

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-430**

**ENVIRONMENTAL ASSESSMENT**



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

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Memorandum

**Date:** March 27, 2009

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

**To:** Jeannie David  
OPS/ONDQA

**Through:** Jon Clark, M.S.  
OPS/IO/PARS

**Subject:** **Review of Environmental Assessment**  
**NDA 22-430**  
**Lysteda™ (Tranexamic Acid) 650 mg Modified-Release Tablets**

**Sponsor:** Xanodyne Pharmaceuticals, Inc.

**A. Background**

Xanodyne Pharmaceuticals is requesting approval for a new NDA (022-430) for Lysteda (Tranexamic Acid) 650 mg modified release tablets. Tranexamic Acid is an antifibrinolytic agent indicated for the treatment of menorrhagia (heavy menstrual bleeding [HMB]) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities. The proposed action is to seek approval for Tranexamic Acid 650 mg as an antifibrinolytic agent to prevent and reduce heavy bleeding after surgery, an injury, or during heavy menstrual bleeding. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

**B. Discussion**

The following review was conducted by Ruth Ganunis, Ph. D., under contract to CDER/OPS on March 23, 2009, and approved by Raanan A. Bloom, Ph.D., OPS/IO/PARS, Senior Environmental Officer.

**Executive Summary**

This environmental assessment (EA) dated October 28, 2008, supports the new drug

application for Tranexamic Acid 650 mg Modified Release Tablets for use as an antifibrinolytic agent to prevent and reduce heavy bleeding after surgery, an injury, or during heavy menstrual bleeding. The EA was prepared in accordance with 21 CFR Part 25 by Xanodyne Pharmaceuticals, Inc.

Tranexamic acid is currently approved for use as an injectable drug product (Cykloapron, NDA 19-281).

Tranexamic acid is a carboxylic acid and a synthetic derivative of the amino acid lysine. Due to its high solubility, low Log  $K_{ow}$ , and low Log  $K_{oc}$ , tranexamic acid is expected to enter and remain in the aquatic environment. Tranexamic acid is very stable, and there are no environmentally relevant depletion mechanisms.

The toxicity of tranexamic acid to aquatic environmental organisms was characterized. The ratio of the  $LC_{50}$  for the most sensitive species (fathead minnows) to the EIC is greater than         , which is significantly greater than the tier 2 assessment factor of 100. The results suggest tranexamic acid would be nontoxic in the aquatic environment.

b(4)

A FONSI is recommended.

### Review of October 28, 2008, Environmental Assessment

- I. EA DATE: 28-OCT-2008
- II. APPLICANT: Xanodyne Pharmaceuticals, Inc
- III. ADDRESS: One Riverfront Place, Suite 900  
Newport, Kentucky 41071-4563
- IV. PROPOSED ACTION:
  - a. Requested Approval: Xanodyne Pharmaceuticals Inc. is requesting approval for Tranexamic Acid 650 mg Modified Release Tablets, packaged in HDPE bottles and unit dose PVC blisters. This EA has been submitted pursuant to 21 CFR part 25.
  - b. Need for Action: Tranexamic Acid is an antifibrinolytic agent indicated for the treatment of menorrhagia (heavy menstrual bleeding [HMB]) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities. The proposed action is to seek approval for Tranexamic Acid 650 mg Modified Release Tablets as an antifibrinolytic agent to prevent and reduce heavy bleeding after surgery, an injury, or during heavy menstrual bleeding.
  - c. Locations of Use: Hospital, clinics and patients homes throughout the United States.
  - d. Disposal Sites: Empty or partially empty containers from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy or clinic procedures. Empty or **partially empty containers from home use typically will be disposed by a community's solid waste management system** which may include landfills, incineration and recycling, while

minimal quantities of the unused drug may be disposed in the sewer system.

ADEQUATE

## V. IDENTIFICATION OF CHEMICALS

### Nomenclature:

Established Name (USAN): Tranexamic Acid

Proposed Trade Name: Tranexamic Acid 650 mg Modified Release Tablets

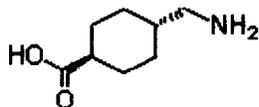
Chemical name: *Trans*-4-(Aminomethyl)cyclohexanecarboxylic acid monohydrochloride

Chemical Abstracts Service (CAS) Registration Number: 1197-18-8

Molecular Formula: C<sub>8</sub>H<sub>15</sub>NO<sub>2</sub>

Molecular Weight: 157.21

Chemical Structure:



ADEQUATE

## VI. ENVIRONMENTAL ISSUES

### a. Environmental Fate of Released Substances

#### i. Identification of Substances of Interest

Tranexamic acid is expected to be the only substance entering the environment.

