CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-526/S004

ENVIRONMENTAL ASSESSMENT

1.12.14 Environmental Assessment

Introduction

Ranexa® (ranolazine) 500 mg extended-release (ER) tablet was approved for the treatment of chronic angina in a restricted population on 27 January 2006 (NDA 21-526). Marketing approval was also granted for the bid formulation of Ranexa 1000 mg ER tablet on 12 February 2007. CV Therapeutics, Inc. (CVT), is filing an sNDA for the use of Ranexa as first-line therapy for the treatment of chronic angina.

As part of the original NDA submission, dated 27 December 2002, a Categorical Exclusion was claimed per 21 CFR 25.31(b), as the Expected Introduction Concentration (EIC) of ranolazine was projected to be less than 1 part per billion (ppb). This Environmental Assessment (EA) on the use of ranolazine has been prepared based on the revised projection of sales in the United States (U.S.). This EA is presented in accordance with *FDA Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications* (July 1998).

1 DATE

15 August 2007

2 NAME OF APPLICANT/PETITIONER

CV Therapeutics, Inc.

3 ADDRESS

3172 Porter Drive
Palo Alto, California 94304
USA

4 DESCRIPTION OF PROPOSED ACTION

4.1 Requested Approval

Based on the revised projection of sales in the U.S., a Categorical Exclusion is claimed per 21 CFR 25.31(b), as the updated EIC of ranolazine is projected to be less than 1 part per billion (ppb). If only the production volume of the drug substance is considered, the quantity of material would increase the EIC to a concentration slightly greater than 1 ppb. However, based on the metabolism and excretion of the pharmacologically active ingredient, the actual amount of pharmacologically active material with the potential for environmental impact would be at most approximately (b) (4) [refer to Appendix 12(b), Confidential Appendix – Calculation of Environmental Introduction Concentration (EIC) of Ranolazine].

Data developed to date indicate a low toxicity potential for ranolazine in the environment. As compared to the EIC and the Expected Environmental Concentration (EEC) of (b) (4) there is a margin of safety of > 1000 from the No Observed Effect Concentrations (NOECs) of studies conducted to date. Therefore, in addition to the Categorical Exclusion based on the EIC of the active pharmacological material being < 1 ppb, it should be noted that there is very little or no risk associated with the excretion of these low concentrations of ranolazine in the environment based on the endpoints measured.

4.2 Need for Action

Ranolazine, the drug substance in ranolazine ER tablets, is a novel compound for the treatment of chronic angina. Ranolazine is believed to improve diastolic function by preventing and/or decreasing ischemia-induced Ca^{2+} overload through inhibition of late I_{Na} (late sodium channel current).

4.3 Locations of Use

Ranolazine ER tablets, which are administered orally, may be used by individuals throughout the U.S. in hospitals, clinics, and/or homes. Use of this product is not expected to be concentrated in any particular geographic region.

4.4 Disposal Sites

In U.S. hospitals, pharmacies, or clinics, empty or partially empty containers of the drug will be disposed of according to hospital, pharmacy, or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling. Minimal quantities of unused drug may be disposed of in the sewer system.

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

5.1 Nomenclature

Established Name:

Ranolazine (generic name, INN, USAN)

Brand/Proprietary Name/Tradename:

Tradename: Ranexa®

Chemical Names:

IUPAC Nomenclature

N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy) propyl]piperazinyl}acetamide

Chemical Abstracts Nomenclature[1]

1-piperazineacetamide, *N*-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-

Chemical Abstracts Service (CAS) Registration Number:

95635-55-5

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[1] 9th Collective Index

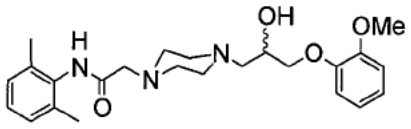
Molecular Formula:

$C_{24}H_{33}N_3O_4$

Molecular Weight:

427.54

Structural Formula:



Ranolazine

6 ENVIRONMENTAL ISSUES

6.1 Environmental Fate of Released Substances

Identification of Substances of Interest

The drug substance, ranolazine, is the primary compound expected to enter the environment from patient use. Metabolism studies in humans demonstrate that ranolazine is extensively metabolized (Report CVT 3019 in Item 6, Section 6.19, of the original NDA, 27 Dec 2002). Following a clinically relevant dose in humans, < 5% of the administered dose is recovered in urine and feces as intact ranolazine.

