration of drugs with moderate QTc interval change (~ 15 ms), and 3.) administration of fexofenadine in patients with pre-existing conditions (e.g., congenital long QT syndrome). Therefore, cardiac safety profiles in high risk clinical scenarios as a supplement to the clinical and post-marketing experience would provide more definitive evidence and bring additional confidence in using fexofenadine in the general patient population.

Figure 1: Chemical Structure of Terfenadine and Fexofenadine

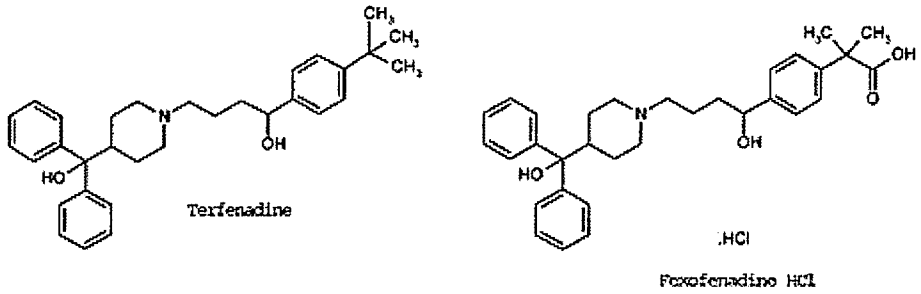

Table 1: IC_{50} Values for Antihistamine Blockade of Cloned Human Cardiac Potassium Channels [1]

	Estimated IC_{50} value		
Antihistamine	HERG	*Kv4.3*	*Kv1.5*
Terfenadine	56 nM	3 μM	367 nM
Astemizole	5.0 nM	17 μM	1.52 μM
Loratadine	2.8 μM	9 μM	808 nM
Ebastine	83 nM	ND	337 nM
Fexofenadine	23 μM	112 μM	214 μM
Cetirizine	> 300 μM	336 μM	140 μM

ND = not determined.

Table 2: Comparison of Terfenadine Treatment Groups in Drug-Drug Interaction Studies with Erythromycin (A) and Ketoconazole (B)

Table 6–327. Comparison of Terfenadine and MDL 16,455A in Change From Baseline in QTc, When Administered Concomitantly With Erythromycin		
Protocol/Treatment	*Average QTc Mean± SE*	*95% Confidence Interval*
9918–1–C–183 / Erythromycin Alone (N=12)	3.3 ± 3.9	(–5.3, 11.9)
Terfenadine Alone (N=12)	0.5 ± 4.1	(–8.5, 9.5)
Erythromycin Plus Terfenadine (N=12)	11.7 ± 4.8	(1.1, 22.2)
SEPR0022 / Erythromycin Alone (N=14)	6.3 ± 1.5	(3.1, 9.5)
Terfenadine (N=15)	0.6 ± 2.3	(–4.3, 5.5)
Erythromycin Plus Terfenadine (N=13)	25.2 ± 2.6	19.5, 30.9)
PJPR0018 / Erythromycin Alone (N=20)	2.2 ± 2.4	(–2.8, 7.2)
MDL 16,455A Alone (N=18)	–4.6 ± 3.3	(–11.6, 2.4)
Erythromycin†Plus MDL 16,455A (N=19)	1.6 ± 2.5	(–3.7, 6.9)
Supporting Data:		*Page*
Table 6–326. Change From Baseline in Mean and Maximum QTc. (b) (4) Read ECG Data		*S6–V1.82–P50*

(A)

Table 6–356. Comparison of Terfenadine and MDL 16,455A in Change from Baseline in QTc, When Administered Concomitantly With Ketoconazole.		
Protocol / Treatment	*Average QTc Mean ± SE*	*95% Confidence Interval*
9918–1–C–166/		
Ketoconazole Alone* (N=11)	2.6 ± 3.0	(–4.1, 9.3)
Terfenadine Alone* (N=5)	–1.5 ± 10.2	(–29.9, 26.9)
Ketoconazole† Plus Terfenadine† (N=11)	29.1 ± 5.5	(16.8, 41.4)
PJPR0028/		
Ketoconazole Alone* (N=24)	–2.0 ± 2.3	(–6.8, 2.8)
MDL 16,455A Alone* (N=23)	–4.7 ± 2.2	(–9.2, –0.05)
Ketoconazole* Plus MDL 16,455A* (N=23)	3.1 ± 2.3	(–1.7, 7.9)
* Steady State † Single–Dose		
Supporting Data:		*Page*
Table 6–355. Change from Baseline in Mean and Maximum QTc. (b) (4) (b) (4)–Read ECG Data		*S6–V1.86–P45*

(B)

Reference

1. C. PRATT, A. M. BROWN, D. RAMPE, J. MASON, T. RUSSELL, R. REYNOLDS and R. AHLBRANDT. Cardiovascular safety of fexofenadine HCl. *Clinical and Experimental Allergy,* 1999, Volume 29, Supplement 3, pages 212–216

Clinical Reviewer's Opinion:

- *Please refer to QT-IRT review dated August 9, 2010 for detailed review of post-marketing and clinical trial data*

- *Please refer to OSE review dated October 8, 2010 by Melinda Wilson, PharmD*

Fexofenadine hydrochloride (terfenadine carboxylate) is the major active metabolite of terfenadine. Terfenadine is a potent hERG blocker with an IC_{50} of 56 nmol/L[1]. By contrast, the IC_{50} value for fexofenadine for hERG channels is reported to be 65.1±8.3 μmol/L. Interestingly, in *in-vitro* preparations it is reported to rescue trafficking-defective LQT2 mutations at concentrations around 350-fold lower than IC-50 for hERG channel blockade[2].

In dogs (30 mg/kg/orally twice daily for 5 days) and rabbits (10 mg/kg, intravenously over 1 hour), fexofenadine hydrochloride did not prolong QTc. In dogs, the plasma fexofenadine concentration was approximately 9 times the therapeutic plasma concentrations in adults receiving the maximum recommended daily oral dose. In rabbits, the plasma fexofenadine concentration was approximately 20 times the therapeutic plasma concentration in adults receiving the maximum recommended daily oral dose. No effect was observed on calcium channel current, delayed potassium channel current, or action potential duration in guinea pig myocytes, sodium current in rat neonatal myocytes, or on several delayed rectifier potassium channels cloned from human heart at concentrations up to 1×10^{-5} M of fexofenadine hydrochloride (*ALLEGRA package insert*).

TdP with terfenadine use without overdose was first documented in a patient who was taking the recommended prescribed dose of this drug in addition to cefaclor, ketoconazole, and medroxyprogesterone. Measured serum concentrations of terfenadine and its main metabolite showed excessive levels of parent terfenadine and proportionately reduced concentrations of metabolite, suggesting inhibition of terfenadine metabolism[3]. Other authors have also confirmed that hERG blockade and consequent QT prolongation are mainly the result of accumulation of the parent compound terfenadine and not the major active metabolite in both *in-vitro* and clinical pharmacokinetic-pharmacodynamic studies[4,5]. Significant QT prolongation with terfenadine in the clinical setting was mainly reported with metabolic inhibition and not with terfenadine alone.

---

[1] Pratt CM, Mason J, Russell T, et al. Cardiovascular safety of fexofenadine Hcl. *Clin Exp Allergy*. 1999;3:212–216

[2] Sridharan Rajamani, Corey L. Anderson, Blake D. Anson and Craig T. January. Pharmacological Rescue of Human K+ Channel Long-QT2 Mutations: Human Ether-a-Go-Go-Related Gene Rescue Without Block. (*Circulation*. 2002;105:2830-2835).

[3] Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr. Department of Medicine, National Naval Medical Center, Bethesda, MD. Torsades de pointes occurring in association with terfenadine use. *JAMA*. 1990 Dec 5;264(21):2788-90.

[4] Woosley, Raymond L.; Chen, Yiwang; Freiman, Joel P.; Gillis, Richard A. Mechanism of the Cardiotoxic Actions of Terfenadine. *JAMA*. Volume 269 (12), 24 Mar 1993, pp 1532-1536.

[5] Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Terfenadine- ketoconazole interaction. Pharmacokinetic and electrocardiographic consequences. *JAMA*. 1993 Mar 24-31;269(12):1513-18.

Fexofenadine is reported not to affect the QT interval even when administered in doses that exceed 10-fold recommendations[6].

The sponsor has reported 32 million patient-years of exposure to fexofenadine. Serious ventricular arrhythmic events that have occurred post-marketing have been addressed in our previous review. A significant cardiac disease burden or concomitant QT-prolonging medication use was reported in most cases. There were 3 cases of reported TdP, sudden death and cardiac arrest reported in young girls that were concerning: ventricular tachycardia and asystole (no documented TdP or preceding QT-prolongation), AV block followed by asystole and confirmed sudden death in the patient with congenital long-QT syndrome. Contributory role for fexofenadine is possible with these cases, but incomplete information limits assessment. However, these cases also have to be assessed in the context of 32 million patient-years exposure to fexofenadine. TdP was never documented in the cases described above and has only been documented in 3 other patients with multiple confounders without preceding documented QT prolongation. Although TdP is a rare event and hard to document it was clearly detected with drugs like terfenadine and cisapride.

Information from clinical trials has also been reviewed in detail in the previous memo. As indicated earlier the available clinical trial data are inadequate to rule out small effects on the QT interval (< 10 ms) as defined by the ICH E-14 guidance, since the trials have some limitations which include absence of a positive control, time-averaged instead of time-matched analyses and no reported exposure-response analysis. However the data do provide some re-assurance that fexofenadine is not associated with large changes in QTc. The maximum expected increase in exposure is around two-fold in patients with severe renal impairment (for whom reduced dosing is recommended) and treatment with erythromycin or ketoconazole (fexofenadine has been shown to exhibit minimal metabolism and this exposure increase is though to be related to increased bio-availability). High exposures were evaluated in the following studies and no mean increases in ECG intervals with fexofenadine use were noted:

- PJPR0007 evaluated the 400-mg b.i.d. dose for 6.5 days with serial ECG measurements. C_{max} at steady state in this study was 3355 (% CV 36.2) ng/mL. The steady state C_{max} with 180-mg q.d. dosing is approximately 603 ng/mL.
- The sponsor has conducted ECG assessments in erythromycin and ketoconazole interaction studies.

In addition, excluding effects less than 10 ms is more of a concern when limited post-marketing information is available and does not apply to this scenario.

In summary, the non-clinical data and clinical information from the literature, the clinical trial data and the post-marketing experience when considered in total provides reasonable re-assurance that pro-arrhythmic liability for fexofenadine is negligible and a TQT assessment is not required for fexofenadine.

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[6] Pratt CM, Mason J, Russell T, et al. Cardiovascular safety of fexofenadine Hcl. *Am J Cardiol.* 1999b: 83: 1451-1454.

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/s/

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Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	08 October 2010
To:	Andrea Leonard-Segal, MD, MS, Director Division of Non-Prescription Clinical Evaluation (DNCE) Office of Drug Evaluation IV
Through:	Ann McMahon, MD, MS, Deputy Director Min Chen, RPh, MS, Associate Director Susan Lu, RPh, Team Leader Division of Pharmacovigilance I (DPV I) Office of Surveillance and Epidemiology (OSE)
From:	Melinda Wilson, Pharm.D, Safety Evaluator Division of Pharmacovigilance I (DPV I) Office of Surveillance and Epidemiology (OSE)
Subject:	Postmarketing Safety Review of death, liver failure, and Torsade de Pointes reports associated with fexofenadine
Drug Name(s):	Allegra® (fexofenadine hydrochloride)
Application Type/Number:	NDA 201-613, 201-373, and 21-909
Applicant/sponsor:	Sanofi-Aventis
OSE RCM #:	2010-1422

CONTENTS

EXECUTIVE SUMMARY

The Division of Nonprescription Clinical Evaluation (DNCE) requested the Office of Surveillance and Epidemiology (OSE) Division of Pharmacovigilance (DPV) review serious events reported with fexofenadine; such as QT prolongation, Torsade de Pointes, liver failure, and deaths, to assist in the determination of an acceptable safety profile to allow for the switch to nonprescription status. DNCE also requested a datamining analysis of the Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) database to confirm the Sponsor's analysis of potential postmarketing safety signals. Initially, this review provides an overview of all postmarketing reports in the AERS database with fexofenadine compared with the Sponsor's analysis of postmarketing reports from the Sanofi-Aventis pharmacovigilance database. Next, this review evaluates the following topics: all new postmarketing reports received by the FDA since the previous OSE reviews of safety issues such as deaths, Torsade de Pointes, and hepatotoxicity with fexofenadine, all reports submitted directly to the FDA, and datamining of the AERS database. Lastly, the review focuses on the specific topics requested by DNCE: reports of death, serious QT prolongation and Torsades de Pointes, and liver failure associated with fexofenadine.

This review documented the following:

Overview of All Postmarkeing Reports in AERS

- As of 20 July 2010, the AERS database contained 3,663 postmarketing reports of adverse events associated with fexofenadine (crude counts). The majority of adverse events reported with fexofenadine represent labeled events.
- Compared with the Sponsor's analysis of the Sanofi-Aventis Pharmacovigilance database (14,572 reports), the AERS database represents a smaller sample of reports that are consistent with the Sponsor's database.
- The Sponsor's analysis of postmarketing reports did not identify new safety issues and concluded that the events reported with fexofenadine are consistent with the currently recognized safety profile of fexofenadine.

New Postmarketing Reports Received by the FDA since the Last OSE Review:

- New postmarketing reports received since the last OSE are consistent with all postmarketing reports for fexofenadine in AERS, which did not reveal new safety issues with fexofenadine.

Deaths:

- We did not identify a pattern of causal events attributable to fexofenadine or new safety issues with fexofenadine from the reports with an outcome of death.

Serious Torsade de Pointes and QT Prolongation:

- Our review of serious QT prolongation or Torsade de Pointes with fexofenadine produced similar conclusions as previous OSE reviews and the DCRP QT Interdisciplinary team's assessment of postmarketing reports. These reviews of postmarketing safety data were suggestive, but not conclusive, of a direct association with fexofenadine and serious QT prolongation or Torsade de Pointes.

Liver Failure:

- We did not identify cases of liver failure and did not establish a causal association with fexofenadine in cases suggestive of liver failure.

Direct Reports:

- Reports received directly by the FDA are consistent with all postmarketing reports for fexofenadine in AERS, which did not reveal new safety issues with fexofenadine.

Datamining:

- The datamining analysis of AERS confirmed the Sponsor's findings regarding fexofenadine.

Overall, we did not identify new safety issues with fexofenadine in this review. We agree with the conclusions of the previous OSE safety reviews regarding QT prolongation and Torsade de Pointes. We did not identify any new safety concerns regarding liver failure. We do not have specific recommendations at this time.