ADEQUATE

#### ii. Physical and Chemical Characterization

Tranexamic acid is a carboxylic acid and a synthetic derivative of the amino acid lysine.

Test	Endpoint
Physical Description	White crystals or crystalline powder which is odorless and has a bitter taste
Melting Point	386-392°C
Water Solubility (at ambient temperature)	167,000 mg/L
Dissociation Constants	pKa: 4.93 ± 0.90

	pKa: $10.09 \pm 0.17$
Log Octanol/Water Partition Coefficient (log $K_{ow}$ ) (OECD 107)	$-0.0906 \pm 0.105$ (at pH 5) $-1.18 \pm 0.112$ (at pH 7) $-0.949 \pm 0.262$ (at pH 9)
Log Organic Carbon Partition Coefficient (log $K_{oc}$ )	1.53 (estimated)
Vapor Pressure	5.06E-10 mm Hg
Impurities	There are no impurities in the drug substance at a level greater than 1%.

Tranexamic acid is freely soluble in water. The Partition Coefficient n-Octanol/Water (log  $K_{ow}$ ) is less than zero at pH 5, 7, and 9. A value less than 3.5 indicates that the compound is not likely to bioaccumulate. In addition, the low Log Organic Carbon Partition Coefficient (log  $K_{oc}$ ) suggests that the compound is not likely to bioaccumulate. The low vapor pressure suggests the compound is not likely to move into the atmosphere.

Based on the test data, tranexamic acid is expected to enter and remain in the aquatic environment.

ADEQUATE

**iii. Environmental Depletion Mechanisms**

The firm conducted forced degradation studies including exposure to acid (0.1 N HCl) and base (0.1 N NaOH) hydrolysis studies, exposure to heat (64 °C), and exposure to light (long and shortwave ultraviolet). The forced degradation studies on tranexamic acid did not result in any detectable degradation of tranexamic acid. Tranexamic acid is therefore expected to be very stable under normal environmental conditions.

ADEQUATE

**iv. Environmental Concentration**

The maximum predicted amount of tranexamic acid drug substance manufactured for direct use in any of the next five years is \_\_\_\_\_ kg/year. Assuming no metabolism or environmental depletion, the firm determines the EIC to be \_\_\_\_\_  $\mu\text{g/L}$ .

b(4)

Since tranexamic acid is freely soluble in water and has a low propensity to adsorb to solids based on its octanol/water partition coefficient and soil adsorption coefficient, it is not expected to enter the terrestrial environment in significant amounts.

Tranexamic acid has a low vapor pressure and is not expected to volatilize and enter the atmospheric environment.

Since no environmental depletion mechanisms were identified for tranexamic acid, the expected environmental introduction concentration in the aquatic environment can be considered the maximum expected environmental concentration in the aquatic environment (EIC = MEEC<sub>aquatic</sub>).

ADEQUATE

v. **Summary**

Tranexamic acid is highly water soluble, has a low vapor pressure, and has a low soil adsorption coefficient. Therefore tranexamic acid will enter and remain in the aquatic compartment upon release into the environment. Forced degradation studies showed that tranexamic acid is very stable under normal conditions.

ADEQUATE

b. **Environmental Effects**

Test Organism (Test Method)	Condition	Result
Microbial Inhibition (OECD Guideline 209)	Microbial growth inhibition	EC <sub>50</sub> > 1000 mg/L (30 min)
Acute Algal Growth Inhibition ( <i>Pseudokirchneriella subcapitata</i> ) (OECD Guideline 201)	Acute toxicity	EC <sub>50</sub> > 105 mg/L (72 h) NOEC = 105 mg/L (72 h)
Acute Daphnid Immobility ( <i>Daphnia magna</i> ) (OECD Guideline 202)	Acute toxicity	EC <sub>50</sub> > 105 mg/L (48 h) NOEC = 105 mg/L (48 h)
Acute Fish Mortality Fathead Minnow ( <i>Pimephales promelas</i> ) (OECD Guideline 203)	Acute toxicity	LC <sub>50</sub> > 104 mg/L (96 h) NOEC = 104 mg/L (96 h)

