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RESEARCH**

*APPLICATION NUMBER:*

**22-114**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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NDA: 22-114	Submission Date(s): 11/24/06
Brand Name	Zingo™
Generic Name	Lidocaine HCl monohydrate
Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Anesiva, Inc. South San Francisco, CA
Relevant IND(s)	54,740
Submission Type; Code	Original NDA; New formulation (standard review)
Formulation; Strength(s)	Zingo™ is supplied as a sterile, single-use device comprised of a cassette Needle-free helium powered delivery system containing 0.5 mg lidocaine powder; powered helium will accelerate lidocaine powder into the epidermis
Indication	For use on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation in pediatric subjects
Dosage and Administration	Administer 1-3 minutes before venipuncture or cannulation. Product is removed from the pouch, placed on the application site and sealed against the patient's intact skin. The safety interlock is released, and the device is actuated by pressing the start button. A 'pop' sound is emitted at the time the dose is delivered.

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## 1 Executive Summary

### 1.1 Recommendation

NDA 22-114 is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement can be reached between the Agency and the sponsor with regard to language in the package insert.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of CPB Findings

Anesiva Inc. submitted NDA 22-114 to support use of Zingo™ on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation. Zingo™, the sterile lidocaine HCl monohydrate product, is a single-use, disposable, needle-free injection system capable of delivering 0.5 mg of powdered lidocaine hydrochloride monohydrate (LHM) drug particles through the stratum corneum into the epidermis in a relatively small (10-12 mm diameter) area of skin to provide rapid (within 1-3 minutes), local anesthesia to reduce or eliminate the pain associated with venipuncture or cannulation procedures in pediatric subjects. This product is a drug/device combination to be utilized by trained and licensed health care professionals prior to a venipuncture and intravenous cannulation in pediatric subjects (3 – 18 years old).

Anesiva is referring to the findings of safety and efficacy of the approved products Synera™ and Lidoderm® in this 505(b)(2) application. General information on clinical pharmacology of lidocaine and warnings and precautions of lidocaine use are also referred from Synera label. SYNERA™ (lidocaine 70 mg and tetracaine 70 mg) is a peel and stick topical anesthetic patch designed to provide local dermal analgesia for superficial venous access procedures. Lidoderm® patch (lidocaine patch 5%) is used to relieve the pain of post-herpetic neuralgia with application on intact skin with no blisters.

There are nine clinical studies in the current submission. Five clinical studies (3268-3-003-1, 3268-3-004-1, 3268-2-002-1; 3268-4-400-001, and 3268-4-401-001) were conducted to demonstrate safety and efficacy in the prevention of pain following peripheral venous cannulation or venipuncture in children. Two additional safety and efficacy studies (3268-1-100-001 and 3268-1-102-001) were conducted in the adult population utilizing the same dose and pressure as for the pediatric population. An open label study to determine the sound emission levels produced by Zingo™ was conducted in healthy adult volunteers (3268-1-005-1). One pharmacokinetic study (3268-1-101-001) was also conducted whose results are described below. Overall, about 800 pediatric subjects and 200 adult subjects were exposed to Zingo™ in the above indicated clinical studies.

The clinical pharmacology program for this product consists of data from a Phase 1 safety, tolerability, and pharmacokinetics study (#3268-1-101-001) in 38 adult subjects (18 -45 yrs old). Each subject received a single dose of Zingo™ to the antecubital fossa of either the left or right arm, as determined by randomization. Blood samples were collected at 0 minutes, and at 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes and plasma samples were analyzed for lidocaine employing a validated analytical method. Lidocaine drug concentrations were below the limits of detection (5 ng/mL) in all treated subjects at every time point in the study; therefore, the pharmacokinetic parameters could not be estimated leading to the conclusion that there is no meaningful systemic absorption of lidocaine. As such, no further pharmacokinetic studies were conducted.

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## 2 QBR

### 2.1 General Attributes

Anesiva submitted a 505(b)(2) application seeking approval of their product "Zingo™" for use on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation in pediatric subjects (3 – 18 years old). Zingo™ is a single-use, disposable, needle-free injection, sterile lidocaine HCl monohydrate product. The device is capable of delivering 0.5 mg of powdered lidocaine hydrochloride monohydrate (LHM) drug particles under helium gas power in to skin.