1 INTRODUCTION

The Division of Nonprescription Clinical Evaluation (DNCE) requested the Office of Surveillance and Epidemiology (OSE) Division of Pharmacovigilance (DPV) review serious events reported with fexofenadine; such as QT prolongation, Torsade de Pointes, liver failure, and deaths, to assist in the determination of an acceptable safety profile to allow for the switch to nonprescription status. DNCE also requested a datamining analysis of the Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) database to confirm the Sponsor's analysis of potential postmarketing safety signals. The first section of this review provides an overview of all postmarketing reports in the Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) database with fexofenadine compared with the Sponsor's analysis of postmarketing reports from the Sanofi-Aventis pharmacovigilance database. Next, the review evaluates the following topics: all new postmarketing reports received by the FDA since the previous OSE reviews of safety issues such as deaths, Torsade de Pointes, and hepatotoxicity with fexofenadine, reports submitted directly to the FDA, and datamining of the AERS database. Lastly, the review focuses on the specific events requested in DNCE's consult: reports of death, serious QT prolongation and Torsades de Points and liver failure associated with fexofenadine.

2 BACKGROUND

On 25 March 2010, Sanofi-Aventis submitted a New Drug Application (NDA), which requested a change from prescription to nonprescription status of Allegra® (fexofenadine hydrochloride) 30, 60, and 180 mg tablets. Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective H1-receptor antagonist activity that is currently marketed as a prescription treatment for seasonal allergic rhinitis in patients ≥ 2 years of age and chronic idiopathic urticaria in patients ≥ 6 months of age.[1] The proposed nonprescription use of fexofenadine is for the temporary relief of symptoms due to hay fever or other upper respiratory allergies (runny nose, sneezing, itchy, watery eyes, itching of nose or throat), as well as for the reduction of hives and the relief of itching due to hives (urticaria) in adults and children ≥ 6 years of age.

As part of the NDA, the Sponsor submitted an Integrated Summary of Safety, which included a datamining analysis of the FDA's AERS database from 1 February 1969 to 30 June 2009 using Qscan.[2] According to the Sponsor's analysis, the Empirical Bayes Geometric Mean (EBGM) analyses of the FDA AERS database by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) level revealed safety signals for tachycardia, palpitation, extrasystole, arrhythmia, electrocardiogram QT prolonged, torsade de pointes, and hepatitis acute. To address these signals, the Sponsor provided a detailed discussion of cardiac and hepatic adverse event reports from the Sanofi-Aventis Pharmacovigilance database in a separate section of the submission entitled 'Review of Postmarketing Spontaneous Reports Received for Fexofenadine Hydrochloride'.

The Sponsor's analysis of the Sanofi-Aventis Pharmacovigilance database identified 14,572 spontaneous reports with fexofenadine from 25 July 1996 to 30 September 2009.[3] Most of these

reports originated from the United States, Japan and Canada. The *Prescribing Information* for fexofenadine reflects the most frequently reported events identified in this analysis. Serious events accounted for 6.5% (946 reports) of all reports, including 44 deaths. The most frequently reported serious events included hypersensitivity reactions, currently labeled adverse effects, or adverse events related to the antihistamine class in general (for example convulsion, syncope, other cardiac events, or hepatic injury).

The Sponsor's review provided an in-depth analysis of adverse events generally recognized as suspected class effects of antihistamines. The Sponsor concluded that cardiac events such as tachycardia and palpitations were not uncommon; however, reports of malignant arrhythmic events were rare and usually confounded by significant cardiac disease burden and/or concurrent use of drugs with known cardiotoxicity. The Sponsor concluded that the hepatic adverse event reports were uncommon, nonserious and not suggestive of a drug effect. Other events, such as convulsions, renal events, anaphylaxis and somnolence, did not present safety issues or were consistent with the currently recognized safety profile of fexofenadine.

2.1 PREVIOUS POSTMARKETING REVIEWS

Previous reviews by OSE-DPV evaluated the safety profile of fexofenadine in response to a request to switch fexofenadine to nonprescription status. Such reviews focused on cardiovascular disorders and deaths, supraventricular arrhythmias, ventricular arrhythmias, seizures, and drug interactions with fexofenadine and antifungals, macrolides, and warfarin.[4,5,6] In all of the postmarketing safety reviews which investigated cardiovascular disorders, the evidence was inconclusive to establish a direct association with cardiac adverse events (i.e.,QTc prolongation and ventricular arrhythmias). Many of the cases documented preexisting cardiovascular disease or concomitant medications that make the association with the cardiac events and fexofenadine uncertain. A review of drug interactions suggest that, given the metabolism of fexofenadine via the CYP3A4 pathway, the causal role of fexofenadine in a small number of drug interaction cases involving clarithromycin, fluconazole, itraconazole, and warfarin that utilize this pathway cannot be excluded. A previous review concluded that fexofenadine was 'possibly associated' with cases of new onset seizures and an increase in seizure frequency.

An additional review of hepatoxicity, initiated by foreign regulatory activity, identified 60 cases of hepatotoxicity, including one case of severe life-threatening injury with liver failure.[7] Most of the cases identified were mild to moderate, had additional risk factors or contributing factors and did not present a clear mechanism of liver injury. The majority of severe cases originated outside of the United States (US). Although the reviewer recommended consideration be given to insertion of a statement in the labeling that increased hepatic transaminases, hyperbilirubinemia, cholestasis, and clinically significant liver injury have been reported in the postmarketing setting with fexofenadine, the Division of Pulmonary and Allergy Products (DPAP) concluded that labeling updates were not warranted at the time.[8] DPAP based this position on the varied types of liver injury, confounding due to concomitant medications or illness, origination of most reports outside of the US, and extensive patient exposure to fexofenadine.

In response to a Citizen Petition filed in July of 1998 which requested the FDA remove the prescription–dispensing requirements of section 503(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act for fexofenadine and loratadine, the FDA reviewed NDA databases, the AERS reporting system and the published literature for safety data with fexofenadine and loratadine.[9] The OTC Switch Review Team did not identify safety concerns with either antihistamine. They also concluded that fexofenadine does not inhibit the main subunit of the HERG K^+ channel, which is responsible for cardiac arrhythmias with terfenadine, and the cardiovascular events and deaths observed with terfenadine were considered unlikely to be relevant for fexofenadine.

2.2 REGULATORY HISTORY

The FDA first approved fexofenadine in 1996 for seasonal allergic rhinitis (SAR) as a 60 mg capsule formulation. Although the capsule formulation is no longer marketed in the United States (US), Sanofi-Aventis submitted subsequent submissions providing for 30 mg, 60 mg, and 180 mg tablets formulations in 2000 and 2005 for SAR in patients ≥ 2 years of age and chronic idiopathic urticaria (CIU) in patients ≥ 6 months of age.

2.3 PRODUCT LABELING

The *Prescribing Information* for fexofenadine contains the following information regarding hepatic metabolism and QT prolongation:

> **Hepatic:**
>
> Approximately 5% of the total dose of fexofenadine hydrochloride was eliminated by hepatic metabolism.
>
> **QT prolongation:**
>
> No statistically significant increase in mean QTc interval compared to placebo was observed in 714 adult subjects with seasonal allergic rhinitis given fexofenadine hydrochloride capsules in doses of 60 to 240 mg twice daily for 2 weeks. Pediatric subjects from 2 placebo- controlled trials (n=855) treated with up to 60 mg fexofenadine hydrochloride twice daily demonstrated no significant treatment- or dose-related increases in QTc. In addition, no statistically significant increase in mean QTc interval compared to placebo was observed in 40 healthy adult subjects given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days, or in 230 healthy adult subjects given fexofenadine hydrochloride 240 mg once daily for 1 year. In subjects with chronic idiopathic urticaria, there were no clinically relevant differences for any ECG intervals, including QTc, between those treated with fexofenadine hydrochloride 180 mg once daily (n = 163) and those treated with placebo (n = 91) for 4 weeks.
>
> In dogs (30 mg/kg/orally twice daily for 5 days) and rabbits (10 mg/kg, intravenously over 1 hour), fexofenadine hydrochloride did not prolong QTc.

3 OVERVIEW OF REPORTS WITH FEXOFENADINE FROM THE AERS DATABASE

3.1 METHODS AND MATERIALS

We searched the AERS database on 20 July 2010 with the following criteria:

- Drug terms: Active ingredient (fexofenadine, fexofenadine hydrochloride), Trade name (Allegra)
- MedDRA terms: all terms
- Time period: all reports until 20 July 2010
- Age range: all ages

To address the Sponsor's datamining analysis, we conducted an independent analysis of fexofenadine reports in the AERS database at the MedDRA PT level using Empirica Signal® 7.0 software and the Multi-item Gamma Poisson Shrinker (MGPS) [10,11] data mining algorithm on 27 July 2010. Appendix 1 describes the data-mining methods, limitations, and results.

3.2 RESULTS

3.2.1 Overview of Fexofenadine Reports

The search identified 3663 postmarketing reports associated with fexofenadine in the AERS database (crude counts). Table 1 summarizes the crude counts of all AERS reports with fexofenadine from approval to 20 July 2010. Appendix 1, Table 1 presents the results of the datamining analysis.

Table 1. Crude Counts[a] of AERS Reports with Fexofenadine from Approval to 20 July 2010 (n=3663)

Age (years) [N=2622]	Average (48), Median (48), Range (1 hour to 97 years)
Gender (N=3342)	Male (1111), Female (2231)
Country (N=3550)	US (2837), Foreign (713); [including Japan (283), France (100), Great Britain (72)]
Report Type (N=3663)	Expedited (1358), Direct (355), Periodic (1950)
Event year (N=3663)	1996 (37) 1997 (571) 1998 (134) 1999 (987) 2000 (438) 2001 (337) 2002 (141) 2003 (153) 2004 (122) 2005 (117) 2006 (128) 2007 (115) 2008 (143) 2009 (148) 2010 (92)
Frequently reported PTs[d] (3663 reports listing 9769 PTs)	Drug ineffective (374), Dizziness (218), Nausea (174), Headache (167), Dyspnoea (142), Palpitations (139), Insomnia (127), Urticaria (115), Pruritus (115), Diarrhoea (109), Dermatitis (102), Drug Interaction (100)
Outcomes[b] (1687 serious reports with 1938 serious outcomes)	Death (144), Congenital Anomaly (16), Disability (56), Hospitalization (544), Life-threatening (119), Other Medically Serious (1010), Required intervention (49)
Most frequently reported PTs[c] in reports with a serious outcome (N=1687 reports)[e]	Dizziness (110), Dyspnea (97), Convulsion (80), Syncope (74), Urticaria (70), Drug interaction (70), Drug Ineffective (70), Palpitaitons (68), Nausea (68), Headache (66), Condition aggravated (64), Loss of consciousness (63), Malaise (62), Tachycardia (57), Pruritius (57), Vomiting (52), Hypersensitivity (52).
Most frequently reported PTs in reports with a fatal outcome (N=144)[c,f]	Completed suicide (46), Cardiac arrest (16), Myocardial infarction (13), Drug toxicity (13), Death (12), Toxic Epidermal Necrolysis (10), Cardiorespiratory Arrest (10).
Primary suspect medication[g] (N=3663)	Fexofenadine (2493), other medications (1170)

Table 1. Crude Counts[a] of AERS Reports with Fexofenadine from Approval to 20 July 2010 (n=3663)	
• Daily dose of fexofenadine (N=1234)	Average (127 mg), Median (120 mg), Range (8 mg to 720 mg)
• Duration of therapy of fexofenadine (days)[N=1891]	Average (32.9), Median (0), Range (0 days to 10 years)
• Most Frequent Reasons for fexofenadine use (N=1510)	Allergies (544), Allergic rhinitis (210), Urticaria (77), Seasonal Allergies (32), Allergy (31), Seasonal Allergic Rhinitis (27), Rhinitis Allergic (25), Allergy symptoms (23), Pruritis (18), Hives (14), Chronic Urticaria (14), Rash (14), Sinusitis (14), Itching (13), Rhinitis (13), Eczema (12), Pollinosis (12), Seasonal Allergy (12), Sinus infection (10)
[a] May include duplicates [b] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events. Reports may include multiple outcomes. [c] Each case may have multiple PTs [d] PTs with ≥ 100 occurrences [e] PTs with ≥ 50 occurrences [f] PTs with ≥ 10 occurrences [g]Daily dose, duration of therapy and reason for use determined based on reports indicating fexofenadine at the primary suspect	

3.2.2 Reports with Fexofenadine Received by the FDA since the Last OSE Review

Since OSE conducted several reviews of postmarketing reports with fexofenadine, we analyzed reports received since the last review on 30 January 2006 to identify new safety issues. Table 2 describes the reports received since the last review by OSE (30 January 2006 to 20 July 2010).

Table 2. Crude Counts[a] of AERS Reports with Fexofenadine Since the Previous OSE Review (30 January 2006 to 20 July 2010) (n=615)		
Age (years) [N=423]	Average (48), Median (49), Range (7 months to 97 years)	
Gender (N=571)	Male (188), Female (383)	
Country (N=615)	US (319), Foreign (296), [including Japan (158)]	
Report Type (N=615)	Expedited (444), Direct (128), Periodic (43)	
Event year (N=615)	2006 (117) 2007 (115) 2008 (143)	2009 (148) 2010 (92)
Most frequently reported PTs[c] (615 reports describing 2099 PTs)[d]	Dizziness (49), Drug ineffective (45), completed suicide (42), product quality issue (30), nausea (29), headache (25), hepatic function abnormal (23), rash (22), malaise (22), pruritus (21), urticaria (20), loss of consciousness (20), dyspnoea (20)	
Outcomes[b] (518 serious reports	Death (81), Congenital Anomaly (5), Disability (27),	

Table 2. Crude Counts[a] of AERS Reports with Fexofenadine Since the Previous OSE Review (30 January 2006 to 20 July 2010) (n=615)	
indicating 610 serious outcomes)	Hospitalization (160), Life-threatening (39), Other Medically Serious (296), Required intervention (2)
Most frequently reported PTs[c] in reports with a serious outcome (N=518)[d]	Dizziness (42), completed suicide (42), nausea (25), hepatic function abnormal (23), drug ineffective (22), malaise (21), headache (20)
Most frequently reported PTs in reports of death (N=81)[c,e]	Completed Suicide (42), drug toxicity (12), toxic epidermal necrolysis (10)

[a] May include duplicates
[b] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events. Reports may include multiple outcomes.
[c] Each case may have multiple PTs
[d] PTs with ≥ 20 occurrences
[e] PTs with ≥ 10 occurrences

3.2.3 Deaths

In response to DNCE's consult request, we evaluated all reports with fexofenadine that indicated an outcome of death. The AERS database contained 144 reports of deaths associated with fexofenadine. After excluding 58 duplicate reports and 42 reports that indicated a medication other than fexofenadine as the primary suspect, the case series included 44 reports of death associated with fexofenadine. Among the 42 excluded reports, the majority involved a combination of fexofenadine and pseudoephedrine or indicated fexofenadine as a secondary suspect along with multiple other medications. Five reports involved the fexofenadine and pseudoephedrine combination product (Allegra-D®). The events most frequently described in the remaining 37 reports were completed suicides, overdoses, or drug toxicity, involving multiple medications (24 cases). These 44 postmarketing reports of fatalities with fexofenadine from the AERS database are also described in the Sponsor's submission (Review of Postmarketing Spontaneous Reports Received for Fexofenadine Hydrochloride, 4.4 Cases with Fatal Outcome, pages 28-31). Table 2 describes the characteristics of the post-marketing cases of fatalities with fexofenadine from AERS as of 20 July 2010.