The most sensitive species tested is the fathead minnow, with a LC<sub>50</sub> > 104 mg/L.

c. **Summary**

The toxicity value derived for the most sensitive aquatic species (the LC<sub>50</sub> for the fathead minnow) was compared to the Maximum Expected Environmental Concentration (MEEC) of tranexamic acid. The calculated assessment factor (LC<sub>50</sub>/MEEC) is       , which is significantly greater than the tier 2 assessment factor of 100. **b(4)**

ADEQUATE

**VII. MITIGATION MEASURES**

Information not required because no potential adverse environmental effects were identified.

ADEQUATE

**VIII. ALTERNATIVES**

Information not required because no potential adverse environmental effects were identified.

ADEQUATE

**IX. EA PREPARER**

Job titles and qualifications for Tim Verslycke, Ph.D. and Manu Sharma, M.S. were provided.

ADEQUATE

**X. REFERENCES**

Provided.

ADEQUATE

**XI. APPENDIX**

Non-confidential appendices

Appendix I. Data Summary Table

Confidential appendices

Appendix II. Five year US Forecast

Appendix III. EIC Calculation

Appendix IV. Tranexamic Acid: Determination of N-Octanol/Water Partition Coefficient

Appendix V. Tranexamic Acid: Determination of the Dissociation Constant

Appendix VI. Tranexamic Acid: Activated Sludge, Respiration Inhibition Test

Appendix VII. Tranexamic Acid: Growth Inhibition Test with Unicellular Green Alga

Appendix VIII. Tranexamic Acid: Acute Toxicity to the Water Flea, *Daphnia Magna*

Appendix IX. Tranexamic Acid: Acute Toxicity to the Fathead Minnow, *Pimephales*

*Promelas*

Appendix X. Xanodyne Pharmaceuticals, Inc Validation Procedure and Results for  
Methodology Used for Finished Product and Stability Testing

**ADEQUATE**

**C. Comments and Conclusions**

Based on an evaluation of the information provided in this EA and previous EAs and 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 introduction of tranexamic acid residues into the environment due to the use of Lysteda as an antifibrinolytic agent to prevent and reduce heavy bleeding after surgery, an injury, or during heavy menstrual bleeding.

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

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

/s/

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Raanan Bloom  
3/27/2009 02:54:15 PM  
ENV ASSESSMENT

Jon E. Clark  
3/27/2009 03:31:50 PM  
CHEMIST

**ENVIRONMENTAL ASSESSMENT**

**FINDING OF NO SIGNIFICANT IMPACT**

**for**

**Lysteda™ (Tranexamic Acid)  
650 mg Modified-Release Tablets**

**NDA 22-430**

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

**March 27, 2009**

## **FINDING OF NO SIGNIFICANT IMPACT**

**for**

**NDA 22-430**

**Lysteda™ (Tranexamic Acid) 650 mg Modified-Release Tablets**

**Antifibrinolytic Agent**

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 effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

NDA 22-430 requests approval for Tranexamic Acid 650 mg Modified Release Tablets as an antifibrinolytic agent to prevent and reduce heavy bleeding after surgery, an injury, or during heavy menstrual bleeding. In support of the application for Tranexamic Acid Modified Release Tablets, Xanodyne Pharmaceuticals, Inc. prepared an environmental assessment (attached) in accordance with 21CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

Tranexamic acid may enter the aquatic environment from patient use and disposal. The toxicity of tranexamic acid to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

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 by a community's solid waste management system which may include landfills, incineration and recycling. Minimal quantities of the unused drug are expected to be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. 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:**

Raanan A. Bloom, Ph.D.  
Senior Environmental Officer  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

**CONCURRED BY:**

Jon Clark, M.S.  
Associate Director for Policy  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

**CONCURRED BY:**

Moheb Nasr, Ph.D.  
Director, Office of New Drug Quality Assessment  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

Attachment: October 28, 2008, Environmental Assessment (confidential appendices removed)

**Environmental Assessment for  
Tranexamic Acid 650 mg Modified Release Tablets**

Prepared for  
Xanodyne Pharmaceuticals, Inc.  
One Riverfront Place, Suite 900  
Newport, Kentucky 41071-4563

Prepared by  
Gradient Corporation  
20 University Road  
Cambridge, MA 02138

October 28, 2008

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**1 DATE**

October 28, 2008

**2 NAME OF APPLICANT**

Xanodyne Pharmaceuticals, Inc.

