CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-909

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

Allegra ODT (Fexofenadine HCl)
Orally Disintegrating Tablet, 30 mg

NDA 21-909

Food and Drug Administration
Center for Drug Evaluation and Research

March 26, 2007

FINDING OF NO SIGNIFICANT IMPACT

for

NDA 21-909

Allegra ODT (Fexofenadine HCl)
Orally Disintegrating Tablet, 30 mg

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

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant impact on the quality of the human environment. An environmental impact statement, therefore, will not be prepared.

This new drug application requests the approval of Allegra (Fexofenadine HCl) Orally Disintegrating Tablets (ODT). Fexofenadine HCl, the active ingredient of Allegra, is a non-sedating antihistamine with selective H_1-receptor antagonist activity. In support of this new drug application, Sanofi Aventis U.S. LLC, prepared an environmental assessment (EA; attached) in accordance with 21 CFR Part 25 which evaluates potential environmental impacts from the use and disposal of this product.

Fexofenadine HCl and its metabolites may enter the aquatic environment from patient drug use and disposal. The toxicity of Fexofenadine HCl to environmental organisms (fish, *Daphnia* and algae) was characterized. Microbial inhibition studies were also conducted. Results indicate that the compound and its metabolites are not expected to be toxic to aquatic organisms or to inhibit microbial activity at expected environmental introduction concentrations.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital or clinic procedures. Empty or partially empty containers from home use typically will be disposed of through community solid waste management systems which typically include landfills, incineration, and recycling. Minimal quantities of unused drug are expected to be disposed of through sanitary sewer systems.

The Center for Drug Evaluation and Research has concluded that this product can be used and disposed of without any expected adverse environmental impacts. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY:

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CONCURRED BY:

Jon Clark, M.S.
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Center for Drug Evaluation and Research

Attachment:

Environmental Assessment
Appended Electronic Signature Page

sanofi aventis

Science and Medical Affairs
Bridgewater, NJ

ENVIRONMENTAL ASSESSMENT

Fexofenadine HCl Orally Disintegrating Tablet, 30 mg

Date: 15-Aug-2006

1 ENVIRONMENTAL ASSESSMENT – FEXOFENADINE HYDROCHLORIDE ORALLY DISINTEGRATING TABLET

1.1 DATE

15-Aug-2006

1.2 NAME OF APPLICANT

Sanofi-aventis U.S. LLC

1.3 ADDRESS OF APPLICANT

200 Crossings Blvd.
Bridgewater, NJ 08807-0890

1.4 DESCRIPTION OF THE PROPOSED ACTION

1.4.1 Description of the Requested Approval

Sanofi-aventis U.S. LLC has filed an NDA per section 505(b) of the Food, Drug and Cosmetic Act for fexofenadine hydrochloride (fexofenadine HCl) in a new orally disintegrating tablet formulation. This environmental assessment summary has been prepared pursuant to 21 CFR part 25 and the Guidance for Industry Environmental Assessment of Human Drugs and Biologics Applications, July 1998 CMC 6 Revision 1 (1) because the proposed action is projected to increase use of fexofenadine HCl, the active ingredient. The tablets each contain 30 mg fexofenadine HCl which are packaged in aluminum foil/aluminum foil blisters. The purpose of this report is to cross-reference the earlier environmental assessments for fexofenadine HCl and complement them with information relevant to this current filing.

An environmental assessment of this active ingredient has previously been presented in the NDA for ALLEGRA-D® (combination fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg tablets)(2). This product is now identified as ALLEGRA-D® 12 Hour. In addition, an environmental assessment for ALLEGRA® Tablets (fexofenadine HCl) was also presented (3). An algal growth inhibition test per the OECD 201 protocol was conducted with fexofenadine HCl in 2002 (4).

1.4.2 Need for the Proposed Action

The orally disintegrating tablet formulation of fexofenadine HCl offers a pediatric dosage in a convenient form.

1.4.3 Locations of Use and Disposal Sites

The locations of use and disposal sites for fexofenadine HCl product are described in the NDA for ALLEGRA-D®(2).

1.5 IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

The nomenclature and physical chemical data for fexofenadine HCl, the active moiety in the formulation are described in the NDA for ALLEGRA® Capsules, NDA 20-625 (5).

1.6 ENVIRONMENTAL ISSUES

As stated previously, an environmental assessment of fexofenadine HCl was presented in the NDA for ALLEGRA-D® 12 Hour (combination fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg tablets) (2) and the NDA for ALLEGRA® Tablets (fexofenadine HCl) (3). A discussion of the Environmental Issues for fexofenadine HCl is presented there.

The Environmental Introduction Concentration (EIC) of fexofenadine HCl from patient use is greater than 1 part per billion (ppb). Calculation of the EIC from all dosage forms and strengths and related applications is included in *Section 1.11.2 Confidential Appendix.*

Using the tiered approach given in the FDA EA Guidance document (1), the Maximum Expected Environmental Concentration (MEEC) of fexofenadine HCl is calculated assuming no metabolism, environmental depletion mechanisms or dilution, therefore the MEEC = EIC = Expected Environmental Concentration.

The highest sensitivity to fexofenadine HCl was shown in the algal toxicity study (4) with a 72-hour EC_{50} (mean effects concentration, biomass) of >200 mg/L. This EC_{50} value divided by the MEEC is greater than the Tier 1 assessment factor of 1000, so no further testing is necessary.