Table 2. Characteristics of Post-Marketing Cases of Fatalities with Fexofenadine as of 20 July 2010 (N=44)		
Age (years) [N=37]	Average (54), Median (56), Range (1 day to 92 years)	
Gender (N=41)	Male (25), Female (16)	
Country (N=38)	US (15), Foreign (23)	
Report Type (N=44)	Expedited (44)	
Event year (N=44)	1997 (1)	2004 (2)
	1998 (3)	2005 (2)
	1999 (6)	2006 (1)
	2000 (9)	2007 (1)
	2001 (6)	2008 (2)

Table 2. Characteristics of Post-Marketing Cases of Fatalities with Fexofenadine as of 20 July 2010 (N=44)	
	2002 (5) 2009 (2) 2003 (4)
Indication (N=23)	Urticaria (6), allergic rhinitis (5), allergies (3), atopic complaints (1), congestion (1), eczema (1), hay fever (1), mother's pollinosis (1), nasal discharge secondary to common cold (1), pruritus (1), sinus congestion (1), atopic dermatitis (1)
Daily Dose (N=20)	Average (132 mg), Median (120 mg) 120 mg (10), 180 mg (7), 60 mg (3)
Time to Event (days) [N=33]	Average (9.6), Median (0), Range (0 to 222 days)
Most frequently reported PTs [a] (44 cases reporting 142 PTs)[b]	Myocardial infarction (8), death (5), sudden death (5), arrhythmia (5), cardiac arrest (4), respiratory failure (3), eosinophilia (3), renal failure (3), malaise (3), circulatory collapse (3), cardiac failure (3), ventricular fibrillation (2), thrombocytopenia (2), syncope (2), shock (2), sepsis (2), pulmonary oedema (2), jaundice (2), fall (2), electrocardiogram QT prolonged (2), dyspnoea (2)
[a] Each case may have multiple PTs [b] PTs occurring on ≥2 occurrences	

3.3 DISCUSSION

3.3.1 Overview of All Reports with Fexofenadine in AERS

The search identified 3,663 reports with fexofenadine from approval to 20 July 2010 in the AERS database. Forty-six percent of all reports indicated a serious outcome while 21% of all reports resulted in death, hospitalization, or were life threatening. The most frequently reported events described in postmarketing reports are currently included in the *Prescribing* Information for fexofenadine, with the exception of palpitations (N=139). Among the events frequently reported in cases with a serious outcome, most events are included in the label with the exception of convulsion, syncope, palpitation, loss of consciousness, malaise, and tachycardia. In an effort to identify whether the aforementioned events are present in cases that resulted in an outcome of death, we provide further analysis in section 3.3.4. Since many of these events may also occur in cases of Torsade de Pointes or QT prolongation, Section 5 focuses on Torsade de Pointes or QT prolongation events reported in cases with a serious outcome. Overall, the majority of adverse events reported in AERS database with fexofenadine represent labeled events.

Manufacturers submitted the majority of reports with fexofenadine in the AERS database (90%, 3308 of 3663 reports). Compared with the Sponsor's pharmacovigilance database, the AERS database contains only a fraction of the postmarketing reports with fexofenadine (3,663 reports in AERS versus 14,572 reports in the Sanofi-Aventis pharmacovigilance database). Thus, the Sponsor's Review of Postmarketing Spontaneous Reports Received for Fexofenadine Hydrochloride is a more complete description of the postmarketing experience with fexofenadine.

Ten percent (355 of 3663) of reports with fexofenadine in the AERS database were sent directly to the FDA by a party other than the manufacturer. Consumers submitted the most direct reports (84), followed by pharmacists (80) and physicians (79). Two-hundred and ninety-five direct

reports implicate fexofenadine as the primary suspect medication in the report (83%). Direct reports frequently describe product quality issues (product quality issue [49]), efficacy issues (drug ineffective [47], therapeutic response unexpected with drug substitution [29]), or labeled events (palpitations [29], dizziness [28], dyspnoea [25]). Most direct reports did not indicate a serious outcome, yet among the reports in which fexofenadine was the primary suspect there was one death, two disabilities and 22 hospitalizations. The death report (ISR#3936721, CTU 170590) was a duplicate of another report submitted to AERS by the sponsor (ISR#3959201, 200217201US). Both the Sponsor's Review of Postmarketing Spontaneous Reports Received for Fexofenadine Hydrochloride and Section 3.3.4 of this review describe this case among other fatalities reported in cases with fexofenadine. While some of the remaining direct reports may not be included in the Sponsor's database, the overall number of direct reports is comparatively small, mostly non-serious, limited by poor documentation, and document labeled events or product issues.

3.3.2 Reports with Fexofenadine Received by the FDA Since the Last OSE Review

Since the datalock date (30 January 2006) of the last OSE review, the FDA received 615 reports with fexofenadine. These reports are similar to the other reports in the AERS database with fexofenadine based on age, report source, reporting country, and preferred terms. Manufacturers submitted most of these reports, which originated mainly from the US. Consumers or healthcare providers sent only 128 reports directly to the FDA. The most recent reports include the same PTs as older reports, with the exception of Hepatic function abnormal (N=23). To evaluate the serious manifestations of hepatic dysfunction, section 4 provides further evaluation of liver failure cases reported with fexofenadine. Overall, the majority of PTs from the more recent reports are included in the *Prescribing Information* for fexofenadine and are similar to the PTs reported with fexofenadine in the AERS database since approval.

3.3.3 Datamining

Similar to the Sponsor's datamining analysis, our datamining analysis identified potential cardiac and hepatic signals. The Sponsor's submission discusses the individual cases that contribute to significant safety signals involving cardiac and hepatic disorders. This review investigates serious manifestations of these signals by evaluating serious QT prolongation and Torsade de Pointes and liver failure. Other signals identified by this analysis represent events which are labeled (dysmenorrhoea, swelling face, hypersensitivity, nervousness), related to the indication (rhinitis, rhinorrhoea), involve a small number of reports ($\leq$ 25 reports: lymphocyte stimulation test positive, nasal dryness, gastrointestinal pain) or are uninformative (therapeutic response unexpected with drug substitution, product substitution issue, medication residue).

3.3.4 Death

Both the AERS database and the Sponsor's submission describe the same cases, which reported an outcome of death associated with fexofenadine. The Sponsor's analysis of fatal postmarketing reports is complete and serves as a secondary analysis of these cases. The causal role of fexofenadine is difficult to establish in the majority of these cases due to the presence of underlying diseases, concomitant medications, or insufficient information. We did not identify a pattern of causal events attributable to fexofenadine and did not identify new safety issues with fexofenadine among cases that reported an outcome of death. In response to the initial consult request, this review also focuses on deaths and other events associated with QT Prolongation and Torsade de Pointes in section 5 and deaths and other events associated with liver failure in Section 4.

4 LIVER FAILURE

4.1 METHODS AND MATERIALS

To capture all reports of liver failure, we searched AERS on 13 August 2010 using the following criteria:

- Drug terms: Active ingredient (fexofenadine, fexofenadine hydrochloride), Trade name (Allegra)
- MedDRA terms: OSE case definition search strategy for liver failure reports. See Appendix 3 for a description of the terms used in this search.
- Time period: all reports until 13 August 2010
- Age range: all ages
- Outcome: all serious outcomes

4.2 RESULTS

The AERS search identified 12 reports from the search for liver failure with fexofenadine. This included two duplicate reports. We excluded five additional reports from further analysis (one for previous history of cirrhosis and primary suspect medication valacyclovir, one report associated with fexofenadine and pseudoephedrine, two due to concomitant diseases and one due to lack of information and an unevaluable event). Table 3 summarizes the remaining five reports.

Table 3. Characteristics of Liver Failure Cases with Fexofenadine as of 13 August 2010 (N=5)	
Age (years) [N=5]	Average (57) Median (56), Range (34 to 74 years)
Gender (N=5)	Male (3), Female (2)
Country (N=5)	US (1), Foreign (4); [including Japan (3)]
Report Type (N=5)	Expedited (5)
Indication (N=4)	Seasonal allergy (1), rhinitis allergic (1), skin eruption (1), urticaria (1)
Daily Dose (N=1)	180 mg (1), unknown (4)
Time to Event (days) [N=5]	Average (21), Median (12), Range (0 to 61 days)
Most frequently reported PTs[a,b] (5 cases reporting 50 PTs)	Hepatitis (3), jaundice (2), hepatitis fulminant (2), alanine aminotransferase increased (2), aspartate aminotransferase increased (2), hepatic necrosis (2), chromaturia (2)
Outcomes[b] (5 cases indicating 6 serious outcomes)	Death (1), Hospitalization (2), Life-threatening (1), Other Medically Serious (2)
[a] PTs occurring on ≥2 occasions [b] Each case may have multiple PTs	

4.3 DISCUSSION

All of the AERS cases identified from this search for liver failure were analyzed in the previous OSE review of hepatotoxicity (datalock date 25 October 2004), with the exception of two additional recent cases. One case describes eosinophilic hepatitis in a 34 year-old that resolved after discontinuation of fexofenadine and, in the absence of other explanations, is suggestive of causality with fexofenadine (ISR#5956201, 200812883US). The other case documents acute

hepatitis resulting in death in a 74-year-old female; however, the clinical picture and temporality from this case was inconsistent with fexofenadine causality (ISR#6199993, 200910011JP). The Sponsor also describes these cases in their submission (Review of Postmarketing Spontaneous Reports Received for Fexofenadine Hydrochloride, 7.2 Hepatic Adverse Event Reports, pages 67-70).

As mentioned previously, we identified one case of death associated with fexofenadine from the search of AERS for liver failure. We found an additional case of death due to hepatic failure from the search of all postmarketing reports of death with fexofenadine in the AERS database. This case (ISR#3923058, 20021184FR) was included in the previous OSE review of hepatic events. The sponsor's analysis of postmarketing deaths and hepatic events includes both fatalities due to hepatic events (ISR#6199993,200910011JP; ISR#3923058,2002118474FR)(Review of Postmarketing Spontaneous Reports Received for Fexofenadine Hydrochloride, 7.2 Hepatic Adverse Event Reports, pages 67-70).

Similar to the cases in the previous OSE review of hepatotoxicity, most of the cases in this liver failure series contained additional risk factors for hepatotoxicity or concomitant potential hepatotoxic medications, originated outside of the US, and described a varied pattern of liver injury. Three out of the five cases originated from Japan and only one case involved a US patient. The pattern of liver injury ranged from cholestatic (1), hepatocellular (1), eosinophilic hepatitis (1), and unassessable (2). The search of AERS did not identify cases of liver transplant associated with fexofenadine. The Sponsor submitted a complete analysis of all hepatic events, including the cases of liver failure we identified in AERS. Overall, we did not establish a pattern of events suggesting causality with fexofenadine and did not identify new safety issues regarding liver failure based on the review of postmarketing reports in AERS.

5 QT PROLONGATION AND TORSADE DE POINTES

5.1 METHODS AND MATERIALS

We searched AERS on 13 August 2010 for adverse event reports using the following criteria:

- Drug terms: Active ingredient (fexofenadine, fexofenadine hydrochloride), Trade name (Allegra)
- MedDRA terms: PTs from the Narrow Scope Torsade de Point/QT Prolongation Standardized MedDRA Query (SMQ). Appendix 4 lists the terms employed in this search.
- Time period: all reports until 20 July 2010
- Age range: all ages
- Outcome: all serious outcomes

5.2 RESULTS

The AERS search for serious QT prolongation and Torsade de Pointes identified 61 reports. We excluded nine duplicate reports and three reports that mentioned the use of the fexofenadine and pseudoephedrine combination product (Allegra-D®). Table 4 summarizes the remaining 49 reports.

Table 4. Characteristics of Serious QT Prolongation and Torsade de Pointes Cases with Fexofenadine as of 13 August 2010 (N=49)	
Age (years) [N=40]	Average (45), Median (45), Range (3 to 81 years)

Table 4. Characteristics of Serious QT Prolongation and Torsade de Pointes Cases with Fexofenadine as of 13 August 2010 (N=49)	
Gender (N=46)	Male (13), Female (33)
Country (N=43)	US (23), Foreign (20); [including Germany (3), Japan (2), Canada (2), France (2), Great Brittan (2)]
Report Type (N=49)	Expedited (41), Direct (7), Periodic (1)
Indication (N=27)	Allergic rhinitis (5), seasonal allergies (3), allergies (3), hay fever (2), allergy (2), urticaria (1), chronic urticaria (1), cold symptoms (1), dermatologic skin reactions (1), drug use for unknown indication (1), chronic urticaria (1), itching (1), photodermatitis at the face (1), pruritis (1), rash (1), allergic rhinitis due to pollen (1), swollen eyes (1)
Daily Dose (N=25)	Average (225 mg), Median (120 mg), Range (60mg to 2160 mg)
Time to Event (days) [N=21]	Average (84); Median (16); Range (0 to 518 days)
Most frequently reported PTs[a,b] (49 cases reporting 219 PTs)	Electrocardiogram QT prolonged (32), ventricular tachycardia (16), syncope (8), arrhythmia (8), torsade de pointes (7), ventricular fibrillation (6), dizziness (6), ventricular extrasystoles (4), loss of consciousness (4), convulsion (4), bradycardia (4), hypokalemia (3), palpitations (4), cardiac arrest (4), bradycardia (4), hypokalaemia (3), condition aggravated (3), circulatory collapse (3), tremor (2), atrioventricular block complete (2), suicide attempt (2), chest pain (2), sudden death (2), coma (2), bundle branch block right (2), nausea (2), malaise (2), intentional overdose (2), brain injury (2), grand mal convulsion (2), electrocardiogram T wave inversion (2), depressed level of consciousness (2), dyspnoea (2), drug interaction (2)
Outcomes[b] (49 cases indicating 64 serious outcomes)	Death (5), Disability (1), Hospitalization (24), Life-threatening (10), Other Medically Serious (23), Required Intervention (1)
[a] PTs occurring on ≥ 2 occasions [b] Each case may have multiple PTs	

5.3 DISCUSSION

Since the datalock date (30 January 2006) of the last OSE review which evaluated cardiovascular death and ventricular arrhythmias, the FDA received seven additional reports of serious QT prolongation or Torsade de Pointes with fexofenadine. All of these reports originated from manufacturers. Consistent with previous OSE reviews, these cases mentioned concomitant medications, provided limited information, or described a history of cardiovascular disease. One of the cases (ISR#6761996, AUR-APL-2010-01388) involved a sudden death. Although the FDA documented receipt of this report on 7 June 2010, it was not available in the AERS database on 20 July 2010 when we searched for all deaths associated with fexofenadine. This report also falls outside of the date range used in the Sponsor's 120-day Safety update report (31 March

2010) and is not included in either submission.[12,3] Del Rosario et al published this case in Missouri Medicine and suggest the patient may have had undiagnosed congenital long QT and received multiple medications, two of which (azithromycin and tizanidine) were associated with QT prolongation.[13] The authors do not discuss the causal role of fexofenadine in this case. We provide the case narrative for reference in Appendix 10.4.