Anesiva is referring to the findings of safety and efficacy of the approved products Synera™ and Lidoderm® in this 505(b)(2) application. General information on clinical pharmacology of lidocaine and warnings and precautions of lidocaine use are also referred from "Synera" product label.

Zingo™ is not approved for any indication any where else in the world.

### 2.2 General Clinical Pharmacology

There are nine clinical studies in the current submission. Five clinical studies (3268-3-003-1, 3268-3-004-1, 3268-2-002-1, 3268-4-400-001, and 3268-4-401-001) were conducted to demonstrate safety and efficacy in the prevention of pain following peripheral venous cannulation or venipuncture in children. Two additional safety and efficacy studies (3268-1-100-001 and 3268-1-102-001) were conducted in the adult population utilizing the same dose and pressure as for the pediatric population. An open label study to determine the sound emission levels produced by Zingo™ was conducted in healthy adult volunteers (3268-1-005-1). One pharmacokinetic study (3268-1-101-001) was also conducted whose results are described below. Overall, about 800 pediatric subjects and 200 adult subjects were exposed to Zingo™ in the above indicated clinical studies.

The clinical pharmacology program for this product consists of data from a Phase 1 safety and tolerability study (#3268-1-101-001), where pharmacokinetics of lidocaine following application of Zingo™ was assessed in 38 adult subjects (18 -45 yrs old). Each subject received a single dose of ALGRX 3268 (configured to deliver 0.5 mg lidocaine, at crystal size 35 µm, and 20 bar pressure) to the antecubital fossa of either the left or right arm, as determined by randomization. The lot number for each device used in this study was C0110L001 and the lot number for the drug substance was C0106R006. Blood samples were collected at 0 minutes, and at 1; 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes following a single dose application of Zingo™ and plasma samples were analyzed for lidocaine employing a validated analytical method. Lidocaine drug concentrations were below the limits of detection (5 ng/mL) in all treated subjects at every time point in the study; therefore, the pharmacokinetic parameters could not be estimated. Synopsis of the pharmacokinetic study is attached to this review (Page 14).

### 2.3 Intrinsic Factors

Detectable plasma levels were not noted following single dose application of this drug product. In addition, the total drug content (0.5 mg) contained in Zingo™, relative to

other products for similar indications, may be considered low. Notable systemic exposure to lidocaine results following various routes of administration (topical, caudal, epidural, and intravenous). Anesiva Inc. has conducted pediatric efficacy and safety studies following single dose of Zingo. Although plasma samples were noted collected in these studies to assess lidocaine levels, significant levels are not anticipated considering the total amount of lidocaine in the product and the dosing regimen.

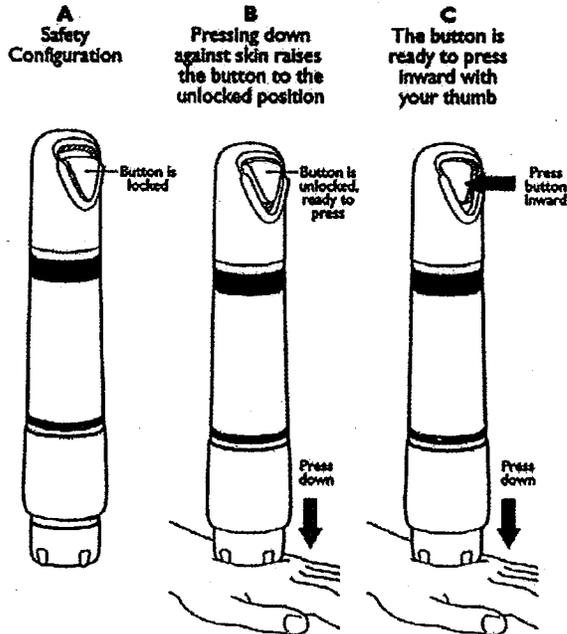
Taken together, additional studies are not necessary to evaluate effect of age, gender, race on the pharmacokinetics of lidocaine following application of Zingo.

