CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201373Orig1s000

ENVIRONMENTAL ASSESSMENT

Environmental Assessment
Finding of No Significant Impact

NDA 201-373
Allegra (fexofenadine HCl) oral suspension

Food and Drug Administration
Center for Drug Evaluation and Research

November 30, 2010

FINDING OF NO SIGNIFICANT IMPACT

NDA 201-373

Allegra (fexofenadine HCl) oral suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of the regulatory process.

NDA 201-373 requests approval for Allegra (fexofenadine HCl) oral suspension 30mg/5mL for nonprescription sale for use in the relief of symptoms of seasonal allergic rhinitis, (b) (4) and hives. In support of its application, Sanofi-aventis U.S. LLC., prepared an environmental assessment (EA; attached) in accordance with 21 CFR Part 25, which evaluates the potential environmental impacts of fexofenadine HCl.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact due to approval of this application and has concluded that this action is not expected to have a significant impact on the environment. Therefore, an environmental impact statement will not be prepared.

PREPARED BY:

Raanan A Bloom, Ph.D.
Senior Environmental Officer
Office of Pharmaceutical Science

CONCURRED BY:

Nakissa Sadrieh, Ph.D.
Associate Director for Research Policy and Implementation
Office of Pharmaceutical Science

CONCURRED BY:

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science

Attachment: February 10, 2009, Environmental Assessment

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1.11 APPENDICES

1.11.1 Non confidential Appendix

Table 1 – Fexofenadine HCl Physical/Chemical Data

Physical/Chemical Parameter	Value	Reference
Water Solubility (25°C)	2.44 mg/ml	(2)
Octanol/Water Partition Coefficient (Log Kow at pH=7)	0.30	(2)
Dissociation Constants (pKa at 25°C)	pK_1 = 4.25 pK_2 = 9.53	(2)
Vapor Pressure (mm Hg)	$<5 \times 10^{-10}$	(2)
Melting Point (°C)	>190	(2)
Ultraviolet-Visible Spectrum (absorption maxima, nm)	259 and 254	(2)
Sorption/Desorption (Log Koc)(estimated)	1.54	(2)
Hydrolysis Rate Constant (estimated)	$<10E^{-5}$/second	(2)

Table 2 - Fexofenadine HCl Environmental Fate Data

Test	Value	Test Method	Reference
Aerobic Biodegradation in Water- Mineralization (%CO_2)	0	FDA 3.11	(2)
Aerobic Biodegradation in Water- Biotransformation (% degradation products)	3.3	FDA 3.11	(2)

Table 3 - Fexofenadine HCl Environmental Effects Data

Test	EC_{50} Value (mg/L)	NOEC Value (mg/L)	Test Method	Reference
Microbial Inhibition			FDA 4.02	(2)
Pseudomonas fluorescens, Bacillus megaterium, Azotobacter chroococcum, Aspergillus clavatus, Penicillium canescens and Chaetomium globosum	>1,000 (MIC)	-		
Anabaena flos-aquae	400 (MIC)	-		
Algal (*Desmodesmus subspicatus*) Toxicity (72 hr.)	>200 (E_bC_{50}, biomass)	25	OECD 201	(5)
	>200 (E_rC_{10}, growth rate)	25		
Daphnia magna Acute Toxicity (48 hr.)	780	330	FDA 4.08	(2)
Fish (*Lepomis macrochirus*) Acute Toxicity (96 hr.)	>940	570	FDA 4.11	(2)

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/s/

RAANAN A BLOOM
11/30/2010

NAKISSA SADRIEH
11/30/2010

MOHEB M NASR
11/30/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: November 30, 2010

From: Raanan A. Bloom, Ph.D.
OPS/IO/SRS

To: Khushboo Sharma
OPS/ONDQA

Through: Nakissa Sadrieh, Ph.D.
OPS/IO/SRS

Subject: NDA 201-373 / Allegra (fexofenadine HCl) oral suspension 30mg/5mL
Environmental Assessment Review

Submission Date: March 25, 2010

Sanofi-aventis U.S. LLC
55 Corporate Drive
Bridgewater, NJ 08807

Background

This Environmental Assessment (EA) dated February 12, 2010, supports new drug application NDA 201-373 / Allegra (fexofenadine HCl) oral suspension 30mg/5mL for nonprescription sale for use in the relief of symptoms of seasonal allergic rhinitis, (b) (4) and hives.