Five cases had an outcome of death (ISR#4195747, 199920119HMRI; ISR#3148871, 199810506RGB; ISR#3401425, 199920910HMRI; ISR#3914224, 200212306GDDC; ISR#6761996, AUR-APL-2010-01388). Only one of the cases (ISR#6761996, AUR-APL-2010-01388), described above, was not included in previous OSE reviews or in the Sponsor's submission. The Sponsor describes the remaining four cases in their submission, as well as 17 additional deaths identified from a broader search for cardiac adverse events (Review of Postmarketing Spontaneous Reports Received for Fexofenadine Hydrochloride, 7.1 Cardiac Adverse Event Reports, pages 57-66). All of the cases mention underlying cardiovascular disease, however we cannot rule out the causal role of fexofenadine in a population at high risk for QT prolongation. Incomplete information in many of these cases limits our assessment of the contributory role of fexofenadine.

Since many of the cases in this series were confounded by multiple medications, we evaluated each case to determine if the serious QT prolongation and Torsade de Pointes events could have resulted from a drug interaction with fexofenadine. We search this case series for co-suspect medications which could be associated with increased fexofenadine plasma levels (ketoconazole and erythromycin), the PT Drug Interaction, and the narrative for each case for a description of a possible drug interaction. This search identified five cases of possible drug interactions. For completeness, we also searched all cases of death and liver failure for the PT Drug Interaction but did not indentify additional cases. Medications involved in these cases include azithromycin (2), fluconazole (1), valproic acid (1), and d-chlorpheniramine (1). One of these cases describes ventricular arrhythmias with azithromycin and fexofenadine, which re-occurred after dechallenge with azithromycin (ISR#4866130, 200520584GDDC). Another case involved multiple medications, including azithromycin and fexofenadine, which resulted in QT prolongation and sudden death (ISR#6761996, AUR-APL-2010-1388, see Appendix 10.4 for case narrative). Alternative etiologies exist in the remaining drug interaction cases. It is also important to note that prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and Torsades de Pointes, have been seen in treatment with macrolide antibiotics, such as azithromycin. Previous OSE reviews identified drug interaction cases involving fexofenadine and macrolide antibiotics, antifungals and warfarin. Most cases reported cardiovascular and central nervous system (CNS) events associated with the drug interaction. Across all three reviews, the authors could not rule out the possibility that fexofenadine may have had a causal role in a small number of drug interaction cases. Consistent with the findings from previous OSE reviews, the interaction with fexofenadine could contribute to the events reported in these cases.

The FDA Center for Drug Evaluation and Research (CDER) Division of Cardiovascular and Renal Products (DCRP) QT interdisciplinary review team evaluated ECG data from clinical trials and adverse events with fexofenadine in response to a consult from DNCE regarding the Rx-to-OTC switch of fexofenadine.[14] The team's assessment of the Sponsor's submission of postmarketing adverse event reports for cases of malignant arrhythmic events concluded that most cases were confounded by significant cardiac disease or concomitant QT-prolonging medications. In a few cases, the contributory role of fexofenadine is possible although incomplete information limited their assessment. The majority of the cases from the AERS search for serious QT prolongation or Torsade de Pointes with fexofenadine originated from manufacturers, with only seven direct reports. The majority of cases included multiple medications, provided limited information, reported a history of cardiovascular disease, or resulted from overdose. The direct

reports provide limited information to aid in the assessment of causality with fexofenadine. We did not identify new safety issues regarding serious QT prolongation or Torsade de Pointes. Overall, the findings from the AERS database are consistent with the conclusions from the DCRP QT Interdisciplinary team's assessment of postmarketing reports from the Sponsor's submission.

6 CONCLUSIONS

We did not identify new safety issues with fexofenadine in this review. This conclusion is supported by the following observations:

- Based on a review of the entire AERS database, the majority of adverse events reported with fexofenadine represent labeled events.
- Compared with the sponsor's analysis of the Sanofi-Aventis Pharmacovigilance database, the AERS database represents a smaller sample of reports that are consistent with the reports in the Sponsor's database. The Sponsor's analysis of postmarketing reports did not identify new safety issues and concluded that the events reported with fexofenadine are consistent with the currently recognized safety profile. The datamining analysis of AERS confirmed the Sponsor's findings regarding fexofenadine.
- Direct reports received by the FDA are limited by poor documentation and mainly describe non-serious events and report similar PTs as the manufacturer's reports.
- An analysis of all reports with fexofenadine received by the FDA since the last OSE review in 2006 did not identify new safety issues.
- Among cases that reported outcome of death, we did not identify a pattern of causal events attributable to fexofenadine and did not identify new safety issues with fexofenadine.
- Our review of serious QT prolongation and Torsade de Pointes with fexofenadine produced similar conclusions as previous OSE reviews and the DCRP QT Interdisciplinary team's assessment of postmarketing reports. These reviews of postmarketing safety data were suggestive, but not conclusive, of a direct association with fexofenadine and serious QT prolongation or Torsade de Pointes.
- We did not identify cases of liver transplant and did not establish a causal association with fexofenadine in cases suggestive of liver failure.

7 RECOMMENDATIONS

Overall, we did not identify new safety issues with fexofenadine in this review. We agree with the conclusions of the previous OSE safety reviews regarding QT prolongation and Torsade de Pointes. We did not identify any new safety concerns regarding liver failure. We do not have specific recommendations at this time.

8 REFERENCES

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[3] Sanofi-Aventis NDA 201613 Submission, Amendment 9 (2 July 2010). Module 5.3.5.3 Integrated Summary of Safety, Section 6.2.1 Food and Drug Administration's Adverse Event Reporting System (pages 109-112).

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13 Del Rosario M, Weacher R, Flaker G. Drug-induced QT prolongation and sudden death. Missouri Medicine 2010; 107(1):53-58

[14] CDER DCRP QT Interdisciplinary Review Team. QT/IRT Consult to NDA 201613/ NDA 201373, sNDA 21909. August 9, 2010.

9 APPENDICES

9.1 APPENDIX 1: EMPERICA SIGNAL DATAMINING METHODOLOGY, LIMITATIONS, AND RESULTS

Methodology:

Empirica Signal® software and the Multi-item Gamma Poisson Shrinker (MGPS) datamining algorithm quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted EB05 and EB95, respectively.

Limitations:

The association between fexofenadine and the particular event in AERS is a result of the relative reporting for various events among all drugs in the database. The scores discussed in this section provide an indication of the reporting association between fexofenadine and various adverse events (High Level Terms, HLTs). ***It is important to note that these scores are not measures of causality or risk.*** These scores merely indicate reporting relationships of adverse events (by HLT) for fexofenadine using the rest of the AERS data (all drugs and events) as a background "expected."

Adverse events coded in AERS reports are not mutually exclusive; cases may be coded with many HLTs. Also, the exact case count may not match the case count in AERS because of different data lock dates and the case duplicate removal system employed by the Empirica® software.

The exact degree of risk or causality for the various associations between benzonatate and these HLTs (in all patients ever exposed to the drug worldwide) cannot be elicited from this data mining analysis alone, because obviously the association scores (EBGM values) are generated from AERS which consists of spontaneous adverse events reports. Finally, reporting and detection biases can occur in AERS and effects of concomitant illnesses or therapy cannot be fully controlled in data mining analyses using MGPS. Because of the spontaneous nature of reporting, the results of this analysis should not be interpreted as a formal comparison of treatment groups or of their relative risks.

Table 1: Results from Empirca Signal Datamining Analysis from approval to 27 July 2010							
Generic name	**Preferred Term**	**High Level Term**	**High Level Group Term**	**System Organ Class**	**N**	**EBGM**	**EB05**
Fexofenadine	Therapeutic response unexpected with drug substitution	Therapeutic and nontherapeutic responses	Therapeutic and nontherapeutic effects (excl toxicity)	Genrl	29	17.4	12.5
Fexofenadine	Dysmenorrhoea	Menstruation and uterine bleeding NEC	Menstrual cycle and uterine bleeding disorders	Repro	27	9.74	6.3
Fexofenadine	Electrocardiogram QT prolonged	ECG investigations	Cardiac and vascular investigations (excl enzyme tests)	Inv	41	5.7	4.4
Fexofenadine	Nasal dryness	Nasal disorders NEC	Upper respiratory tract disorders (excl infections)	Resp	13	6.9	3.9
Fexofenadine	Gastrointestinal pain	Gastrointestinal and abdominal pains (excl oral and throat)	Gastrointestinal signs and symptoms	Gastr	12	7.3	3.9
Fexofenadine	Cholestatic liver injury	Hepatocellular damage and hepatitis NEC	Hepatic and hepatobiliary disorders	Hepat	4	35.5	3.5
Fexofenadine	Palpitations	Cardiac signs and symptoms NEC	Cardiac disorder signs and symptoms	Card	125	4.0	3.5
Fexofenadine	Rhinitis	Upper respiratory tract infections	Infections - pathogen unspecified	Infec	41	4.4	3.4
Fexofenadine	Lymphocyte stimulation test positive	White blood cell analyses	Haematology investigations (incl blood groups)	Inv	7	10.2	3.2
Fexofenadine	Arrhythmia	Rate and rhythm disorders NEC	Cardiac arrhythmias	Card	54	3.6	2.9
Fexofenadine	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	Cardiac arrhythmias	Card	22	3.8	2.7
Fexofenadine	Rhinorrhoea	Upper respiratory tract signs and symptoms	Respiratory disorders NEC	Resp	16	4.0	2.6

Table 1: Results from Empirca Signal Datamining Analysis from approval to 27 July 2010							
Generic name	**Preferred Term**	**High Level Term**	**High Level Group Term**	**System Organ Class**	**N**	**EBGM**	**EB05**
Fexofenadine	Product substitution issue	Product quality issues NEC	Product quality issues	Genrl	10	4.5	2.6
Fexofenadine	Swelling face	Dermal and epidermal conditions NEC	Epidermal and dermal conditions	Skin	17	3.2	2.1
Fexofenadine	Hypersensitivity	Allergic conditions NEC	Allergic conditions	Immun	81	2.5	2.1
Fexofenadine	Nervousness	Anxiety symptoms	Anxiety disorders and symptoms	Psych	58	2.5	2.0
Fexofenadine	Atrial tachycardia	Supraventricular arrhythmias	Cardiac arrhythmias	Card	6	4.3	2.0
Fexofenadine	Medication residue	Product quality issues NEC	Product quality issues	Genrl	9	3.5	2.0

9.2 APPENDIX 3: AERS SEARCH STRATEGY FOR ACUTE LIVER INJURY REPORTS

AERS search strategy (MedDRA 13.0) for acute liver injury reports (OSE Case Definition –, Dr. Joyce Weaver, MedDRA version 13.0, revised 25 May 2010)

- Hepatic failure and associated disorders (HLT)
- Hepatic fibrosis and cirrhosis (HLT)
- Hepatic necrosis (PT)
- Liver transplant (PT)
- Hepatitis fulminant (PT)
- Liver and small intestine transplant (PT)
- Renal and liver transplant (PT)

9.3 APPENDIX 4: AERS SEARCH STRATEGY FOR QT/QTC PROLONGATION AND TORSADE DE POINTES REPORTS

AERS search strategy (MedDRA 13.0) for Torsade de Pointes reports (OSE Case Definition –, Dr. Paula Gish, MedDRA version 13.0, revised 21 May 2010. Torsade de Pointes/QT Prolongation Narrow Standardized MedDRA Query (SMQ))

- Electrocardiogram QT prolonged(PT)
- Electrocardiogram QT interval abnormal (PT)
- Long QT syndrome (PT)
- Long QT syndrome congenital (PT)
- Torsade de pointes (PT)
- Ventricular tachycardia (PT)*

* PT is listed under the Higher Level Term (HLT) *Ventricular arrhythmias and cardiac arrest*

9.4 CASE NARRATIVE

ISR#6761996, AUR-APL-2010-01388, US: A 27-year-old female used fexofenadine for an unknown duration. She was at home resting when she had a witnessed episode of sudden generalized loss of consciousness. No jerking or seizure-like movements were noted. Her husband called 911 and performed CPR. On arrival, paramedics determined that the patient was in ventricular fibrillation and successfully defibrillated her. Lidocaine IV bolus was given, after which brief episodes of self-terminating polymorphic ventricular tachycardia were noted. EKG revealed sinus rhythm with no evidence of pre-excitation, no changes consistent with infarction, injury or ischemia, and a QTc of 459 msec. Cardiovascular examination revealed normal heart sounds with no murmurs or gallops. Serum potassium was 3.1 mEq/l, while ionized calcium and magnesium levels were normal. An echocardiogram showed normal left and right ventricular systolic function and normal ventricular size. Serum and urine toxicology screens only showed elevated levels of benzodiazepine, which was given during transit to control severe myoclonic jerking. She became comatose due to anoxic brain injury. After 72 hours, a thorough evaluation confirmed that she had sustained severe, irreversible brain injury. The author concluded her cardiac arrest was from ventricular fibrillation or hemodynamically unstable torsades de pointes.

Concomitant medications included azithromycin, bupropion, trazodone, zolpidem, and tizanidine. Concomitant PRN medications include tramadol, ibuprofen, and sumatriptan. Her medical history included fibromyalgia, depression, anxiety, and chronic low back pain. She did not have a family history of sudden death. ***Reviewer Comments:*** *This is a published report by Del Rosario MD, Weachter R,MD and Flaker GC,MD. Drug-induced QT prolongation and sudden death. Mo Med. 2010;107(1):53-8. Concomitant medications associated with Torsade de Pointes include azithromycin and tizanidine. Based on the data reported, we cannot rule out the possibility of congenital long QT syndrome.*

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

/s/

MELINDA WILSON
10/08/2010

SUSAN L LU
10/08/2010

ANN WARD W MCMAHON
10/08/2010
I concur.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 9, 2010

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Janice- Adams-King
Regulatory Project Manager
Division of Non-prescription Clinical Evaluation (DNCE)

Subject: QT-IRT Consult to NDA 201613 / NDA 201373 / sNDA 21909

This memo responds to your consult to us dated March 25, 2010 regarding evaluation of ECG data and cardiac adverse event data for fexofenadine, as part of the Rx-to-OTC switch of fexofenadine (Allegra) tablets, oral disintegrating tablets, and oral suspension (NDA 201-613, 201-373 and 21-909).sponsored by Sanofi Aventis. The QT-IRT received and reviewed the following materials:

- Your consult
- Integrated summary of Safety
- CSRs for studies PJPR 0028, PJPR0018, and M016455/1105

QT-IRT Comments for DNCE

We recommend excluding small effects on the QTc and evaluating other ECG intervals with a TQT study prior to OTC conversion for the following reasons:

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- The available clinical trials suggest that fexofenadine is unlikely to be associated with large changes in QTc interval. However, all available clinical trials appear to be inadequate to rule out small effects on QTc interval (<10 ms) as defined by ICH E14 guidance. We would have had some re-assurance if large multiples of the proposed dose

(i.e. over 1 g) had been evaluated. We note that the maximum dose evaluated is a single dose of 800 mg in study PJPR0002.