The 11 most abundant metabolites of ranolazine (present above 1% relative to ranolazine in human plasma) were evaluated for binding and functional receptor activity as compared to the parent molecule. The effects of these metabolites on the ion channels, I_{Kr}, I_{Ks}, and late I_{Na}, were determined at a minimal concentration of 10 μM in order to exceed by at least 5-fold the plasma concentration achieved by the most abundant metabolite at peak therapeutic plasma levels of ranolazine. The IC_{50} values for the 11 metabolites tested at I_{Kr} and I_{Ks} were > 50 μM. All 11 metabolites inhibited late I_{Na} by 12% to 57% at a concentration of 10 μM (CVT Technical Report CVT303.063-P). Three of the metabolites exhibited activity at α_1-, β_1- and β_2-adrenergic receptors, and at the $5HT_{1A}$ receptor,with potencies similar to or less than those of ranolazine (Technical Reports CVT303.029-N and CVT303.030-N, and Cerep Report 951006 and 951009 summary).

These data suggest that of the total dose administered, approximately 60% ranolazine equivalent [ranolazine (5%) plus a maximum of 0.57 (57%) of remaining 95% (conservative estimate of all) metabolites with biological activity (approximately 54%)] is

pharmacologically active, and therefore, potentially environmentally active. Thus, only this amount of the administered dose should be considered in assessing the potential environmental impact of the manufacture and use of ranolazine.

Physical and Chemical Characterization

The physical and chemical properties of ranolazine that are environmentally relevant are summarized below and in Appendix 12(a),Table A-1, Ranolazine Data Summary Table.

Aqueous Solubility

A study was conducted according to OECD Guideline 105 and Good Laboratory Practice (GLP) to determine the water solubility of ranolazine (in the form of the hydrochloride salt, RS-43285-003) at a range of environmentally relevant pH values (KZY 003/043550). Ranolazine was found to exhibit the greatest solubility in water at pH 4, with a value of > 200 g/L being recorded. At pH 7, the solubility was found to be 433 ± 6 mg/L, and at pH 10, the solubility was 148 ± 2 mg/L. Although there was a reduction in solubility with increasing pH, ranolazine was shown to be readily soluble in aqueous matrices at environmentally relevant pH values.

Dissociation Constants

As presented in the drug substance section of the original NDA (Section 4.3.1.3.5), the acid dissociation constant (pK_a) for the monoprotonated and diprotonated forms are 7.2 and 2.2, respectively.

Partition Coefficient

The partition coefficient was determined using three different ratios of octanol:water. The log P for ranolazine was measured at 2.07 ± 0.06. The log $P(^{+})$ was measured at −0.06 ± 0.09 (Section 4.3.1.3.3 of original NDA).

Vapor Pressure

Ranolazine is considered to be non-volatile.

Ultraviolet – Visible Absorption Spectrum

The UV spectrum exhibits two absorbance maxima consistent with the ranolazine structure. The absorbance maximum at 272 nm ($E_{1\%} \approx 60$) is due to the catechol diether ring, and stronger absorption at wavelengths shorter than ~225 nm is due to the aromatic moieties of ranolazine (Section 4.3.1.4.2 of original NDA).

Environmental Depletion Mechanisms

Based on available data along with the aqueous solubility and octanol:water partition coefficient of ranolazine, it is expected that ranolazine will reside in water, with a relatively small proportion adsorbing to soil. Although ranolazine does not appear to degrade, the concentration of the active pharmacological species is below the criteria of 1 ppb.

Ready Biodegradability

A ready biodegradability study was conducted according to OECD Guideline 301 and GLP to determine the extent to which ranolazine is biodegraded in the presence of a standardized microbial inoculum (Study 47842). Ranolazine only degraded by a mean value of 1.8% by Day 29 of the study (compared with 94% in a positive control using a readily biodegradable material). These results indicated that microbial biodegradation was minimal, and therefore, ranolazine cannot be classified as readily biodegradable.