**3 ADDRESS**

One Riverfront Place, Suite 900  
Newport, Kentucky 41071-4563

**4 DESCRIPTION OF PROPOSED ACTION**

**4.1 REQUESTED APPROVAL**

Xanodyne Pharmaceuticals, Inc. is filing a New Drug Application (NDA 22-430) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tranexamic Acid 650 mg modified release tablets, packaged in HDPE bottles and unit dose PVC blisters. This environmental assessment has been submitted pursuant to 21 CFR part 25, and its format is in accordance with FDA guidance (FDA, 1998).

**4.2 NEED FOR ACTION**

Tranexamic Acid is an antifibrinolytic indicated for the treatment of menorrhagia (heavy menstrual bleeding [HMB]) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities. The proposed action is to seek approval for Tranexamic Acid 650 mg modified release tablets as an antifibrinolytic agent to prevent and reduce heavy bleeding after surgery, an injury, or during heavy menstrual bleeding.

**4.3 LOCATIONS OF USE**

Tranexamic Acid 650 mg modified release tablets are manufactured in the U.S. in compliance with applicable state and federal environmental regulations, and will be used in hospitals, clinics and/or by patients in their homes throughout the U.S.

**4.4 DISPOSAL SITES**

At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures. From patients with in-home use, 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 the unused drug may be disposed to sewer or septic systems.

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

The new drug for which this application is prepared is Tranexamic Acid 650 mg modified release tablets. The active drug substance is Tranexamic Acid.

### **5.1 ESTABLISHED NAME (USAN)**

Tranexamic Acid

### **5.2 BRAND/PROPRIETARY NAME/TRADENAME**

Tranexamic Acid 650 mg modified release tablets

### **5.3 CHEMICAL NAME**

*Trans*-4-(Aminomethyl)cyclohexanecarboxylic acid

### **5.4 CAS NUMBER**

1197-18-8

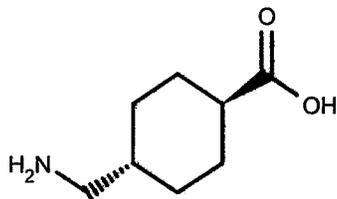
### **5.5 MOLECULAR FORMULA**

$C_8H_{15}NO_2$

### **5.6 MOLECULAR WEIGHT**

157.21

### **5.7 STRUCTURAL FORMULA**



## 6 ENVIRONMENTAL ISSUES

### 6.1 ENVIRONMENTAL FATE OF RELEASED SUBSTANCES

#### 6.1.1 Identification of Substances of Interest

Tranexamic acid, the parent compound, is expected to be the only substance entering the environment. Tranexamic acid is stable under normal conditions. Conditions of instability include excess heat and reaction with oxidizing agents (MSDS, 2004).

#### 6.1.2 Physical and Chemical Characterization

**Physical Description:** White crystals or crystalline powder which is odorless and has a bitter taste (MSDS, 2004)

**Melting Point:** 386-392 °C (decomposition) (MSDS)

**Water Solubility:** 167,000 mg/l (The Merck Index, 1996)

**Log Octanol/Water Partition Coefficient** (see Appendix IV – Confidential):

log  $K_{OW}$   $-0.0906 \pm 0.105$  (at pH 5)

log  $K_{OW}$   $-1.18 \pm 0.112$  (at pH 7)

log  $K_{OW}$   $-0.949 \pm 0.262$  (at pH 9)

**Dissociation Constant(s):** (see Appendix V – Confidential)

pKa  $4.93 \pm 0.90$  (determined by titration with HCl)

pKa  $10.09 \pm 0.17$  (determined by titration with NaOH)

**Log Organic Carbon Partition Coefficient:**

log  $K_{OC}$  1.53, (Estimated using the PCKOCWIN™ model in EPI Suite™, USEPA, 2008)

**Vapor Pressure:** 5.06E-10 mm Hg (Meylan and Howard, 1995)

**Impurities:** There are no impurities in the drug substance at a level greater than 1%.

#### 6.1.3 Environmental Depletion Mechanisms

Forced degradation studies, including acid (0.1 N HCl) and base (0.1 N NaOH) hydrolysis studies, as well as exposure to heat (64 °C) and light (long and shortwave ultraviolet) did not result in any detectable degradation of tranexamic acid ( — Analytical Method Validation Study Aug 8 2005 – see Appendix X - Confidential). Tranexamic acid is therefore expected to be very stable under normal environmental conditions.