1.6.1 Summary

In conclusion and per the FDA EA Guidance document (1), since the EC_{50}/MEEC ratio for fexofenadine is greater than the Tier 1 assessment factor of 1000, we conclude that there are not any adverse effects expected from the introduction of fexofenadine HCl into the environment. In addition, to the applicant's knowledge, the requested action will not result in extraordinary circumstances per 21 CFR Section 25.21 since no significant effect to the quality of the human environment is expected.

1.7 MITIGATION MEASURES

Environmental impacts associated with the manufacturing, shipment, distribution, use, and waste disposal of the drug substance and active moiety fexofenadine HCl will be made negligible through the use of appropriate control measures as required by permitting and other procedures

and regulatory requirements. In addition, since no adverse environmental effects have been identified, no mitigation measures are needed.

1.8 ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy in a convenient new dosage form. The approval of the proposed action will provide an important benefit to patients with the indicated disorders with no significant environmental risk.

1.9 LIST OF PREPARERS

Peter Wilson
Bachelor of Science, Biology
Masters, Environmental Pollution Control
Manager, Environment
Sanofi-aventis U.S. Inc.

1.10 REFERENCES

(1) US FDA Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications, July 1998, CMC 6 Revision 1

(2) NDA 20-786, Section 3.E, (submitted December 20, 1996 and approved December 24, 1997)

(3) NDA 20-872, Section 3.E, (submitted July 17, 1998 and approved February 25, 2000)

(4) Aventis Pharma Deutschland GmbH – ProTox, 2002, Fexofenadin HCl Growth Inhibition Test with Freshwater Algae (*Desmodesmus subspicatus*), Report No. PT02-0046, Hattersheim, Germany

(5) NDA 20-625, Section 3.A, (submitted July 31, 1995 and approved July 25, 1996)

1.11 APPENDICES

1.11.1 Nonconfidential Appendix

Data Summary Tables

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 Pseudomonas fluorescens, Bacillus megaterium, Azotobacter chroococcum, Aspergillus clavatus, Penicillium canescens and Chaetomium globosum Anabaena flos-aquae	>1,000 (MIC) 400 (MIC)	- -	FDA 4.02	(2)
Algal (*Desmodesmus subspicatus*) Toxicity (72 hr.)	>200 (E_bC_{50}, biomass) >200 (E_rC_{10}, growth rate)	25 25	OECD 201	(4)
Daphnia magna Acute Toxicity (XX hr.)	780	330	FDA 4.08	(2)
Fish (*Lepomis macrochirus*) Acute Toxicity (XX hr.)	>940	570	FDA 4.11	(2)

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/s/

Jon E. Clark
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: March 26, 2007

From: Raanan A. Bloom, Ph.D.
OPS/PARS

To: OPS/ONDQA/DPA-1

Through: Jon Clark,
OPS/PARS

Subject: Allegra ODT, Orally Disintegrating Tablet, 30 mg
Environmental Assessment Review

NDA # 021-909
Submission Date: 9/28/2007

Sanofi-Aventis
200 Crossing Blvd, PO Box 6890
Bridgewater, NJ 08807-0890

Background

This environmental assessment (EA) dated August 15, 2006, supports new drug application NDA 21-909 for Allegra ODT (Fexofenadine HCl; Orally Disintegrating Tablet) 30 mg, indicated for the treatment of seasonal allergic rhinitis (SAR) and uncomplicated skin complications of chronic idiopathic urticaria (CIU) in children 6 to 11 years of age. Fexofenadine HCl, the active ingredient of Allegra is a non-sedating antihistamine with selective H_1-receptor antagonist activity. Allegra 60 mg capsules and tablets administered twice daily (BID) have previously been approved for the relief of symptoms associated with SAR and the treatment of uncomplicated skin manifestations of CIU in adults and children 12 years of age and older. Allegra 30 mg BID is currently approved for the treatment of SAR and CIU in children 6 to 11 years of age.

Review of the Current Submission

The EA was prepared in accordance with 21 CFR Part 25 by Sanofi Aventis U.S. LLC, 200 Crossing Blvd., Bridgewater, NJ 08807-0890. The EA cross references EAs previously submitted and approved for fexofenadine HCl (NDA 20-786, 20-872) and supplements the

information in these EAs with information relevant to this current filing. Nomenclature, physical-chemical, and environmental fate and environmental effects data were previously submitted for fexofenadine HCl in the referenced EAs.

The sponsor estimates that in the first five years of predicted sales of Allegra ODT, the highest yearly quantity of fexofenadine HCl marketed in the United States, for all dosage forms and strengths, will be [redacted]. Using this information and the algorithm described in the FDA EA Guidance for Industry document, the Expected Introduction Concentration (EIC) of fexofenadine HCl in the aquatic environment is estimated to be [redacted] ppb). b(4)

This estimate assumes that fexofenadine HCl 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.

Environmental effects data submitted include toxicological studies in fish, *Daphnia*, and algae, and microbial inhibition studies. The most sensitive species tested is algae. In the algal toxicity study, the 72-hour EC_{50} (mean effective concentration, biomass) for fexofenadine HCl exposure was reported to be >200,000 µg/L (ppb). The EC_{50} divided by the MEEC is greater than the Tier 1 assessment factor of 1000 (116, 279).

Comments and Conclusions

Based on an evaluation of the information provided in this EA and the provided FDA guidance, no further testing is required and no adverse effects are expected from the introduction of fexofenadine HCl into the environment due to the use of Allegra.

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

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/s/

Raanan Bloom
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ENV ASSESSMENT

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CHEMIST