#### 2.4 Extrinsic Factors

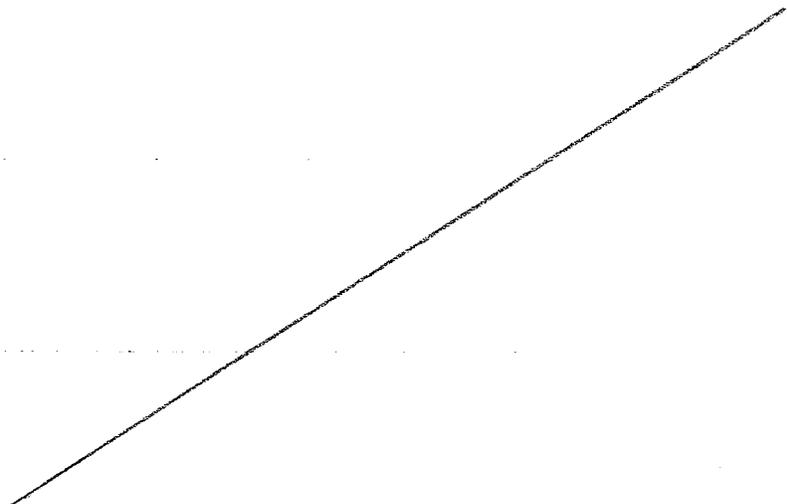
Since significant plasma levels were not noted following single dose application of drug product. Hence, it is not necessary to evaluate the effect of extrinsic factors on the pharmacokinetics of lidocaine following application of Zingo.

#### 2.5 General Biopharmaceutics

Zingo™ contains 0.5 mg of sterile lidocaine hydrochloride monohydrate as a sized white crystalline powder. Zingo™ is removed from the pouch, placed on the application site and sealed against the patient's intact skin. The safety interlock is released, and the device is actuated by pressing the start button. The device emits lidocaine hydrochloride monohydrate (40 µm nominal particle size) through the device using pressurized helium when the device is actuated. A "pop" sound is emitted at the time the dose of Zingo™ is delivered. The venipuncture or intravenous cannulation procedure should be started 1–3 minutes after administering the dose.



A list of developmental device products used in different clinical studies is presented below.



**b(4)**

- <sup>a</sup> Includes primary stability lots.
- <sup>b</sup> Sieved powders designated by sieve sizes. Particle size distribution of air classified powders produced from 2000 through Phase 3 determined by Aerosizer. Particle size distribution of air classified powders used in the primary stability lots determined by PSD3603.
- <sup>c</sup> Commercial configuration powder particle size distribution determined by PSD 3603.
- <sup>d</sup> Nominal mean particle size.

As noted above, the device used in the clinical pharmacokinetic study, configured to deliver 0.5 mg lidocaine at crystal size 35  $\mu\text{m}$  and 20 bar pressure, is similar to the devices used in the Phase 3 clinical studies and the commercial product. The minor difference in the drug substance particle size and pressure of drug dispersion is not anticipated to result in any difference in product performance. Detailed descriptions of the device and drug product may be found in the chemistry and device (CDRH) reviews.

## 2.6 Analytical

Plasma levels of lidocaine were detected employing a validated LC/MS/MS method. See attached summary of analytical method validation report (page 17).

## 3 Labeling

Highlights of sponsor proposed text relevant to Clinical pharmacology of lidocaine is presented in regular font, while additions and deletions are noted in bold type and strike-through text.

### FULL PRESCRIBING INFORMATION

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

...