## 6.1.4 Environmental Concentrations

### 6.1.4.1 Expected Introduction Concentration (EIC) From Use

The projected maximum annual production volume of tranexamic acid for direct use in all formulations and for all indications based on five-year production estimates was utilized for all calculations (see Appendix II – confidential).

#### *Aquatic Environment*

The EIC for the aquatic compartment is calculated using the maximum quantity of tranexamic acid expected to be produced for direct use in the next five years according to FDA guidance (FDA, 1998) and is shown in confidential Appendix III. The EIC was calculated, assuming that all the drug substance produced is used, evenly distributed throughout the USA, and no metabolism or depletion mechanisms exist.

#### *Terrestrial Environment*

Pharmaceuticals typically enter the terrestrial environment predominantly through land application of biosolids removed from waste water treatment plants. Since tranexamic acid is freely soluble in water (167 g/L) and has a low propensity to adsorb to solids based on its octanol/water partition coefficient ( $\text{Log } K_{\text{OW}} \leq -0.0906$  at pH 5, 6, and 9) and soil adsorption coefficient ( $\text{Log } K_{\text{OC}} = 1.53$ ), it is not expected to enter the terrestrial environment in significant amounts.

#### *Atmospheric Environment*

Tranexamic acid has a low vapor pressure (5.06E-10 mm Hg) and is not expected to volatilize and enter the atmospheric environment.

### 6.1.4.2 Maximum Expected Environmental Concentration (MEEC) From Use

Since no environmental depletion mechanisms were identified for tranexamic acid, the expected environmental introduction concentration in the aquatic environment can be considered the maximum expected environmental concentration in the aquatic environment ( $\text{MEEC}_{\text{aquatic}}$ ; calculated in confidential Appendix III). The MEEC is only calculated for the aquatic environment since this is the environmental compartment in which tranexamic acid will predominantly amass.

## 6.1.5 Summary

Tranexamic acid is a carboxylic acid and a synthetic derivative of the amino acid lysine and will be used to prevent and reduce heavy bleeding. Tranexamic acid is stable under normal conditions, highly water soluble, has a low vapor pressure, and low soil adsorption coefficient, and will therefore amass primarily in the aquatic compartment upon release into the environment. The following section describes studies performed to assess the potential effects of tranexamic acid at maximum expected environmental concentrations on wastewater treatment processes and aquatic organisms.

## 6.2 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

### 6.2.1 Effects on Activated Sludge Microorganisms in a Wastewater Treatment Plant

#### 6.2.1.1 Objective

The purpose of this study was to determine the effects of tranexamic acid on activated sludge microorganisms by measuring the potential inhibition of the respiration rate under defined conditions in the presence of varying concentrations of the test substance. The study was conducted under GLP standards and in accordance with OECD Guideline 209. The final study report is included in Appendix VI (confidential).

#### 6.2.1.2 Test Design

Five nominal concentrations of tranexamic acid (10, 32, 100, 320, and 1,000 mg/L), two negative controls (non-chlorinated well water), and a nominal 1,000 mg/L abiotic control, were tested. A positive control substance, 3,5-dichlorophenol, was tested at three concentrations (3.2, 10, and 32 mg/L).

The microbial inoculum used in the test was activated sludge, which was collected the day before the test from a wastewater treatment plant. The concentration of suspended solids in the microbial inoculum was determined in triplicate and ranged from 3.6 to 4.4 g/L. The inoculum was kept aerated before the test at  $20 \pm ^\circ\text{C}$  and at a pH of 7.81. After mixing the inoculum with well water, a sewage feed solution, and the appropriate amount of test or reference substance, the respiration rates were determined in single replicates. The abiotic control did not contain the inoculum.

#### 6.2.1.3 Results

The respiration rates and percent inhibitions for the five test substance flasks, the abiotic control, and the positive control are presented below.