- The sponsor's reports of post-marketing adverse events and med-watch forms for select cases of malignant ventricular arrhythmic events were reviewed. While a significant cardiac disease burden or concomitant QT-prolonging medication use was reported in most cases, contributory role for fexofenadine is possible in a few of the cases although incomplete information limits assessment.

BACKGROUND

Fexofenadine is a selective H1-receptor antagonist that has been approved under the trade name ALLEGRA ®, as a mono-product (capsule, oral suspension, and an orally disintegrating tablet). The capsule is no longer marketed in the USA. The tablet formulation was subsequently approved for the treatment of seasonal rhinitis (SAR), chronic idiopathic urticaria (CIU) or hives. Based on the current PI, the recommended dose of ALLEGRA tablets in adults is 60 mg twice daily or 180 mg once daily. A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. In children 2-11 years the recommended dose is 30 mg bid and 30 mg qd in patients with decreased renal function.

In the current submission, the sponsor has intended to change status from prescription to non-prescription use of fexofenadine 30, 60, and 180 mg tablets. The division is re-examining the safety profile of fexofenadine as part of the switch applications. The current submission includes an analysis of ECGs obtained in clinical studies submitted for previously approved fexofenadine NDAs, in addition to new ECG data not previously submitted to the agency. The analyses include the evaluation of changes of ECG parameters from baseline and frequencies of potentially clinically significant ECG changes.

SUMMARY OF CLINICAL PHARMACOLOGY:

ADME features:

Fexofenadine is absorbed following oral administration of capsules and tablets. The maximum concentration occurs at 2.6 hours post-dose. After administrating of a single 60-mg capsule to healthy adults, the mean C_{max} was 131 ng/mL. Following single dose oral administration of either the 60 or 180 mg tablet to healthy adult male subjects, the mean C_{max} were 142 and 494 ng/mL, respectively. Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and α1-acid glycoprotein. Fexofenadine undergoes negligible biotransformation according to the mass balance study. The study further indicated a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine dose in the feces and urine, respectively. The mean elimination half-life of fexofenadine was 14.4 hours. Fexofenadine exhibits linear pharmacokinetics up to the dose of 120 mg BID. The steady-state dose AUC ratio (accumulation ratio) was 1.02 at 120 mg QD and 1.22 at 180 mg QD.

Intrinsic Factors:

No clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine. In elder patients (65 years of age and older), peak plasma levels of fexofenadine were 99% greater than in younger subjects (less than 65 years of age). The individual apparent

oral clearance estimates of fexofenadine were on average 44% lower in pediatric patients 6 month to 12 years of age compared to adult subjects. In subjects with mild to moderate and severs renal impairment, C_{max} of fexofenadine was 87% and 111% greater respectively, and the mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy subjects. In subjects on dialysis, C_{max} were 82% greater and half-life was 31% longer than observed in healthy subjects. The pharmacokinetics of fexofenadine in subjects with hepatic impairment did not differ substantially from that observed in healthy subjects.

Extrinsic Factors:
Co-administration of 180 mg fexofenadine tablet with a high fat meal decreased the mean AUC and C_{max} of fexofenadine by 21% and 20%, respectively. 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%. 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. The exposure increase appears to be related to the increase in the bioavailability of fexofenadine. Fruit juices such as grapefruit, orange, and apple may reduce the bioavailability and exposure of fexofenadine.

(Source: Clinical Overview, P-17 to P-20)

Reviewer's Comments:

1. *The maximum concentration under the highest recommended therapeutic dose (i.e., 180 mg QD) is 494 ng/mL. Following multiple doses, the steady state C_{max} is approximately 603 ng/mL.*
2. *For patients with severe renal impairment, the mean C_{max} increases 111%. Co-administration of ketoconazole yields 135% increase in steady state C_{max}. The clinical worst case scenario is that a patient with severe renal impairment with no dose adjustment also receives ketoconazole. The expected maximum concentration should be 740 ng/mL, which is 1.5-fold higher than the typical maximum concentrations.*

CLINICAL EXPERIENCE:
Clinical Studies
In the clinical studies, a total of 18,361 subjects have been exposed to fexofenadine and 910 subjects to the fixed-dose combinations of fexofenadine and pseudoephedrine compared to 6397 subjects exposed to placebo.

ECG data that were in the global integrated database (GIDB) were pooled for all studies by study category if data were available for baseline and follow-up assessments. Post-baseline ECG assessments were performed in 8 of the 25 studies that were not previously submitted. All 8 studies were in the adult population. The sponsor states that ECG data from the 8 studies are not in the GIDB for 3 reasons. First, the studies enrolled healthy subjects, second the ECG data were not read centrally by the same contract research organization and third the data collection for the GIDB from these 8 studies was focused on adverse events. In addition to these 8 studies, 2 other

pharmacokinetic studies conducted for formulation development in adults (M016455C/1108 and M016455C/1111), are not included in the GIDB for similar reasons.

There were no clinically relevant ECG findings in any of the 10 studies or any cardiac adverse events except for study M016455J/006. Subject 24 in study M016455J/006 first experienced an event of chest tightness about 2 days after treatment in session I (120 mg fexofenadine) and a similar symptom occurred during session III (60 mg terfenadine). The symptom resolved spontaneously both times. A standard 12 lead ECG performed while the subject felt chest tightness detected no abnormalities.

Most ECG data were read centrally at eResearch Technology, during the course of the study and shortly thereafter. This applied to all the pivotal controlled and long-term safety studies in the adult population and all the pivotal and other controlled studies in the pediatric population.

Table 1: Results from PD studies in adult subjects:

Project Code / Study Number / Analysis: M016455 / OVERALL / ISS

5.3.5.3.5.3 Descriptive statistics for electrocardiogram data - Human PD Studies - Mono-Products - Adults - Safety evaluable population

Parameter / Timepoint	Fexofenadine N	Mean	SD	Median	Min	Max
PR INTERVAL (msec)						
Baseline [a]	290	156.659	21.690	156.000	100.00	224.00
Maximum post baseline [b]	222	169.297	23.222	167.000	104.00	244.00
Maximum change [c]	221	10.421	13.809	10.000	-48.00	57.00
QRS INTERVAL (msec)						
Baseline [a]	291	89.711	9.976	88.000	63.00	128.00
Maximum post baseline [b]	222	94.356	10.916	92.000	66.00	127.00
Maximum change [c]	222	4.167	6.452	4.000	-16.00	28.00
QTcF INTERVAL (msec)						
Baseline [a]	24	412.409	21.332	412.783	377.95	454.50
Maximum post baseline [b]	24	410.645	19.783	406.131	382.52	468.24
Maximum change [c]	24	-1.764	18.775	0.096	-47.95	46.78
RR INTERVAL (msec)						
Baseline [a]	331	994.460	181.466	997.000	545.67	1564.33
Maximum post baseline [b]	262	1108.873	175.432	1094.333	659.34	1621.62
Maximum change [c]	262	88.513	144.345	85.137	-395.35	739.27

Fexofenadine includes data from all study periods in crossover trials regardless of treatment.
[a] Baseline is the reading prior to the first dose in the first study period. It is the average of readings prior to the first dose in the first study period in the case of serial assessments.
[b] Maximum post baseline is the maximum of all readings post baseline for a subject.
[c] Maximum change is the maximum change from baseline for all readings post baseline for a subject.
Table includes subjects from studies: PJPR0002, PJPR0003, PJPR0007, PJPR0048, M016455/4102, M016455I/1120, M016455A/4136, M016455I/1118, M016455/4049 and PJPR0050.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/1os006.sas OUT=REPORT/OUTPUT/1os006t_x.rtf (25JAN2010 - 15:41)

Source: M016455 ISS Appendix 5.3.5.3
Reviewer's Comments: The timing of ECGs in the individual studies varied but there appear to be no large effects.

Table 2: Results from the biopharmaceutics, pharmacokinetic, and pharmacodynamic studies in adult subjects receiving doses of 180 mg twice daily or higher

Project Code / Study Number / Analysis: M016455 / OVERALL / ISS

5.3.5.3.5.5 Descriptive statistics for electrocardiogram data - Biopharmaceutics and Human PK and PD Studies with doses 180mg bid or higher - Safety evaluable population

Parameter ISS treatment code Timepoint	N	Mean	SD	Median	Min	Max
PR INTERVAL (msec)						
Placebo						
Baseline [a]	29	159.586	18.492	158.000	129.00	203.00
Maximum post baseline [b]	29	170.862	15.939	171.000	134.00	206.00
Maximum change [c]	29	11.276	11.087	9.000	-6.00	39.00
Fexofenadine >180 - <360 mg daily						
Baseline [a]	15	159.133	26.736	158.000	121.00	219.00
Maximum post baseline [b]	15	168.933	26.575	163.000	129.00	219.00
Maximum change [c]	15	9.800	12.219	8.000	-8.00	42.00
Fexofenadine >=360 mg daily						
Baseline [a]	36	155.667	20.670	153.500	117.00	209.00
Maximum post baseline [b]	36	170.694	22.089	167.500	139.00	230.00
Maximum change [c]	36	15.028	13.250	13.000	-10.00	52.00

Project Code / Study Number / Analysis: M016455 / OVERALL / ISS

5.3.5.3.5.5 Descriptive statistics for electrocardiogram data - Biopharmaceutics and Human PK and PD Studies with doses 180mg bid or higher - Safety evaluable population

Parameter ISS treatment code Timepoint	N	Mean	SD	Median	Min	Max
QRS INTERVAL (msec)						
Placebo						
Baseline [a]	29	84.034	10.598	83.000	64.00	110.00
Maximum post baseline [b]	29	90.103	10.939	90.000	67.00	119.00
Maximum change [c]	29	6.069	5.574	5.000	-8.00	15.00
Fexofenadine >180 - <360 mg daily						
Baseline [a]	15	84.000	10.717	85.000	63.00	112.00
Maximum post baseline [b]	15	89.067	14.023	87.000	66.00	127.00
Maximum change [c]	15	5.067	5.612	2.000	0.00	16.00
Fexofenadine >=360 mg daily						
Baseline [a]	36	86.028	7.500	86.000	64.00	104.00
Maximum post baseline [b]	36	92.000	8.029	93.000	67.00	106.00
Maximum change [c]	36	5.972	4.520	4.500	0.00	22.00

Project Code / Study Number / Analysis: M016455 / OVERALL / ISS

5.3.5.3.5.5 Descriptive statistics for electrocardiogram data - Biopharmaceutics and Human PK and PD Studies with doses 180mg bid or higher - Safety evaluable population

Parameter ISS treatment code Timepoint	N	Mean	SD	Median	Min	Max
QTcB INTERVAL (msec)						
Placebo						
Baseline [a]	29	374.375	21.512	371.259	327.91	422.36
Maximum post baseline [b]	29	400.419	20.566	393.270	371.04	447.85
Maximum change [c]	29	26.464	16.193	27.487	-8.17	64.96
Fexofenadine >180 - <360 mg daily						
Baseline [a]	15	376.598	27.462	386.377	318.03	406.33
Maximum post baseline [b]	15	404.669	20.394	408.931	372.02	434.97
Maximum change [c]	15	28.070	18.522	28.137	1.89	54.63
Fexofenadine >=360 mg daily						
Baseline [a]	36	376.536	21.012	378.818	325.74	420.71
Maximum post baseline [b]	36	405.101	25.248	404.456	340.82	454.91
Maximum change [c]	36	28.566	23.100	25.088	-9.45	78.15

Fexofenadine includes data from all study periods in crossover trials regardless of treatment.
[a] Baseline is the reading prior to the first dose in the first study period. It is the average of readings prior to the first dose in the first study period in the case of serial assessments.
[b] Maximum post baseline is the maximum of all readings post baseline for a subject.
[c] Maximum change is the maximum change from baseline for all readings post baseline for a subject.
Table includes subjects from studies: PJPR0002 and PJPR0003.
PGM=PRODOPS/M016455/OVERALL/ISS/REPORT/PGM/los0961t.sas OUT=REPORT/OUTPUT/los0961t_x.rtf (25JAN2010 - 15:37)

Source: M016455 ISS Appendix 5.3.5.3
Reviewer's Comments: QTcF was not reported for the above studies.

Pharmacodynamic study PJPR0007 in adult subjects

Study PJPR0007 was a single-center, double-blind, randomized, placebo-controlled, 4-period crossover trial in which doses of fexofenadine up to 400 mg bid were administered and plasma and urine drug concentrations were measured to characterize PK. Forty (40) normal healthy subjects (20 male and 20 female) were evaluated over four 11-day treatment periods during which the subjects were dispensed medication on Days 1 through 8. During each period, subjects received one of 4 treatments: placebo, 40 mg, 200 mg, or 400 mg of fexofenadine BID for 6.5 days. Serial ECGs were collected during placebo lead-in on Day 1, after the first dose on Day 2, and after the last steady-state dose on Day 8 of each treatment period.

Table 3: Mean effects- study PJPR0007

Table 49 – Primary analysis of daily mean QTc

		Daily mean QTc (msec)		
Treatment (BID)	N	Mean[b] ± SE Baseline: Day 1	Mean[b] ± SE Day 2 (Day 2 – Day 1)	Mean[b] ± SE Day 8 (Day 8 – Day 1)
Placebo	39[a]	393.9 ± 2.8	395.3 ± 2.8 (1.4± 1.5)	398.5 ± 2.8 (4.6 ± 1.5)
40 mg	40	397.1 ± 2.8	395.0 ± 2.8 (-2.1 ± 1.5)	399.2 ± 2.8 (2.1 ± 1.5)
200 mg	40	396.0 ± 2.8	397.6 ± 2.8 (1.6± 1.5)	399.8± 2.8 (3.8 ± 1.5)
400 mg	40	397.9 ± 2.8	397.7 ± 2.8 (-0.3 ± 1.5)	403.3 ± 2.8 (5.4 ± 1.5)

	Difference between treatments in change from baseline mean QTc (msec)					
	Day 2			Day 8		
Comparison	mean ± SE	90% CI	p-value[b]	mean ± SE	90% CI	p-value[b]
40 mg – Placebo	-3.5 ± 2.2	(-7.1, 0.1)	0.1056	-2.5 ± 2.2	(-6.1, 1.1)	0.2518
200 mg – Placebo	0.2 ± 2.2	(-3.4, 3.8)	0.9149	-0.8 ±2.2	(-4.4, 2.8)	0.7175
400 mg - Placebo	-1.7 ± 2.2	(-5.3, 1.9)	0.4390	0.7 ±2.2	(-2.8, 4.3)	0.7312

[a] Subject 0009/00037 was dropped from the study on Day 2 of Treatment Period 4 (placebo). Thus, N=39 for the placebo treatment group.
[b] Adjusted treatment means and p-values are from an analysis of variance model which adjusted for period, day, treatment, day by treatment interaction, and carryover.
BID = twice daily; CI = confidence interval

Source: Table 49, ISS, Outlier results are included in table 1
Reviewer's comments: C_{max} at steady state in this study for the 400 mg bid dose was 3355 (% CV 36.2) mg/ml. The maximum expected steady state C_{max} with the 180 mg qd dosing is 740 mg/ml.