Environmental Effects of Released Substances

Several studies have been conducted on the environmental effects of ranolazine, all indicating a low potential for toxicity at expected environmental concentrations. The lowest NOEC of these studies was 3.7 mg/L. These studies are summarized as follows.

Activated Sludge, Respiration Inhibition (OECD 209)

A study was conducted according to OECD Guideline 209 and GLP to determine the potential of ranolazine to inhibit microbial respiration in an activated sludge suspension (Study 47841). The inhibition observed was ≤ 2% at all test concentrations. Therefore, the EC_{50} value for respiration inhibition was determined to be > 1000 mg/L, the highest concentration tested. Ranolazine was not found to have adversely affected the respiration rate of activated sludge, and therefore, is not considered likely to present an unacceptable risk to the populations of degradative microbial flora associated with sewage treatment facilities.

Static Acute Toxicity of Ranolazine to Daphnia

A study was conducted according to OECD Guideline 202 and GLP to assess the acute toxicity of ranolazine to Daphnia under static exposure conditions (KZY 005/043649). The 48-hour EC_{50} value was 51 mg/L, and the NOEC was 3.7 mg/L.

Semi-static Acute Toxicity of Ranolazine to Rainbow Trout

A study was conducted according to OECD Guideline 203 and GLP to assess the acute toxicity of ranolazine to rainbow trout (*Oncorhynchus mykiss*) under semi-static exposure

conditions (KZY 006/043649). The 96-hour EC_{50} value was > 85 mg/L, and the NOEC was 40 mg/L.

Algal Growth Inhibition with Ranolazine

A study was conducted according to OECD Guideline 201 and GLP to assess the inhibition by ranolazine of growth of the unicellular green alga, *Selenastrum capricornutum* (KZY 004/043647). The 72-hour EbC_{50} value (biomass) was 44 mg/L, and the 72-hour ErC_{50} value (growth rate) was 97 mg/L. The NOEC was 8.4 mg/L.

Environmental Concentrations

The metabolism of ranolazine will result in excreted drug substance introduced into the environment primarily through municipal sewage treatment plants or septic tanks from patient use.

Expected Introduction Concentration (EIC)

If the EIC entering the aquatic environment from patient use is calculated without consideration of metabolism or environmental depletion mechanisms that occur in the waste treatment process, the EIC is based on the highest annual quantity of the active moiety in all dosage forms and strengths which are expected to be produced for direct use during the next 5 years.

The following calculation of the EIC for the aquatic environment assumes that: [1] all drug products produced in a year are used and enter the publicly owned treatment works (POTWs); [2] there is even distribution throughout the U.S. per day; and [3] there are no metabolism or depletion mechanisms:

EIC – Aquatic (ppb) = A x B x C x D
where: A = kg/year production (as active moiety) for direct use
B = $1/1.214 \times 10^{11}$ (1/liters per day entering POTWs)
C = year/365 days
D = 10^9 µg/kg (conversion factor)

Using this calculation, the EIC from patient use would slightly exceed 1 µg/L. However, this calculation does not consider metabolism, environmental depletion mechanisms, or dilution that occurs in the waste treatment process.

As stated in the July 1998 EA guidance document:

"The calculation of the expected introduction concentration (EIC) of an active moiety entering into the aquatic environment from patient use can consider the extent of metabolism to less pharmacologically active or inactive compounds, if that information is available. The pharmacological activity of metabolites relative to the active moiety shall be considered when calculating the EIC. The weighted contribution of the metabolite to the EIC should be calculated (e.g., kg/year active moiety x 10% x 0.5 for a metabolite found at a level of 10% and that has half the pharmacological activity of the active moiety). If the pharmacological activity of the metabolite is unknown, it can be assumed to be the same as the active moiety."

As described above, the pharmacokinetic and pharmacology data suggest that of the total dose administered, approximately 60% ranolazine equivalent [ranolazine (5%) plus a maximum of 0.57 (57%) of the remaining 95% (conservative estimate of all) metabolites with biological activity (approximately 54%)] is pharmacologically active, and therefore, potentially environmentally active. Thus, only this amount of the administered dose should be considered in assessing the potential environmental impact of the manufacture and use of ranolazine.