*Table 1. Respiration rates and percent inhibition*

Treatment	Respiration Rate (mg O <sub>2</sub> L <sup>-1</sup> hr <sup>-1</sup> )	% Inhibition <sup>1</sup>
Control A <sup>2</sup>	155.4	-
Control B <sup>2</sup>	159.6	-
<i>Tranexamic Acid</i>		
10 mg/L	188.7	0
32 mg/L	138.1	12.4
100 mg/L	137.5	12.8
320 mg/L	127.1	19.4
1,000 mg/L	125.4	20.4
Abiotic Control	0.5	-
<i>3,5 - Dichlorophenol<sup>3</sup></i>		
3.2 mg/L	133.6	15.2
10 mg/L	57.8	63.3
32 mg/L -	23.7	85.0

<sup>1</sup>Refer to detailed study report in Appendix VI for %inhibition calculation.

<sup>2</sup>The respiration rates of the two control flasks were within 15% of each other which satisfies the control acceptability criterion outlined OECD Guideline 209.

<sup>3</sup>The 30-minute EC<sub>50</sub> value for 3,5-dichlorophenol was 7.3 mg/L, which was within the 5 to 30 mg/L acceptability range recommended by the OECD Guideline 209.

#### 6.2.1.4 Conclusion

The 30-minute EC<sub>50</sub> value for tranexamic acid could not be calculated since 50% inhibition was not achieved in any of the test substance treatments (*i.e.*, up to 1,000 mg/L). Consequently, it is concluded that the 30-minute EC<sub>50</sub> value for tranexamic acid is greater than 1,000 mg/L.

### 6.2.2 Acute Toxicity to the Unicellular Alga, *Pseudokirchneriella subcapitata*

#### 6.2.2.1 Objective

A 72-hour *Pseudokirchneriella subcapitata* growth inhibition test was conducted under GLP standards and according to OECD Guideline 201 to determine the possible effects of tranexamic acid on the growth of a unicellular alga species. The final study report is included in confidential Appendix VII.

#### 6.2.2.2 Test Design

A 72-hour range-finding test was first conducted at nominal tranexamic acid concentrations of 0 (control), 0.010, 0.10, 1.0, 10, and 100 mg/L, in duplicate. A definitive test was performed as a limit test with a control (0 mg/L) and a single test substance treatment of 105 mg/L. The control and test substance treatment were replicated six times. An additional replicate of the test substance treatment was also prepared and used to evaluate the potential for incorporation of the test substance into the algal biomass. The cell count of the algae was about  $5.0 \times 10^3$  cells/mL at the start of the exposure in each flask. In each flask, the cell density of the algae was determined at 24, 48, and 72 hours after the onset of the incubation and the pH was measured at the beginning and at the end of the incubation period. Temperature was continuously monitored throughout the experiment. The concentrations of tranexamic acid in the definitive test were analyzed using high performance liquid chromatography with ultraviolet detection (HPLC-UV).

#### 6.2.2.3 Results

The analytical method for recovering tranexamic acid from freshwater algal nutrient medium was validated prior to initiating the definitive test. Analysis of triplicate fortifications at concentrations of 5.89 and 134 mg/L resulted in recoveries ranging from 101 to 112% of the nominal concentrations. No residues of tranexamic acid were detected in the matrix blanks above the minimum quantifiable limit (MQL) of 4.03 mg/L.

Test solution temperature, measured at 0 and 72 hours, ranged from 23.6 to 24.5°C. The pH of the control and the 105 mg/L treatment at initiation was 7.5 and 7.4, respectively, and 7.9 in both the control and the 105 mg/L treatment after 72 hours.

The percent change in cell density at 72 hours, as compared to the control mean cell density, was +5, +11, -6, +12, and +8% in the 0.010, 0.10, 1.0, 10, and 100 mg/L treatments, respectively. Due to the lack of growth inhibition in the highest concentration tested, the definitive test was performed as a limit test with a control (0 mg/L) and a single test substance treatment of 105

mg/L. The percent change in mean cell density, as compared to the control, was +1% in the 105 mg/L tranexamic acid treatment at 72 hours.

#### 6.2.2.4 Conclusion

Tranexamic acid does not affect algal growth at concentrations up to 105 mg/L. The 72h-EC<sub>50</sub> for algal growth inhibition is therefore greater than 105 mg/L, and the 72h-NOEC is 105 mg/L.