Reviewer's conclusions related to clinical trial data:
The sponsor also reported changes in mean QTcB and QTcF, along with maximal absolute changes from baseline for the pivotal controlled studies in adult subjects and for the studies conducted in pediatric subjects: mean changes were small and there were no outliers with absolute QTc over 500 ms. Other than acute MI and atrial fibrillation (1 subject each), no other serious cardiac adverse events were reported in the clinical trials. In conclusion while small effects (< 10 ms) on the QT interval cannot be excluded in the absence of a TQT assessment, the clinical trials data appears sufficient to exclude large effects on the QT interval.

Drug Interaction Studies
QTc prolongation effect was further evaluated in drug-drug interaction studies in healthy subjects. The study results were summarized as the follows.

Study M016455/1105:
The was a double-blind, multiple-dose, randomized, 3-treatment, 3-stage, cross-over study using the orthogonal Latin square method, with a 14-day wash-out between the last dose in each period. A total of 18 subjects were randomized to receive either fexofenadine 120 mg BID for 7 days, erythromycin 300 mg 4 times daily for 7 days, or the combination of the 2 drugs for 7 days. Fexofenadine's $C_{max, ss}$ and $AUC_{(0-12)ss}$ increased by 102% and 106%, respectively. Fexofenadine had no effect on the pharmacokinetics of erythromycin.

Table 4: Change From The Mean Diurnal QTc And Maximum Diurnal QTc From Baseline After Treatment with Fexofenadine Alone, Erythromycin Alone, and Fexofenadine + Erythromycin

	Treatment	Mean ± SD on day 0 and day 1	Mean ± SD on day 7 and day 8	Point estimate of the difference (adjusted for the mean)	95% CI
Mean daily QTc	Fexofenadine	384.70 ± 10.72	385.48 ± 13.25	0.16	(–3.61, 3.92)
	EM	385.00 ± 13.99	391.31 ± 11.10	6.80	(3.04, 10.56)
	Fexofenadine + EM	386.22 ± 14.24	390.37 ± 13.57	4.29	(0.53, 8.05)
Maximum daily QTc	Fexofenadine	407.0 ± 13.8	407.0 ± 14.6	–0.69	(–6.26, 4.88)
	EM	407.5 ± 14.2	411.8 ± 31.1	4.58	(–0.99, 10.15)
	Fexofenadine + EM	406.0 ± 16.0	411.3 ±12.8	5.66	(0.09, 11.23)

Treatment column corrected based on table in Section 8.4.2 in the original clinical study report, error in synopsis of original clinical study report

Reviewer's Comments:
The sponsor should analyze QTc interval changes by time rather than using time-averaged values. The study is not designed to rule out small changes in QTc interval. However, fexofenadine does not appear to be associated with large changes in QTc interval.

Study PJPR0018 (Report K-95-0171-DS)
The study was conducted in an open-label, multiple dose, randomized, 3-period complete cross-over design. Twenty-four healthy, nonsmoking, male subjects were enrolled in the study. Each treatment consisted of a dose-free baseline day (Day 0) followed by multiple dosing for days 1 to 7. Subjects were randomized to receive one of the following treatments during each dosing period. There was at least a 10 day washout between the last dose of one period and the first dose of the next period.

- Fexofenadine 120 mg (2 × 60 mg) Q 12 h for 6.5 days (13 doses)
- Erythromycin 500 mg (2 × 250 mg) Q 8 h daily for 6.33 days (19 doses)
- Fexofenadine 120 mg (2 × 60 mg) Q 12 h for 6.5 days (13 doses) concomitantly with erythromycin 500 mg (2 × 250 mg) Q 8 h daily for 6.33 days (19 doses)

Serial 12-lead ECGs were collected at multiple time points during the treatment (Table 5). ECGs were collected prior to the blood sample. The primary analysis parameter was mean QTc. The results were summarized in Table 6. ECG outlier analysis results were summarized in Table 7, where outlier is defined as follows:

- QTc interval duration > 440 ms with an increase from baseline of > 10 ms
- PR interval duration > 200 ms with an increase from baseline > 20 ms
- QRS interval duration > 120 ms with an increase from baseline > 10 ms

Table 5: ECG and PK Sampling Time Points

Table 6–308. Study Event Schedule											
Event	*Day -1*	*Day 0*	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Day 8*	*Day 9*
Admission/ Discharge	1900										0700
Dosing*			0700 1500 1900 2300	0700 1500 1900 2300	0700 1500 1900 2300	0700 1500 1900 2300	0700 1500 1900 2300	0700 1500 1900 2300	0700		
Breakfast Lunch Dinner Snack	 2100	none 1200 1800 2100	0900 1400 2100 2300	0900 1400 2100 2300	0900 1400 2100 2300	0900 1400 2100 2300	0900 1400 2100 2300	0900 1400 2100 2300	none 1200 1800 2100	0800 1200 1800 2100	
Urine		0600 to 0700†							0700 to 1900†		
Plasma		0700‡					0700‡	0700‡	0700‡ 0800‡ 0830† 0900‡ 0930† 1000‡ 1100‡ 1300‡ 1500‡ 1900‡	0700‡	0700‡
12-lead ECG		0700 0900 1000 1100 1300 1500 1900	0900§ 1300§ 2100§	0900§ 1300§ 2100§	0900§ 1300§ 2100§	0900§ 1300§ 2100§	0900§ 1300§ 2100§	0900§ 1300§ 2100§	0700 0900 1000 1100 1300 1500 1900	0700	0700
Heart rate and blood pressure			0600 to 0700 0800 to 0900 1900 to 2000						0600 to 0700 0800 to 0900 1900 to 2000		

* MDL 16,455A+erythromycin at 0700; Erythromycin alone at 1500 and 2300; MDL 16,455A alone at 1900.
† Event occurred only when MDL 16,455A was administered (trmts A&C).
‡ During trmt C, two sets of plasma samples were collected, one for MDL 16,455A and one for erythromycin.
§ ECGs were collected for safety during trmt C only and not analyzed by independent consultant.

Supporting Data: *Page*
Appendix E1: Protocol *S6–V1.84–P2*

Table 6: Change From Baseline QTc Results

Table 6–326. Change From Baseline in Mean and Maximum QTc. (b) (4) Read ECG Data

Mean QTc

Treatment	*N**	*Day 0 mean ± SE*	*Day 7 mean ± SE*	*Change from Day 0 to Day 7 mean ± SE*	*P value†*
MDL 16,455A	18	392.7 ± 5.0	388.0 ± 5.6	–4.6 ± 3.3	.1793
Erythromycin	20	391.4 ± 4.9	393.6 ± 5.0	2.2 ± 2.4	.3839
MDL 16,455A + Erythromycin	19	391.0 ± 5.4	392.6 ± 5.6	1.6 ± 2.5	.5285

Maximum QTc

Treatment	*N**	*Day 0 mean ± SE*	*Day 7 mean ± SE*	*Change from Day 0 to Day 7 mean ± SE*	*P value†*
MDL 16,455A	18	412.7 ± 5.6	407.0 ± 5.8	–5.6 ± 4.1	.1849
Erythromycin	20	412.1 ± 4.7	414.6 ± 5.5	2.5 ± 4.4	.5776
MDL 16,455A + Erythromycin	19	414.3 ± 4.6	412.0 ± 5.6	–2.3 ± 4.1	.5810

* N=24 subjects began the study, 6 subjects withdrew prior to completion.

† P value from t–test or change from Day 0 to Day 7 equals 0.

Supporting Data: *Page*

Appendix C5: Electrocardiograms *S6–V1.83–P1*

Table 7: ECG Outlier Analyses Results

Table 6–328. Percent of Subjects on Each Treatment Meeting Outlier ECG Criteria

ECG Parameter	*Day*	*Trmt A MDL 16,455A* *% (N) Subject PJST0047-*	*Trmt B Erythromycin* *%(N) Subject PJST0047-*	*Trmt C Combination* *%(N) Subject PJST0047-*
QTc	Day 7	6% (1/18) 0018	20% (4/20) 0013, 0017, 0018, 0024	16% (3/19) 0016, 0018, 0024
	Days 8–9	0% (0/18)	0% (0/20)	11% (2/19) 0013, 0023
PR	Day 7	0% (0/18)	10% (2/20) 0014, 0021	0% (0/19)
	Days 8–9	0% (0/18)	5% (1/20) 0010	0% (0/19)

Supporting Data: *Page*

Appendix C5: Electrocardiograms *S6–V1.83–P1*

Table 6–329. Listing of Outlier QTc and/or Maximum Post Baseline Values in Each Treatment, for Patients with Outlier QTc Values			
Subject PJST0047	*Outlier and/or Maximum QT_C Values (msec) During Each Treatment* *QT_C Value (Day, Hour)* *Change From Baseline*		
	MDL 16455A	*Erythromycin*	*MDL 16455A + Erythromycin*
0013	437.3 (Day 8, Hour 24) 20.0	440.7* (Day 7, Hour 4) 24.3	444.0* (Day 9, Hour 48) 16.4
0016	419.2 (Day 7, Hour 6) –3.7	421.3 (Day 8, Hour 24) 16.9	444.2* (Day 7, Hour 12) 45.9
0017	437.7 (Day 7, Hour 6) 33.5	442.1* (Day 7, Hour 6) 45.6	424.3 (Day 8, Hour 24) 26.8
0018	441.4* (Day 7, Hour 6) 26.0	441.6* (Day 7, Hour 6) 21.4 447.9* (Day 7, Hour 12) 27.7	459.4* (Day 7, Hour 6) 41.9
0023	414.7 (Day 7, Hour 12) 5.4	439.2 (Day 7, Hour 3) 20.4	449.3* (Day 9, Hour 48) 53.2
0024	429.5 (Day 7, Hour 12) 42.5	448.5* (Day 7, Hour 6) 61.3 444.0* (Day 7, Hour 12) 56.7	442.0* (Day 7, Hour 12) 37.7
* Indicates outlier QTc values (greater than 440 msec with an increase from baseline of greater than 10 msec).			
Supporting Data:			*Page*
Appendix C5: Electrocardiograms			*S6–V1.83–P1*

Study PJPR0028 (Report K-95-0128 or M016455P-0028)

The study was conducted as an open-label, multiple dose, randomized, 3-period complete crossover study. Twenty-four healthy, nonsmoking, male subjects were enrolled in the study. Each treatment consisted of a dose-free baseline day (Day 0) followed by multiple dosing for days 1 to 7. Subjects were randomized to receive one of the following 3 treatments during each dosing period. There was at least a 10-day washout between treatments.

- Fexofenadine 120 mg (2 × 60 mg) Q 12 h for 6.5 days (13 doses)
- Ketoconazole 400 mg (2 × 200 mg) once daily for 7 days (7 doses)
- Fexofenadine 120 mg (2 × 60 mg) Q 12 h for 6.5 days (13 doses) concomitantly with ketoconazole 400 mg (2 × 200 mg) once daily for 7 days (7 doses)

Serial 12-lead ECGs were taken at multiple time points during the treatment (Table 8). The primary analysis parameter was centrally read mean QTc. Maximum QTc was considered a secondary parameter. The results were summarized in Table 9. ECG outliers were summarized in Table 10, where outliers were defined as:

- PR interval duration > 200 ms and increase of >20 ms from baseline
- QRS interval duration > 120 ms and increase of > 10 ms from baseline
- QTc interval duration > 440 ms and increase of > 10 ms from baseline

Table 8: ECG and PK Sampling Time Points

Table 6–338. Study Event Schedule											
Event	*Day –1*	*Day 0*	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Day 8*	*Day 9*
Admission/ Discharge	1900										0700
Dosing			0700 1900*	0700 1900*	0700 1900*	0700 1900*	0700 1900*	0700 1900*	0700		
Breakfast Lunch Dinner Snack	 2100	none 1200 1800 2100	0900 1400 2100 2300	0900 1400 2100 2300	0900 1400 2100 2300	0900 1400 2100 2300	0900 1400 2100 2300	0900 1400 2100 2300	none 1200 1800 2100	0800 1200 1800 2100	
Urine		0600 to 0700*							0700 to 1900*		
Plasma		0700†					0700†	0700†	0700† 0800† 0830* 0900† 0930* 1000* 1100† 1300† 1500† 1900†	0700†	0700†
12–lead ECG		0700 0900 1000 1100 1300 1500 1900	0900‡ 1300‡ 2100‡	0900‡ 1300‡ 2100‡	0900‡ 1300‡ 2100‡	0900‡ 1300‡ 2100‡	0900‡ 1300‡ 2100‡	0900‡ 1300‡ 2100‡	0700 0900 1000 1100 1300 1500 1900	0700	0700
Heart Rate / Blood Pressure			0600–0700 0800–0900 1900–2000						0600–0700 0800–0900 1900–2000		

* Event occurred only when MDL 16,455A was administered (trts A&C)
† During trt C, two sets of plasma samples were collected, one for MDL 16,455A and one for ketoconazole.
‡ ECGs collected for safety, not analyzed by independent consultant during treatment C only

Supporting Data: *Page*
Appendix E1: Protocol *S6–V1.87–P310*

Table 9: Change from Baseline in Mean and Maximum QTc, Central-Read ECG Data

Table 6–355. Change from Baseline in Mean and Maximum QT_C. (b) (4) -Read ECG Data.

Mean QT_C

Treatment	*N**	*Day 0 mean ± se*	*Day 7 mean ± se*	*Change from Day 0 to Day 7 mean ± se*	*P Value†*
MDL 16,455A	23	398.9 ± 3.1	394.3 ± 2.7	–4.7 ± 2.2	.0465
Ketoconazole	24	396.9 ± 3.3	395.0 ± 2.7	–2.0 ± 2.3	.3960
MDL 16,455A + Ketoconazole	23	395.9 ± 2.9	399.0 ± 3.2	3.1 ± 2.3	.1812

Maximum QT_C

Treatment	*N**	*Day 0 mean ± se*	*Day 7 mean ± se*	*Change from Day 0 to Day 7 mean ± se*	*P Value†*
MDL 16,455A	23	423.8 ± 3.9	420.5 ± 3.9	–3.3 ± 4.4	.4661
Ketoconazole	24	419.9 ± 4.1	417.1 ± 2.6	–2.8 ± 4.2	.5194
MDL 16,455A + Ketoconazole	23	417.2 ± 3.6	425.2 ± 3.6	8.0 ± 4.0	.0597

* N=24 subjects at the beginning of the study, 2 subjects withdrew prior to completion.
† P Value from t test that the change from day 0 to day 7 is equal to zero.