##### Teratogenic Effects

7 Page(s) Withheld

       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

4.2 Individual Study Reviews (PK study 3268-1-101-001 report)

1. **TITLE PAGE**

**CLINICAL PHARMACOKINETIC STUDY REPORT**

**Study Title:** PHASE I STUDY TO QUANTITATE SYSTEMIC LIDOCAINE EXPOSURE AFTER TREATMENT WITH ALGRX 3268

**Name of Investigational Product:** ALGRX 3268

**Brief Description:** Single-Center, Open-Label, Single-Dose, Pharmacokinetic and Safety Study in Healthy Subjects

**Indication:** Local Anesthesia Prior to Needle or Catheter Insertion for Blood Drawing or Cannulation

**Study Number:** 3268-1-101-001  
**IND Number:** 54,740

**Development Phase:** I  
**First Subject Enrolled:** December 11, 2002  
**Last Subject Completed:** December 18, 2002

**Name and Affiliation of Principal Investigator:** Glen Apseloff, MD  
Division of Clinical Pharmacology  
The Ohio State University  
Department of Pharmacology  
5084 Graves Hall, 333 W. Tenth Ave  
Columbus, OH 43210-1239  
(614) 292-8190

**Name of Sponsor Contact/ Sponsor:** Jeffrey D. Lazar, MD, PhD  
AlgoRx Pharmaceuticals, Inc.  
101 Interchange Plaza, Suite 102  
Cranbury, NJ 08512  
(609) 409-2300

**Statement of GCP Compliance:** This study was conducted in compliance with the Declaration of Helsinki and its amendments and Good Clinical Practice for Trials on Medicinal Products, including archiving of essential study documents.

**Date of Report:** March 19, 2003

## 2. SYNOPSIS

<b>Name of Company:</b> AlgoRx Pharmaceuticals, Inc.	
<b>Name of Finished Product:</b> ALGRX 3268	
<b>Name of Active Ingredient:</b> Lidocaine	
<b>Title of Study:</b> Phase I Study to Quantitate Systemic Lidocaine Exposure after Treatment with ALGRX 3268	
<b>Investigator:</b> Glen Apseloff, MD	
<b>Study Center:</b> Division of Clinical Pharmacology, The Ohio State University, Department of Pharmacology, 5084 Graves Hall, 333 W. Tenth Ave., Columbus, OH 43210	
<b>Publication:</b> None	
<b>Study Period (years):</b> 2002 Date of first enrollment: December 11, 2002 Date of last completion: December 18, 2002	<b>Phase of Development:</b> I
<b>Objectives:</b> The primary objective was to determine maximal systemic lidocaine exposure after treatment with ALGRX 3268 using relevant pharmacokinetic metrics. The secondary objectives were to evaluate the comfort of ALGRX 3268 activation, to evaluate clinical safety and tolerability of ALGRX 3268, and to characterize lidocaine pharmacokinetics following ALGRX 3268 administration.	
<b>Methodology:</b> Phase I, single-center, open-label, single-dose, pharmacokinetic and safety study. Following a screening period, each subject received a single administration of ALGRX 3268 (configured at 0.5 mg lidocaine, crystal size 35 µm, and at 20 bar pressure) to the antecubital fossa of either the left or right arm, as determined by randomization. Blood samples to detect lidocaine levels were drawn at 0 minutes, and at 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes post-administration of ALGRX 3268.	
<b>Number of Subjects (planned and analyzed):</b> The study was designed to include 36 evaluable subjects. Forty-one subjects were enrolled in the study and 38 subjects were treated with ALGRX 3268. Thirty-six subjects completed the study.	
<b>Diagnosis and Main Criteria for Inclusion:</b> Normal healthy subjects of either gender aged 18 and above, who were not overweight or obese, and who did not have any skin condition that would preclude and adequate assessment of skin reactions were included in the study.	
<b>Test Product, Dose and Mode of Administration, Batch Number:</b> Each subject received a single dose of ALGRX 3268 (configured to deliver 0.5 mg lidocaine, at crystal size 35 µm, and 20 bar pressure) to the antecubital fossa of either the left or right arm, as determined by randomization. The lot number for each device used in this was study was C0110L001 and the lot number for the drug substance was C0106R006.	
<b>Duration of Treatment:</b> Exposure to treatment was instantaneous upon device activation. Each subject received a single administration of ALGRX 3268 (configured at 0.5 mg lidocaine, crystal size 35 µm and 20 bar pressure).	
<b>Reference Therapy, Dose and Mode of Administration, Batch Number:</b> No reference therapy was administered.	