### 6.2.3 Acute Toxicity to *Daphnia magna* Straus

#### 6.2.3.1 Objective

The purpose of this study was to determine the acute toxicity of tranexamic acid to the daphnid, *Daphnia magna* Straus. The criterion for effect was immobilization. The study was conducted under GLP standards and in accordance with OECD Guideline 202. The final study report is included in confidential Appendix VIII.

#### 6.2.3.2 Test Design

*Daphnia magna* neonates (<24-hours old) were used for all exposures. A range-finding test was first conducted to estimate the nominal exposure concentration range for the definitive test. The nominal concentrations used were: 0 (control), 0.10, 1.0, 10, and 100 mg/L. A definitive 48-hour limit test was then performed at concentrations of 0 (control) and 105 mg/L. The controls and all treatments in the definitive test were tested in quadruplicate. A total of five daphnids were impartially added to a set of labeled containers with each container representing one treatment replicate. The concentrations of tranexamic acid in the definitive test were analyzed using high performance liquid chromatography with ultraviolet detection (HPLC-UV).

#### 6.2.3.3 Results

The analytical method for recovering tranexamic acid from blended freshwater was validated prior to initiating the definitive test. Analysis of triplicate fortifications at concentrations of 5.89 and 134 mg/L resulted in recoveries ranging from 99 to 115% of the nominal concentrations demonstrating that the method was suitable for the analysis of tranexamic acid.

Water temperature during the 48-hour exposure ranged from 20.3 to 20.5°C, dissolved oxygen concentrations ranged from 8.3 to 8.6 mg/L (95 to 101% saturation), and pH readings were 8.4 throughout the test. Total alkalinity, total hardness, and specific conductivity were 156 mg CaCO<sub>3</sub>/L, 152 mg CaCO<sub>3</sub>/L, and 358 µS, respectively.

After 48 hours of exposure, mortality was 0% in both the control and 105 mg/L treatments. There were no sublethal effects noted in any of the control or test substance treatments.

#### 6.2.3.4 Conclusion

Tranexamic acid does not affect mobility of *Daphnia magna* Straus at concentrations up to 105 mg/L. The 48-h EC<sub>50</sub> is therefore greater than 105 mg/L, and the 48-h NOEC is 105 mg/L.

## 6.2.4 Acute toxicity to the Fathead Minnow, *Pimephales promelas*

### 6.2.4.1 Objective

The purpose of this study was to determine the acute toxicity of tranexamic acid to the fathead minnow, *Pimephales promelas*. The criterion for effect was mortality. The study was conducted under GLP standards and in accordance with OECD Guideline 203. The final study report is included in confidential Appendix IX.

### 6.2.4.2 Test Design

A range-finding test was first conducted to estimate the nominal exposure concentration range for the definitive test. The nominal concentrations used were: 0 (control), 0.10, 1.0, 10, and 100 mg/L. A definitive 96-hour limit test was performed at concentrations of 0 (control) and 105 mg/L. The control and test substance treatment were tested in duplicate. A total of 10 fish were distributed to each test chamber resulting in a total of 20 fish for each test substance treatment. Observations for mortality and sublethal responses (e.g., discoloration, loss of equilibrium, animals lying on the bottom of the test chamber, irregular respiration, etc.) were made once every 24 hours ( $\pm 1$  hour) for the duration of the test. Specific conductivity, total alkalinity, and total hardness were measured in a sample of the dilution water collected at test initiation. Temperature, dissolved oxygen concentration, and pH were measured in all test chambers daily throughout the test. The concentrations of tranexamic acid in the definitive test were analyzed using high performance liquid chromatography with ultraviolet detection (HPLC-UV).

### 6.2.4.3 Results

Analytical confirmation of the tranexamic acid within the test solution was performed at 0 and 96 hours. Measured concentrations of the test substance treatment sample collected at 0- and 96-hours were 104 mg/L or 99% of the nominal concentrations at both sample points. No residues of tranexamic acid were detected in the controls above the MQL of 4.03  $\mu\text{g/mL}$ . Recoveries from QC samples ranged from 96 to 104% of the nominal concentrations at 0 and 96 hours. Since the test material was stable under test conditions, the biological response was based on mean measured concentrations.