Supporting Data: *Page*
Appendix C5: Electrocardiograms *S6–V1.87–P1*

Table 10: ECG Outlier Analyses Results

Table 6–357. Percent of Subjects on Each Treatment Meeting Outlier ECG Criteria.

ECG Parameter	*Day*	*MDL 16,455A % (N)*	*Ketoconazole % (N)*	*Combination % (N)*
QT_C	Day 7	17% (4/23) PJST0172–0002, 0008, 0015, 0022	0% (0/24)	17% (4/23) PJST0172–0012, 0015, 0021, 0024
	Days 8–9	9% (2/23) PJST0172–0021, 0023	0% (0/24)	9% (2/23) PJST0172–0002, 0013
PR	Day 7	0% (0/23)	0% (0/24)	0% (0/23)
	Days 8–9	0% (0/23)	0% (0/24)	0% (0/23)
QRS	Day 7	0% (0/23)	0% (0/24)	0% (0/23)
	Days 8–9	0% (0/23)	0% (0/24)	0% (0/23)

Supporting Data: *Page*
Appendix C5: Electrocardiograms *S6–V1.87–P1*

Reviewer's comments:
The sponsor included intensive ECG monitoring in the drug-drug interaction studies with ketoconazole and erythromycin. The scheduled time points are adequate to cover the T_{max} of the parent compound and potential delayed effect up to 10 h post-dose. Time-matched PK samples were taken during the study. However, no exposure-QTc analysis was explored following the treatment of fexofenadine.

No large effects on QTc and other ECG intervals have been identified in the drug-drug interaction studies. The study design is inadequate to rule out small changes in QTc interval as defined by ICH E14 guidance.

Post-Marketing experience-Sponsor's Reports
Source: ISS Section 6.2 and 6.3 and Post Marketing Reports Section 7.1- Cardiac AE Reports
The sponsor also conducted an 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 data from searches of 2 other external databases [Drug Abuse Warning Network (DAWN) and Toxic Exposure Surveillance System (TESS)] are also summarized.

Food and Drug Administration's Adverse Event Reporting System
The sponsor's 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 at the MedDRA preferred term level indicated that these safety signals with fexofenadine were mainly due to signals from events such as tachycardia, palpitation, extrasystole, and arrhythmia. But there was also a signal detected with the preferred term "electrocardiogram QT prolonged" as well as for the preferred term "torsade de pointe" associated with fexofenadine use. There were a total of 8 reports with Torsade de Pointes, but 4 of these were duplicates. Thus, there were 6 individual patients with Torsade de Pointes. Three of the 6 reports for Torsade de Pointes are explained in detail in the post-marketing report. Two of the remaining 3 patients were taking other cardiac medications and the last 1 appeared to have a brain injury from drinking alcohol. Association to study drug was confounded by the underlying conditions or concomitant proarrhythmic drug use. With loratadine, safety signals were suggested for Torsade de Pointes, ventricular tachycardia, and ventricular fibrillation.

World Health Organization Uppsala Monitoring Center (WHO UMC)
A similar analysis of the WHO UMC database was performed using Qscan® to evaluate the profile of spontaneous reporting for all adverse events, serious adverse events, adverse events for safety topics of interest, and adverse events of special interest associated with fexofenadine as well as with cetrizine 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 sponsor reports that the EBGM analyses of the WHO UMC database for serious adverse events by WHO-ART system organ class suggested safety signals for heart rate and rhythm

disorder 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. Data available in the database for individual cases included under the WHO-ART system organ class "myo-endo-pericardial and valve disorders" in association with fexofenadine use were reviewed. The sponsor concluded that "In general, it cannot be ruled out that the underlying conditions or concomitant drug use may have contributed to these cardiac events."

Literature review

The sponsor searched the following databases and reports no new cardiac safety signals.

- MEDLINE®
- Biosis Previews®
- EMBASE
- Derwent Drug File
- MIS (Medical Intelligence Solutions)

Post-marketing reports

The most commonly reported cardiac SAEs were tachycardia and palpitations.

Thirty-eight (38) serious ***tachycardia*** cases have been spontaneously reported since initial approval of fexofenadine. The sponsor reports that most of these either reflect nonspecific diagnoses in cases lacking completed medical details, or are part of other recognized clinical syndromes rather than drug related effects. Most occurred in younger and middle-aged adults (32 of 38 patients, or 84%), with only 3 of the 38 reports (8%) occurring in patients over age 65 years.

The cases of serious tachycardia were assessed as follows by the sponsor:

- Nineteen (19) of the reports describe tachycardia as a symptom of another cardiac diagnosis (e.g., atrial fibrillation, ventricular tachycardia) or part of a non-cardiac syndrome (e.g. hypersensitivity reaction, acute psychotic reaction, acute infection, possible seizure);
- Ten (10) other reports lack adequate clinical and diagnostic details to confirm the occurrence of tachycardia and/or medically assess the event;
- An additional five (5) reports are confounded by concurrent medications (sumatriptan, etilephrine, erythromycin, albuterol, opipramol) also begun prior to the AE start;
- In one (1) other report of tachycardia as a symptom of heart failure, the cardiac failure occurred due to underlying disease decompensation in a patient who had recently elected to stop her digoxin;
- Two (2) additional reports are more likely explained by unstable cardiac disease (prior RV outflow tract tachycardia and recent aortic valve replacement); and
- The remaining (1) report, describing serious syncope and tachycardia but no reported QT prolongation in a 67 year old female (199920900HMRI) who took fexofenadine/pseudoephedrine, is discussed with malignant arrhythmias, association to fexofenadine cannot be excluded based on temporal relationship.

Reviewer's Comments: The med-watch forms for all the above cases were reviewed. As indicated by the sponsor, there were some reports lacking adequate clinical and diagnostic details However, there was temporal association between onset of tachycardia and fexofenadine in

some patients with no other known risk factors. Tachycardia improved with de-challenge in at-least five patients and recurred with re-challenge in a single patient

There were twenty-nine (29) spontaneous reports of ***serious palpitations***. Five of the serious palpitation reports (17%) occurred in patients 65 years or older, and patient age was not reported in 2 cases (7%); the remainder of the reports occurred in young or middle aged adults.

In ten (10) of the twenty-nine reports, the palpitations were a clinical symptom of a cardiac arrhythmia; five of these were associated with tachycardia and are discussed above, four of the cases were symptoms of atrial fibrillation, and the final report (200519142GDDC) occurred with ventricular tachycardia and is discussed with malignant arrhythmias below. In four (4) of the reports, while clinical details are lacking, the sponsor reports that events appear consistent with a hypersensitivity reaction. Seven (7) of the reports lacked adequate clinical detail to make a medical assessment. In four (4) of the reports, underlying cardiopulmonary disease was a confounder; similarly, in one (1) case, while diagnostic work-up details are lacking, the persistence of palpitations after discontinuation of fexofenadine suggests underlying disease as a more likely etiology. In two (2) of the reports, concomitant drug therapy (pseudoephedrine and confirmed phenytoin toxicity) are a likely cause for the palpitations. In a single case, describing the onset of palpitations and supraventricular tachycardia in a 31 year old female on the same day that fexofenadine was begun and which resolved the following day with discontinuation (199922086DDC), the sponsor reports that a causal association cannot be excluded; however, causal assessment is confounded by the concurrent treatment with ciprofloxacin.

Reviewer's Comments: Some of the cases of atrial fibrillation were new-onset in patients with no known risk factors and hence had a temporal association to fexofenadine. Otherwise, the sponsor's assessment of the cases seems reasonable.

<u>QT prolongation</u>
Nine of the sixteen serious reports of QT prolongation lacked information regarding the QT or QTc interval value. The remaining 7 serious reports, containing QT or QTc interval data, are summarized below.

Table 28 – QT interval prolongation cases with reported QT/QTc values

Case ID/ Age/ sex	QT/ QTc interval	Risk factors	Outcome*
199811145RHF 79Y F	QT 520 msec	Hypertension, Hyperlipidemia, Prior QT prolongation, Celiprolol-induced bradycardia	Recovered
199910471DDC 67Y M	QTc 500 msec	Recent discontinuation of carvedilol, ischemic heart disease, LVH, baseline QT prolongation (480 ms)	Not resolved
200010213HMRI 60Y F	QT 490 msec	Cisapride, CHF, CAD, previous myocardial infarction, diabetes mellitus, obesity	Ongoing
200021457DE 29Y F	QT 430 msec	None reported	Recovered
200022718US Unk F	QTc 520 msec	Unknown	Recovered
200121183EU 33Y M	QT 548 msec/ QTc 524 msec	Bradycardia (heart rate 46 bpm)	Recovered
200318736GDDC 13Y F	QT 441 msec	Overdose of metoclopramide and tramadol	Recovered

Source: Spontaneous Line listing for Adverse Events of Interest: TdP/ QT Prolongation (SMQ)_ fexofenadine Hydrochloride
Y- year, F- female, M- male, msec- milliseconds, bpm- beats per minute
* At time of last contact

Reviewer's comments: the sponsor reports that in case 200121183EU, significant bradycardia is a risk factor for repolarization abnormalities, but the case lacks complete medical history; however, bradycardia (55 bpm) and borderline QT prolongation (468 ms) five months after treatment suggests underlying disease. Lack of precision in this case regarding fexofenadine discontinuation date allows no assessment of drug dechallenge. In case 200022718US, a contributory role for fexofenadine cannot be excluded, diagnostic work-up details and identification of the concurrent medications are lacking.

Reports of potential malignant arrhythmia

All potentially significant ventricular arrhythmia events are summarized below.

Table 27 – All potential malignant ventricular arrhythmia events

MedDRA preferred term	No. (%) of events		
	Serious	Nonserious	Total
Total potential malignant arrhythmia AEs	**142**	**38**	**180**
Total potential malignant arrhythmia AE reports	**113**	**37**	**148**
Loss of consciousness	49 (0.2)	20 (0.1)	69 (0.3)
Syncope	35 (0.1)	15 (0.1)	50 (0.2)
Electrocardiogram QT prolonged	16 (0.1)	3 (<0.1)	19 (0.1)
Ventricular tachycardia	14 (<0.1)	0	14 (<0.1)
Cardiac arrest	10 (<0.1)	0	10 (<0.1)

MedDRA preferred term	No. (%) of events		
	Serious	Nonserious	Total
Ventricular fibrillation	8 (<0.1)	0	8 (<0.1)
Torsades de pointes	3 (<0.1)	0	3 (<0.1)
Ventricular arrhythmia	2 (<0.1)	0	2 (<0.1)
Cardiac fibrillation	1 (<0.1)	0	1 (<0.1)
Cardiorespiratory arrest	1 (<0.1)	0	1 (<0.1)

Source- Reported Torsades de Pointes/ QT Prolongation (SMQ) Adverse Events of Interest by SOC_ Spontaneous cases_ Fexofenadine Hydrochloride, *pg. 276*

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3 reports of torsade de pointes:
In the first report(200212306GDDC), a 15 year old female with no relevant medical history became dyspneic, cyanotic and had a sudden collapse while out with friends after complaining of feeling unwell. She was being treated with fexofenadine for allergic reaction to a bug bite. Emergency medical technicians noted ventricular escape rhythm on examination, and resuscitation was attempted without success. The following arrhythmias were noted: AV dissociation, ventricular escape, rapid ventricular rhythm, ventricular tachycardia, ventricular fibrillation and asystole (the specific timing of the TdP was not noted in the report). Postmortem examination revealed no structural cardiac abnormalities. The sponsor reports that congenital long QT syndrome leading to the sudden death of this young woman with no structural heart disease is a possibility. It does not appear that genetic testing was performed in family members.
Reviewer's comment: On review of the Med-Watch form, 24 hour Holters for the patient's mother, sister and brother were reported normal. Contribution by study drug cannot be excluded, especially in the absence of genetic testing information for congenital long QT syndrome.

In the second report, underlying heart disease was a confounder in this 70 year old woman who 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 EKG and Holter. The patient was treated with a DDD pacemaker, atrial flutter recurred approximately 1 month after fexofenadine was discontinued but the patient had no further TdP. In the third report, structural heart disease (HOCM) in association with acute myocardial infarction appears to be the most likely cause for the observed events in this 43 year old woman since no QT prolongation was noted on arrival.

Eight reports described ***ventricular fibrillation***. One of these, 200212306GDDC, also reported torsade de pointes and is presented above. The sponsor reports that three cases (200010507RGB, 200614521GDDC and 199921935HMRI) lack adequate information to allow a reasonable medical assessment. In one case (200820070GDDC), iatrogenic hypokalemia (2.6 mEq/L) from diuretic therapy was a confounding factor for the observed cardiac arrest and ventricular fibrillation in this obese patient with poorly-controlled hypertension although association to study drug could not be excluded. Underlying ischemic heart disease was the confounder in the remaining patients.
Reviewers Comment: Med-Watch forms were reviewed, agree with sponsor's assessment for most cases. One of the older subjects (67 year old male with a QTc of 460-480 ms at baseline)

experienced ventricular tachycardia and fibrillation post-treatment with fexofenadine. QTc interval decreased on dechallenge but did not normalize and increased on re-challenge with a decline when fexofenadine was stopped again. Thallium scan, MIBI scan and echo results were contradictory for ischemia and there was minimal CAD based on the coronary angiography report (wide left ventricle, Cx 40% long stenosis, RCA-wall irregularities, Biopsy: no evident deviations or fibrosis). An outside expert determined that QT/QTc intervals from Holter tracing just before arrhythmia were not prolonged compared to corresponding values from this patient who was diagnosed with a mutant hERG channel on potassium channel gene sequencing.

Fourteen reports described ***ventricular tachycardia*** (VT). Two of these, 200010138HMRI reporting TdP and 199910471DDC describing ventricular fibrillation, are discussed above. The remaining cases were either confounded due to underlying cardiac disease (5 cases) or lacked adequate information for assessment.

Reviewer's Comments: Based on review of the med-watch forms:

- *several subjects had underlying heart disease- RV dysplasia (1), CAD (4), RVOT with ventricular tachycardia (1), biventricular dysfunction (1) and cardiomyopathy (1).*
- *One subject had a history of tachycardia prior to starting the drug and the episodes continued after discontinuation of fexofenadine in another subject. Tachycardia did not occur with re-challenge in one subject who presented with PVT and loss of consciousness.*
- *In one subject tachycardia occurred in the setting of an overdose of allegra with cisapride and flecainide.*
- *Ventricular tachycardia was part of an allergic reaction in one subject.*

In summary most cases were confounded but there was a temporal association in some of the patients. Insufficient information was available in few of the cases to make an assessment.

