

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022529Orig1s000

ENVIRONMENTAL ASSESSMENT



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

Memorandum

Date: September 13, 2010

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

To: Khushboo Sharma
ONDQA

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

Subject: **NDA 022-529: Lorcaserin hydrochloride 10 mg tablets (Lorqess)
Review of Environmental Assessment**

Sponsor: Arena Pharmaceuticals, Inc.

A. Background

Arena Pharmaceuticals, Inc. has filed a New Drug Application pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin hydrochloride (lorcaserin HCl) 10 mg tablets. This environmental assessment (EA) is submitted pursuant to 21 CFR part 25, and its format is in accordance with FDA guidance (FDA, 1998).

B. Discussion

Executive Summary

This EA supports the NDA for lorcaserin HCl 10 mg tablets. The EA was prepared in accordance with 21 CFR Part 25 by Arena Pharmaceuticals, Inc. The EA is compiled in accordance with FDA 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

The sponsor estimates an EIC of (b)(4) µg/L in water, based on a use estimate of (b)(4) in year (b)(4) (the highest year in the 5 year marketing forecasts) used in the United States.

The sponsor uses acute ecotoxicology data to estimate toxicity parameters in the environment. Comparison of the Expected Introductory or Maximum Expected Environmental Concentration (EIC; MEEC) to this value results in a ratio significantly greater than 100, allowing the

conclusion that lorcaserin residues in the environment are not expected to pose an environmental risk.

C. Environmental Assessment Review

1. **Date:** February 10, 2009

2. **Applicant:** Arena Pharmaceuticals, Inc

3. **Address:**

6166 Nancy Ridge Drive
San Diego, CA 92121

4. **Proposed Action:** Lorcaserin HCl is a serotonin 5HT_{2c} receptor agonist indicated for weight management, including weight loss and maintenance of weight loss, to be used in conjunction with a reduced-calorie diet and a program of regular exercise. The proposed action is to seek approval for lorcaserin HCl tablets for the treatment of obesity. The maximum dose will be 10 mg of lorcaserin HCl b.i.d. for chronic treatment of an indefinite duration. .

5. **Identification of Chemicals:**

The drug substance is lorcaserin HCl hemihydrate.

Chemical Name (IUPAC) (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate

CAS Number: 856681-05-5

Molecular formula: C₁₁H₁₅Cl₂N·0.5H₂O

Molecular weight: 241.16 g/mol

Structural formula:



Note: Lorcaserin HCl tablets are manufactured in Switzerland.

6. Environmental Characterization

Environmental Fate Characterization

Lorcaserin HCl hemihydrate is highly water soluble, has a low vapor pressure, and low octanol/water partitioning coefficient. Phys/Chem data indicates Lorcaserin will partition primarily to the aquatic environment.

Physical/Chemical Properties (Appendices 5-7)

Melting Point: Lorcaserin HCl hemihydrate (b) (4) dehydrates to an anhydrous polymorph (b) (4) which melts at 199°C

Water Solubility: > 400,000 mg/L

Dissociation Constant(s): pKa 9.53

Log Octanol/Water Partition Coefficient: log KOW 2.56

Vapor Pressure: 6.4310^{-05} Pa at 25°C

Environmental Depletion Mechanisms

Lorcaserin HCl hemihydrate was very stable and recalcitrant to harsh stress conditions (light, heat, acid, base, oxidation) and is expected to be stable under normal environmental conditions (appendix 4). A biodegradation study was not conducted.

Environmental Concentrations

The expected introduction concentration worst-case (EIC) was calculated according to the FDA Guidance for Industry document using 2004 (1.27x10¹¹ liters/day; 2004 Clean Watersheds Needs Survey Report) effluent values and a production value of (b) (4) kg/yr.

$$\text{EIC} = (b) (4) \text{ ug/L (ppb)}$$

The expected environmental concentration worst-case (EEC) can be derived from the EIC applying a default factor of 10 for dilution in surface waters:

$$\text{EEC} = (b) (4) \text{ ppb.}$$

The calculation assumes that all the drug substance produced is used with even distribution throughout the U.S. per day and no metabolism or depletion occurs.

Environmental Effects Characterization: Ecological Toxicity (see EA for references)

To determine the environmental effects of lorcaserin, the following acute studies were performed. The most sensitive species was algae with a 72h-EC₅₀ = 2.08 mg/L

$$\text{Microbial Inhibition EC}_{50} = (b) (4)$$

Acute Algal Growth Inhibition 72h-EC₅₀ = 2.08 mg/L / 72h-NOEC = (b) (4)
Acute Daphnid Immobility 48h-EC₅₀ = 2.13 mg/L / 48-hour NOEC = (b) (4)
Acute Fish Mortality 96h-LC₅₀ = 2.30 mg/L / 96-hour NOEC = (b) (4)

Environmental Characterization: Discussion

Physical/chemical data indicates lorcaserin is expected to partition primarily to the aquatic environment. The high solubility and low Kow indicate the compound would not be expected to bioaccumulate. The toxicity value derived for the most sensitive aquatic species (i.e., algae 72h-EC₅₀ = 2.08 mg/L) was compared to the EIC (equivalent to the Maximum Expected Environmental Concentration or MEEC) based upon projected highest sales volume within a 5 yr post approval period. The lowest EC₅₀ (2.08 mg/L) or LC₅₀ (2.30 mg/L) is more than 1,000 times higher than the MEEC_{aquatic} for lorcaserin. According to the FDA guidelines (FDA, 1998), no further testing is needed and a determination that no effects are expected on aquatic organisms can be concluded.

Cumulative Environmental Fate and Effects

There are no marketed generic applications or other NDA applications containing lorcaserin. Recalculation of exposure/toxicity ratios is therefore not required.

7. Mitigation Measures and Alternatives

Since no adverse environmental impact is expected, no mitigation methods are addressed.

D. Literature Reviewed

No literature on lorcaserin as related to environmental occurrences, fate, and ecotoxicity were found.

E. Comments and Conclusions

Based on an evaluation of the information provided in this EA, in FDA guidance, and on the scientific validity of the “no effects” conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA..

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

RAANAN A BLOOM
09/13/2010

NAKISSA SADRIEH
09/14/2010

**Environmental Assessment
Finding of No Significant Impact**

**NDA 022-529
Lorcaserin hydrochloride 10 mg tablets**

**Food and Drug Administration
Center for Drug Evaluation and Research**

September 13, 2010

FINDING OF NO SIGNIFICANT IMPACT

NDA 022-529

Lorcaserin Hydrochloride, 10 mg tablets

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 022-529 requests approval for lorcaserin hydrochloride 10 mg tablets for the treatment of obesity. In support of its application, Arena Pharmaceuticals, Inc., prepared an environmental assessment (EA; attached) in accordance with 21 CFR Part 25, which evaluates the potential environmental impacts of lorcaserin hydrochloride.

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 effect on the human environment. Therefore, an environmental impact statement will not be prepared.

PREPARED BY:

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Office of Pharmaceutical Science

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Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science

Attachment: February 10, 2009, Environmental Assessment

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NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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