Based on these data, the value of A in the above equation was calculated for the pharmacologically (and environmentally) active moiety. Using this calculation, the EIC from patient use of ranolazine is (b) (4) [refer to Appendix 12(b), Confidential Appendix – Calculation of Expected Introduction Concentration (EIC) of Ranolazine].

Expected Environmental Concentration (EEC)

No concentration/depletion data are available; however, by applying a standard dilution factor of 10 to the EIC ((b) (4)), the estimated EEC would be approximately (b) (4).

Summary

Aquatic Environment: Ranolazine is expected to predominantly enter the aquatic environment as a result of patient use and is likely to partition into water based on its aqueous solubility and relatively low octanol:water partition coefficient.

Terrestrial Environment: As ranolazine is expected to enter the aquatic environment based on its aqueous solubility and octanol:water partition coefficient, and the concentration of the active pharmacological moiety is below 1 ppb, ranolazine would not be expected to significantly impact the terrestrial environment.

Atmospheric Environment: The solubility of ranolazine in aqueous solutions and its presumed low vapor pressure preclude the air compartment from being affected by

volatilization of this substance at the public sewage treatment plant. Manufacturing controls prevent significant releases into the air during the manufacturing process.

Environmental Effects of Released Substances: To date, data suggest that ranolazine has low toxicity potential in the environment. Ranolazine was not toxic in a respiratory inhibition study, had low acute toxicity in Daphnia, fish and algae. The lowest NOEC of these studies was 3.7 mg/L.

7 CONCLUSIONS

Based on its metabolism, the EIC of ranolazine is calculated to be (b) (4) Therefore, CVT requests categorical exclusion under 21 CFR 25.31(b). To CVT's knowledge, no extraordinary circumstances exist.

In addition, the data suggest a significant margin of safety (> 1000) from the calculated EIC and EEC and the lowest NOEC determined from environmental effects studies conducted to date.

8 MITIGATION MEASURES

CVT and its contract manufacturers have programs and procedures in place to anticipate and prevent potential adverse environmental impacts associated with this proposed action. In addition, emergency plans have been established in the event of an injury, spill, or fire that may happen at any site or while material is transported around the world. All plant operations, including distribution and waste management operations, are carried out by trained personnel under the supervision of qualified personnel with training in both normal and emergency operations. Any incident that would require additional specialized expertise would be provided by local fire, rescue, medical, and emergency authorities, or emergency response contract specialists.

9 ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified for the proposed action; therefore, no alternatives are proposed.

10 LIST OF PREPARERS

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11 REFERENCES

The following references were used in the preparation of this Environmental Assessment. Specific citations from these references may be obtained upon request.

21 CFR Ch. 1
Part 25 Environmental Impact Considerations
Food and Drug Administration, HHS

FDA Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
July 1998

12 APPENDICES

Appendix 12(a)

Table A-1 Ranolazine Data Summary Table

Physical/Chemical Characterization	
Aqueous Solubility	Freely soluble in aqueous solutions at pH levels > 4
Dissociation Constants	Conjugate acid forms of ranolazine exhibit acid dissociation constants (pK_a) of 7.2 (monoprotonated form) and 2.2 (diprotonated form)
Octanol:Water Partition Coefficient	Log P for ranolazine was measured at 2.07 ± 0.06; log $P(^{+})$ was measured at −0.06 ± 0.09
Vapor Pressure	Non-volatile
Depletion Mechanisms	
Hydrolysis	No data available
Aerobic Biodegradation in Water	No data available
Ready Biodegradability	Not readily biodegradable
Photolysis	No data available
Metabolism	Ranolazine is extensively metabolized in humans. Less than 5% is excreted unchanged. Activity of the metabolites is at most 57% of the active.
Environmental Effects	
Microbial Inhibition	Non-toxic. EC_{50} > 1000 mg/L
Acute Toxicity	Algae: The 72-hour EbC_{50} value (biomass) was 44 mg/L, and the 72-hour ErC_{50} value (growth rate) was 97 mg/L. The NOEC was 8.4 mg/L. Daphnia: The 48-hour EC_{50} value was 51 mg/L, and the NOEC was 3.7 mg/L. Rainbow Trout: The 96-hour EC_{50} value was > 85 mg/L, and the NOEC was 40 mg/L.