Ten cases of ***cardiac arrest***, and 1 report of ***cardiopulmonary arrest***, were reported:

- Case 199810618HMRI is described above with TdP cases, and 97001126 and 200820070GDDC with ventricular fibrillation.
- In one case, 200313966US, a newborn exposed to fexofenadine transplacentally during gestation developed cardiac arrest during the high-risk delivery, but rapidly recovered with treatment.
- Case 200115540GDDC lacks sufficient clinical details, but hypokalemia (K+ 2.6 mmol/L) was a confounder. Similarly, in 200120306US, details are lacking, but multiple cardiac risk factors (hypertension, hyperlipidemia, and uncontrolled diabetes on nateglinide) were confounders.
- In 4 cases, severe underlying heart disease provides a more likely explanation for the arrest.
- In the final case, 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.

Reviewer's comment: In this last case, an association to fexofenadine is possible given the lack of structural abnormalities; however, electrophysiologic testing is needed to exclude a latent conduction abnormality.

Three reports described ***sudden death***. One of these, 199810506RGB was due to arrhythmogenic ventricular dysplasia. In one case, 199920119HMRI, confirmed congenital Long QT syndrome provides the most likely cause for the event, although a contributory role for fexofenadine in this high risk patient cannot be fully excluded. In case 200110250JP, adequate information is lacking to assess this report of sudden death in a 44 year old female treated for "infectious urticaria" although concurrent high fevers raise the possibility of viral myocarditis

Reviewer's Comment: Based on the sponsor's reports, among the malignant ventricular arrhythmic events, a significant cardiac disease burden or concomitant QT-prolonging medication use was reported in most cases .Contributory role for study drug is possible in a few of the cases although incomplete information limits assessment. The division has been advised to consult OSE to assess the post-marketing cardiac AE data. Comparison to background rate of events with loratadine would be useful.

Reviewer's MGPS datamining analysis

We conducted an MGPS data mining analyses of the AERS database for cardiac arrhythmia PTs associated with loratadine and fexofenadine where signal scores (EBGM values) were > 2. the EBO5 value for the PT "Electrocardiogram QT prolonged" was greater than 2 for fexofenadine and loratadine. Overall, for fexofenadine EB05 values were greater than 2 only for atrial or supraventricular arrhythmias and extrasystoles. These are weak associations. The cases of TdP were also reviewed here and match the sponsor's reports. Additional cases reported include TdP in an 82 year old female hospitalized for chest pain without QT prolongation and new-onset seizures in a woman (age unknown) one week after taking Allegra or Allegra-D although further information is unavailable. Overall post-marketing safety reports related to cardiac arrhythmias seem comparable or less than loratadine. However, this data is not confirmatory and as already stated earlier, input from OSE is required regarding this issue.

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic (S) **Run ID:** 2950
Dimension: 2 **Selection Criteria:** Generic name(...) + PT(...) **Where:** EBGM > 2.0
39 rows Sorted by Generic name, EBGM desc, PT desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Desloratadine	Tachyarrhythmia	Rate and rhythm disorders NEC	9	15.7	5.10	31.8
Desloratadine	Tachycardia	Rate and rhythm disorders NEC	33	2.68	2.00	3.53
Desloratadine	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	8	2.67	1.48	4.54
Desloratadine	Arrhythmia	Rate and rhythm disorders NEC	18	2.64	1.77	3.80
Desloratadine	Extrasystoles	Rate and rhythm disorders NEC	4	2.22	0.970	4.51
Desloratadine	Supraventricular tachycardia	Supraventricular arrhythmias	5	2.06	0.980	3.94
Fexofenadine	Electrocardiogram QT prolonged	ECG investigations	38	5.35	4.07	6.95
Fexofenadine	Atrial tachycardia	Supraventricular arrhythmias	6	4.28	2.04	9.77
Fexofenadine	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	22	3.83	2.67	5.35
Fexofenadine	Arrhythmia	Rate and rhythm disorders NEC	54	3.63	2.89	4.51
Fexofenadine	Extrasystoles	Rate and rhythm disorders NEC	8	2.98	1.64	5.06
Fexofenadine	Supraventricular tachycardia	Supraventricular arrhythmias	11	2.70	1.63	4.28
Fexofenadine	Atrial fibrillation	Supraventricular arrhythmias	37	2.62	1.98	3.39
Fexofenadine	Ventricular tachycardia	Ventricular arrhythmias and cardiac arrest	17	2.38	1.58	3.46
Fexofenadine	Cardiac flutter	Rate and rhythm disorders NEC	3	2.29	0.889	5.10
Fexofenadine	Tachycardia	Rate and rhythm disorders NEC	80	2.26	1.88	2.71
Fexofenadine	Atrioventricular block second degree	Cardiac conduction disorders	4	2.23	0.975	4.54
Fexofenadine	Bundle branch block right	Cardiac conduction disorders	5	2.22	1.05	4.24
Fexofenadine	Brugada syndrome	Cardiac conduction disorders	2	2.18	0.683	5.84
Fexofenadine	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	8	2.06	1.14	3.50
Fexofenadine And Pseudoephedrine	Supraventricular tachycardia	Supraventricular arrhythmias	4	2.17	0.949	4.41
Loratadine	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	34	6.24	4.63	8.34
Loratadine	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	48	5.59	4.38	7.06

Generic name	PT	HLT	N	EBGM	EB05	EB95
Loratadine	Supraventricular tachycardia	Supraventricular arrhythmias	36	5.58	4.20	7.32
Loratadine	Electrocardiogram QT prolonged	ECG investigations	55	4.95	3.95	6.14
Loratadine	Extrasystoles	Rate and rhythm disorders NEC	17	4.76	3.15	7.01
Loratadine	Ventricular tachycardia	Ventricular arrhythmias and cardiac arrest	55	4.68	3.73	5.81
Loratadine	Ventricular fibrillation	Ventricular arrhythmias and cardiac arrest	31	3.31	2.45	4.40
Loratadine	Atrial fibrillation	Supraventricular arrhythmias	59	3.13	2.52	3.85
Loratadine	Atrioventricular block second degree	Cardiac conduction disorders	8	3.10	1.71	5.28
Loratadine	Arrhythmia	Rate and rhythm disorders NEC	69	2.79	2.28	3.39
Loratadine	Bundle branch block	Cardiac conduction disorders	7	2.65	1.41	4.65
Loratadine	Supraventricular extrasystoles	Supraventricular arrhythmias	7	2.63	1.39	4.61
Loratadine	Atrial flutter	Supraventricular arrhythmias	8	2.55	1.41	4.34
Loratadine	Tachycardia	Rate and rhythm disorders NEC	167	2.43	2.13	2.75
Loratadine And Pseudoephedrine	Supraventricular tachycardia	Supraventricular arrhythmias	17	8.76	4.98	15.6
Loratadine And Pseudoephedrine	Tachycardia	Rate and rhythm disorders NEC	60	3.35	2.70	4.12
Loratadine And Pseudoephedrine	Arrhythmia	Rate and rhythm disorders NEC	16	2.21	1.45	3.26
Loratadine And Pseudoephedrine	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	6	2.10	1.06	3.82

ID:	2950
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As of date:	05/20/2010 00:00:00
Item variables:	Generic name, PT
Stratification variables:	Standard strata
Highest dimension:	2
Minimum count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes

Base counts on cases:	Yes
Use "all drugs" comparator:	No
Apply Yates correction:	Yes
Stratify PRR and ROR:	No
Fill in hierarchy values:	Yes
Exclude single itemtypes:	Yes
Fit separate distributions:	Yes
Save intermediate files:	No
Created by:	Empirica Signal Administrator
Created on:	05/30/2010 22:12:50 EDT
User:	Suchitra Balakrishnan
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 05/20/2010 00:00:00 loaded on 2010-05-30 02:52:15.0

Dimension: 2 **Selection Criteria:** Generic name(Ambroxol And Loratadine, Betamethasone And Loratadine, Desloratadine, Fexofenadine, Fexofenadine And Pseudoephedrine, Herbal Extract And Loratadine, Hydrochlorothiazide And Loratadine, Loratadine, Loratadine And Pseudoephedrine) + PT(Accelerated idioventricular rhythm, Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia neonatal, Arrhythmia supraventricular, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Bifascicular block, Bradyarrhythmia, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac arrest, Cardiac arrest neonatal, Cardiac death, Cardiac fibrillation, Cardiac flutter, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Chronotropic incompetence, Conduction disorder, Electromechanical dissociation, Extrasystoles, Foetal arrhythmia, Foetal heart rate deceleration, Foetal heart rate disorder, Heart alternation, Heart block congenital, Long QT syndrome, Long QT syndrome congenital, Lown-Ganong-Levine syndrome, Neonatal tachycardia, Nodal arrhythmia, Nodal rhythm, Pacemaker complication, Pacemaker generated arrhythmia, Parasystole, Paroxysmal arrhythmia, Postural orthostatic tachycardia syndrome, Rebound tachycardia, Reperfusion arrhythmia, Rhythm idioventricular, Sick sinus syndrome, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Sudden cardiac death, Sudden death, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Tachyarrhythmia, Tachycardia, Tachycardia foetal, Tachycardia paroxysmal, Torsade de pointes, Trifascicular block, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome, Wolff-Parkinson-White syndrome congenital, Convulsion, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Electromechanical dissociation, Presyncope) **Where:** EBGM > 2.0

SELECT * FROM OutputData_2950 WHERE (DIM=2 AND EBGM>2.0 AND ((P1='D' AND ITEM1 IN ('Ambroxol And Loratadine','Betamethasone And Loratadine','Desloratadine','Fexofenadine','Fexofenadine And Pseudoephedrine','Herbal Extract And Loratadine','Hydrochlorothiazide And Loratadine','Loratadine','Loratadine And Pseudoephedrine') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Accessory cardiac pathway','Adams-Stokes syndrome','Agonal rhythm','Anomalous atrioventricular excitation','Arrhythmia','Arrhythmia neonatal','Arrhythmia supraventricular','Atrial conduction time prolongation','Atrial fibrillation','Atrial flutter','Atrial tachycardia','Atrioventricular block','Atrioventricular block complete','Atrioventricular block first degree','Atrioventricular block second degree','Atrioventricular conduction time shortened','Atrioventricular dissociation','Atrioventricular extrasystoles','Bifascicular block','Bradyarrhythmia','Bradycardia','Bradycardia foetal','Bradycardia neonatal','Brugada syndrome','Bundle branch block','Bundle branch block bilateral','Bundle branch block left','Bundle branch block right','Cardiac arrest','Cardiac arrest neonatal','Cardiac death','Cardiac fibrillation','Cardiac flutter','Cardio-respiratory arrest','Cardio-respiratory arrest neonatal','Chronotropic incompetence','Conduction disorder','Electromechanical dissociation','Extrasystoles','Foetal arrhythmia','Foetal heart rate deceleration','Foetal heart rate disorder','Heart alternation','Heart block congenital','Long QT syndrome','Long QT syndrome congenital','Lown-Ganong-Levine syndrome','Neonatal tachycardia','Nodal arrhythmia','Nodal rhythm','Pacemaker complication','Pacemaker generated arrhythmia','Parasystole','Paroxysmal arrhythmia','Postural orthostatic tachycardia syndrome','Rebound tachycardia','Reperfusion arrhythmia','Rhythm idioventricular','Sick sinus syndrome','Sinoatrial block','Sinus arrest','Sinus arrhythmia','Sinus bradycardia','Sinus tachycardia','Sudden cardiac death','Sudden

death','Supraventricular extrasystoles','Supraventricular tachyarrhythmia','Supraventricular tachycardia','Tachyarrhythmia','Tachycardia','Tachycardia foetal','Tachycardia paroxysmal','Torsade de pointes','Trifascicular block','Ventricular arrhythmia','Ventricular asystole','Ventricular extrasystoles','Ventricular fibrillation','Ventricular flutter','Ventricular pre-excitation','Ventricular tachyarrhythmia','Ventricular tachycardia','Wandering pacemaker','Withdrawal arrhythmia','Wolff-Parkinson-White syndrome','Wolff-Parkinson-White syndrome congenital','Convulsion','Electrocardiogram QT interval','Electrocardiogram QT interval abnormal','Electrocardiogram QT prolonged','Electromechanical dissociation','Presyncope')))) ORDER BY ITEM1,EBGM desc,ITEM2 desc

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201613	ORIG-1	SANOFI AVENTIS US LLC	Allegra (Fexofenadine Hcl) oral tablets
NDA-201373	ORIG-1	SANOFI AVENTIS US LLC	FEXOFENADINE HCL
NDA-21909	SUPPL-3	SANOFI AVENTIS US LLC	ALLEGRA (FEXOFENADINE HCL)

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

/s/

SUCHITRA M BALAKRISHNAN
08/09/2010

HAO ZHU
08/09/2010

NORMAN L STOCKBRIDGE
08/09/2010

Filing Review for
Allegra Oral Suspension

SUBMISSION DATES:	March 26, 2010
NDA/SUBMISSION TYPE:	201-373 (PA)
ACTIVE INGREDIENTS:	Fexofenadine 30 mg/5 mL
DOSAGE FORMS:	Suspension
SPONSOR:	Sanofi - Aventis Mary Beth Wigley (610) 889-6792
REVIEWER:	Ayana K. Rowley, Pharm.D.
TEAM LEADER:	Marina Y. Chang, RPh

Submitted Labeling	Representative of Following SKUs
4 oz (120 mL) outer carton (Children's Allergy- Berry Flavor)	N/A
4 oz (120 mL) immediate container (Children's Allergy- No Flavor Noted)	N/A
Dosing Cup Graphic (Allegra Allergy)	N/A
4 oz (120 mL) outer carton (Children's Hives- Berry Flavor)	N/A
4 oz (120 mL) immediate container (Children's Hives- No Flavor Noted)	N/A
Dosing Cup Graphic (Allegra Hives)	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	Yes	PA, This is a RX to OTC switch application
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	[Yes/No]	Not applicable
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	No	Annotated font specifications for the Drug Facts label are missing
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include (b) (4) or similar statements?	Yes	(b) (4)
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	No	
Does a medical officer need to review any clinical issues?	Yes	This is a RX to OTC switch application
If SLR, should ONDQA also review?	Yes	This is a RX to OTC switch application

Information Request:

Project Manager: An information request is necessary; please inform the sponsor that the annotated font specifications are missing.

Reviewer's Comment:

Project Manager: The sponsor has included the phrase (b) (4) . The inclusion of this flag must be cleared by the ODE IV immediate office. Please request the ODE IV immediate office to provide comments regarding the acceptability of this statement.

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

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

/s/

AYANA K ROWLEY
05/11/2010

MARINA Y CHANG
05/11/2010