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**Criteria for Evaluation:**

**Pharmacokinetic:** The study was designed to determine the maximal systemic exposure to lidocaine and to characterize the basic pharmacokinetic parameters of C<sub>max</sub>, T<sub>max</sub>, AUC(0-τ), and apparent terminal elimination rate of lidocaine following administration of ALGRX 3268.

**Safety:** The skin at the site of application was assessed for erythema, edema, pruritus, and hemorrhage/petechiae using a numerically based scale at 0, 1, 15, 30, 60, 120, and 240 minutes post administration. Adverse events (AEs) were collected. Adverse events noted on the numerically based scale for skin assessments were not repeated on the AE form. Tolerability of the device was assessed by each subject using a 10 cm visual analogue scale (VAS).

**Statistical Methods:** C<sub>max</sub>, T<sub>max</sub>, AUC(0-τ), apparent terminal elimination rate constant, and apparent half life were to be estimated using lidocaine concentrations. Summary statistics such as mean, standard deviation, median, range and 95% confidence intervals were to be presented. Summary statistics were also used to describe safety and demographic variables.

**Pharmacokinetic Results:** Lidocaine drug concentrations were below the limits of detection (5 ng/mL) in all treated subjects at every time point in the study; therefore, the pharmacokinetic parameters could not be estimated.

**Safety Results:** Six of 38 subjects reported treatment-emergent adverse events. Four of the events were considered to be possibly related to treatment, which included three reports of lightheadedness and one report of cluster headaches. No serious or severe adverse events were reported. Erythema was noted at the application site to be either very slight or well-defined in all cases and tended to decrease over time. One subject reported edema at one time point and two subjects reported pruritus. No surface bleeding or frank bleeding were reported. Tolerability of the device was assessed by subjects using a 10 cm visual analogue scale (0 for no discomfort and 10 for extreme discomfort). Results were presented on a 100 mm scale and the mean score was 10.2 mm.

**Conclusions:** Administration of ALGRX 3268 (configured at 0.5 mg lidocaine, crystal size 35 μm and 20 bar pressure) did not result in detectable plasma levels of lidocaine in any subject at any time point. Safety and tolerability data indicated that the device was well tolerated.

**Date of Report:** March 19, 2003

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#### 4.3 Analytical method validation

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

4.4 Office of Clinical Pharmacology NDA Filing Review Memo

<b>Office of Clinical Pharmacology</b>				
<b>New Drug Application Filing and Review Form</b>				
<b>General Information About the Submission</b>				
	Information		Information	
<b>NDA Number</b>	22-114	<b>Brand Name</b>	Zingo	
<b>OCP Division (I, II, III, IV or V)</b>	Division 2	<b>Generic Name</b>	Lidocaine	
<b>Medical Division</b>	DAARP	<b>Drug Class</b>	Local Anesthetic	
<b>OCP Reviewer</b>	Srikanth C. Nallani, Ph.D.	<b>Indication(s)</b>	Local Analgesia prior to venipuncture	
<b>OCP Team Leader</b>	Suresh Doddapaneni, Ph.D.	<b>Dosage Form</b>	Powder delivered by a device	
		<b>Dosing Regimen</b>	1-3 minutes before venipuncture	
<b>Date of Submission</b>	11/22/2008	<b>Route of Administration</b>	Topical	
<b>Estimated Due Date of OCP Review</b>	8/22/2008/	<b>Sponsor</b>	Anesiva Inc., South San Francisco, CA	
<b>PDUFA Due Date</b>	8/22/2007	<b>Priority Classification</b>	Standard	
<b>Clinical Division Due Date</b>	8/22/2007			
<b>Clin. Pharm. and Biopharm. Information</b>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:	X	1	1	
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
<b>In-vivo effects on primary drug:</b>				
<b>In-vivo effects of primary drug:</b>				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CP Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	██████	1	1	
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Are the active ingredients significantly absorbed into the systemic circulation?			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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this page is the manifestation of the electronic signature.**  
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/s/

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Srikanth Nallani  
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Suresh Doddapaneni  
7/24/2007 08:04:54 PM  
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