Test solution temperature during the 96-hour exposure ranged from 22.8 to 23.0°C. Dissolved oxygen concentrations ranged from 6.1 to 8.4 mg/L throughout the test, representing 74 to 102% of saturation. Test solution pH values ranged from 7.9 to 8.2 throughout the test. Specific conductivity, total alkalinity, and total hardness values from the dilution water were 330  $\mu\text{S}$ , 142 mg  $\text{CaCO}_3/\text{L}$ , 138 mg  $\text{CaCO}_3/\text{L}$ , respectively.

After 96 hours, mortality was 0% in both the control and 104 mg/L treatments. No sublethal effects were noted in the control or test substance treatment.

### 6.2.4.4 Conclusion

Tranexamic acid does not affect survival of fathead minnow at concentrations up to 104 mg/L. The 96-h  $\text{LC}_{50}$  is therefore greater than 104 mg/L, and the 96-h NOEC is 104 mg/L.

**6.2.5 Summary**

Tranexamic acid, the parent compound, is expected to be the only substance entering the environment. Since tranexamic acid is expected to be primarily present in the aquatic environment, potential effects to aquatic organisms were assessed. The toxicity value derived for the most sensitive aquatic species (*i.e.*, Fish 96h-LC<sub>50</sub> > 104 mg/L) was compared to the Maximum Expected Environmental Concentration (MEEC) of tranexamic acid, which was calculated on the basis of the 5<sup>th</sup> year's projected use volume (confidential Appendix III). The lowest observed EC<sub>50</sub> or LC<sub>50</sub> for tranexamic acid derived from Tier 2 acute testing (fish, aquatic invertebrate, alga) is more than 10,000 times greater than the MEEC (*i.e.* in the influent from a POTW, not taking in stream dilution into account). According to the FDA guidance (FDA, 1998), no further testing is needed if the lowest observed EC<sub>50</sub> or LC<sub>50</sub> derived from Tier 2 acute testing is 100 times higher than the MEEC. Consequently, no effects are expected on the aquatic environment from societal use of tranexamic acid at the highest projected use volume for the next 5 years and using conservative assumption for calculating its predicted environmental concentration. Since tranexamic acid is freely soluble in water and not lipophilic (log Kow = -1.9), no risks for bioaccumulation are expected. Similarly, no significant adsorption to activated sludge or ultimate exposure of terrestrial organisms is anticipated due to tranexamic acid's high affinity for the water phase.

**7. MITIGATION MEASURES**

No adverse environmental effects associated with the proposed action were identified, and therefore, no mitigation measures are needed.

**8. ALTERNATIVES TO THE PROPOSED ACTION**

No adverse environmental effects associated with the proposed action were identified, and therefore, no alternatives to the proposed action are proposed.

**9. LIST OF PREPARERS**

Company	Name	Job Title	Qualifications
Gradient Corporation	Tim Verslycke	Senior Environmental Toxicologist	Ph.D. (Applied Biological Sciences)
Gradient Corporation	Manu Sharma	Principal	M.S. (Civil Engineering), Licensed Professional Engineer (Environmental)

**10. REFERENCES**

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## 11. APPENDICES

Appendices II to X are considered confidential and not for public disclosure.

**Appendix I: DATA SUMMARY TABLE (NON-CONFIDENTIAL)**

PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	167,000 mg/L
Dissociation Constants	pKa $4.93 \pm 0.90$ (acid titration) pKa $10.09 \pm 0.17$ (base titration)
Log Octanol/Water Partition Coefficient (Log K <sub>OW</sub> )	log K <sub>OW</sub> $-0.0906 \pm 0.105$ (pH 5) log K <sub>OW</sub> $-1.18 \pm 0.112$ (pH 7) log K <sub>OW</sub> $-0.949 \pm 0.262$ (pH 9)
Vapor Pressure	5.06E-10 mm Hg
Sorption/Desorption (Log K <sub>oc</sub> )	1.53
DEPLETION MECHANISMS	
Hydrolysis	Not susceptible to hydrolysis
Photolysis	Not susceptible to photolysis
ENVIRONMENTAL EFFECTS	
Microbial Inhibition	30min-EC <sub>50</sub> > 1,000 mg/L
Acute Algal Growth Inhibition	72h-EC <sub>50</sub> > 105 mg/L
Acute Daphnid Immobility	48h-EC <sub>50</sub> > 105 mg/L
Acute Fish Mortality	96h-LC <sub>50</sub> > 104 mg/L

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5/19/2009 09:41:30 AM