Review of the Current Submission

The EA was prepared in accordance with 21 CFR Part 25 by Sanofi-aventis U.S. LLC. The EA cross references EAs previously submitted and approved for NDA 20-786 (ALLEGRA-D® - fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg tablets) Extended Release Tablets (subsequently referred to as ALLEGRA-D® 12-Hour), NDA 20-872 (ALLEGRA® Tablets) and NDA 21-963 (ALLEGRA® oral suspension dosage form), submitted December 15, 2005. Nomenclature, physical-chemical, environmental fate, and environmental effects data were previously submitted for fexofenadine in the referenced EAs. No new information,

except for a change in estimated predicted sales of fexofenadine and the related EIC, is provided. This is basically the same EA as was submitted under NDA 21-963. A FONSI was issued for NDA 21-963, dated April 5, 2006. Refer to NDA 21-963 for a full review of the EA. Accordingly, this review will focus on the adjusted sales estimates.

In the first five years of predicted sales of nonprescription ALLEGRA® Oral Suspension, the highest yearly quantity of fexofenadine HCl estimated by Sanofi-aventis to be marketed in the United States by Sanofi-aventis, for all dosage forms and strengths is (b) (4) projected from the last approval (NDA 21-963). (b) (4) IMS National Sales Perspectives data supports this analysis (see 2008 data below). Using this information and the algorithm described in the FDA EA 'Guidance for Industry' document, the Expected Introduction Concentration (EIC) of fexofenadine in the aquatic environment for all dosage forms and strengths is estimated to be (b) (4). This value is (b) (4) provided under NDA 21-963.

	(b) (4)
FEXOFENADINE TOTAL:	
FEXOFENADINE HCL (Generics)	
ALLEGRA-D 12 HOUR	
ALLEGRA-D	
ALLEGRA	
ALLEGRA ODT	

Note: IMS data is the amount of active ingredient sold at wholesale into the back doors of pharmacies. It understates the amount of drug sold for products sold OTC to stores without pharmacies.

This estimate assumes that fexofenadine is not metabolized, diluted, or depleted in the environment. Therefore, the EIC equals the Maximum Expected Environmental Concentration (MEEC) at the point of introduction into the aquatic environment. It is assumed that product use is evenly distributed throughout the U.S.

The highest sensitivity to fexofenadine HCl was shown in the algal toxicity study with a 72-hour EC50 (mean effects concentration, biomass) of > 200,000 µg/L. This EC50 value divided by the MEEC is approximately 319,000; significantly greater than the Tier 2 assessment factor of 100, indicating that approval of this application is not expected to have a significant risk to the environment.

Cumulative Impacts

IMS National Sales Perspectives data for 2008 for all fexofenadine sales is (b) (4). Even assuming a doubling in sales volume, the algal study EC50 value divided by this value is significantly greater than the Tier 2 assessment factor of 100.

A literature search was conducted. Two articles on the detection of fexofenadine in environmental samples were retrieved:

Environ. Sci. Technol. 2010, 44, 2661–2666: Fexofenadine was detected in Swedish sewage plant effluent at 38 - 146 ng/L.

Environmental Science And Pollution Research 2009 16 (5) 555-564: Fexofenadine was detected in Finland river water at 11 ng/L and wastewater at 100 ng/L.

These values are in general agreement with the modeled EIC values.

Studies on the ecotoxicity of fexofenadine were not found.

Available information does not indicate a need for preparation of a cumulative EA.

Comments and Conclusions

Based on FDA EA guidance and an evaluation of the information provided in this and previous EAs for Allegra, no adverse effects are expected from the introduction of fexofenadine into the environment due to the use of Allegra.

A Finding of No Significant Impact (FONSI) is recommended.

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/s/

RAANAN A BLOOM
11/30/2010

NAKISSA SADRIEH
11/30/2010