

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-430

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use</i>		NDA NUMBER 22-430	
		NAME OF APPLICANT/NDA HOLDER Xanodyne Pharmaceuticals, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME Lysteda			
ACTIVE INGREDIENT(S) Tranexamic Acid		STRENGTH(S) 650 mg	
DOSAGE FORM Modified-Release Tablets		APPROVAL DATE OF NDA OR SUPPLEMENT	
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.			
For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.			
I. GENERAL			
a. United States Patent Number		b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner		Address (of Patent Owner)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
1. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes,"
- the answer to 2.7 is "No."

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) | Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product? Yes No

4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

<p>4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.</p>	<p>Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)</p>
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FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

7. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

8. Declaration Certification

8.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

<p>8.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)</p> <p style="font-size: 1.5em; font-family: cursive;">Thomas P. Jennings</p>	<p>Date Signed</p> <p>01/19/2009</p>
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NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Thomas P. Jennings, Esq.	
Address One Riverfront Place	City/State Newport, KY
ZIP Code 41071	Telephone Number (859) 371-6383
FAX Number (if available) (859) 371-6391	E-Mail Address (if available) tjennings@xanodyne.com

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1. PARAGRAPH II CERTIFICATION

The reference drug for this 505(b) (2) application is Cyklokapron (tranexamic acid 100 mg/mL injectable), NDA # 019281 (Pharmacia and Upjohn). Patent and exclusivity information provided in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book, updated January 16, 2009) indicate that there are no unexpired patents or unexpired exclusivity for this product.



Sabrina R. Girty, Esq.
Associate Director, Regulatory Affairs
Xanodyne Pharmaceuticals, Inc.

EXCLUSIVITY SUMMARY

NDA # 22-430

SUPPL #

HFD # 580

Trade Name Lysteda

Generic Name tranexamic acid

Applicant Name Xanodyne Pharmaceuticals, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-281

Cyclokapron, 100 mg/ml, injectable

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

- 1) XP12B-MR-301
- 2) XP12B-MR-303

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- 1) XP12B-MR-301
- 2) XP12B-MR-303

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 68,096 YES ! NO
! Explain:

Investigation #2 !
!
IND # 68,096 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Nenita Crisostomo, R.N.
Title: Regulatory Health Project Manager
Date: October 11, 2009

Name of Office/Division Director signing form: Scott Monroe, M.D.
Title: Director, Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22430	ORIG-1	XANODYNE PHARMACEUTICS INC	Lysteda

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

/s/

JENNIFER L MERCIER
11/10/2009

SCOTT E MONROE
11/13/2009

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	11 yr. 0 mo.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed):

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	12 yr. 0 mo.	17 yr. 0 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): <u>December 2011</u>						

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: Pediatric studies have been deferred until the product has been determined to be safe and effective for women 18 years and older for the proposed indication.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Nenita Crisostomo, R.N.

Regulatory Health Project Manager

(Revised: 6/2008)

JUSTIFICATION:

This drug product is intended for women who are experiencing symptomatic, excessive menstrual bleeding. It is not indicated for use in pre-menarcheal children. Because the mean age of menarche in the U.S. is approximately 12.5 years, there are too few children less than 12 years of age with this disease/condition and who might derive benefit from treatment with tranexamic acid. Pediatric studies have been deferred until the product has been determined to be safe and effective for women 18 years and older for the proposed indication. The Sponsor plans to conduct a pharmacokinetic (PK) study of tranexamic acid in the adolescent population ranging in age from 12 – 17 years. Final protocol development for this PK study has been deferred until after the approval of this product.

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

/s/

NENITA I CRISOSTOMO
10/17/2009

In accordance with the requirement Section 306(k) of the Federal Food Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Xanodyne Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Act in connection with the development of the Tranexamic Acid 650 mg modified release tablets program for Xanodyne, Inc.

 8/28/2008

Sabrina Girty, Esq.
Associate Director,
Regulatory Affairs
Xanodyne Pharmaceuticals, Inc.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 022430 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Lysteda Established/Proper Name: tranexamic acid Dosage Form: tablet		Applicant: Xanodyne Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Nenita Crisostomo		Division: Reproductive and Urologic Products
<p>NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>NDA 19-281 Cyklokapron (traexamic acid), 100 mg/mL injectable</p> <p>Provide a brief explanation of how this product is different from the listed drug. different formulation and indication</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p style="text-align: center;"><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: October 17, 2009</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		October 30, 2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The Application Information section is (only) a checklist. The Contents of Action Package section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies Comments: <u>The original due date was July 30, 2009, major CMC amendment, the Goal Date was extended to October 30, 2009.</u>	
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: _____	May 27, 2009
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	<input type="checkbox"/> Yes, date
BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist ³	X
--	---

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
---	--

Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
--	--

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval
---	--------------------------------

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
--	--

<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
--	--

<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	November 10, 2009
--	-------------------

<ul style="list-style-type: none"> • Original applicant-proposed labeling 	January 30, 2009
--	------------------

<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
---	--

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
--	---

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
--	--

³ Fill in blanks with dates of reviews, letters, etc.
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<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	November 10, 2009
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	January 30, 2009
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission) 	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	September 15, 2009
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (indicate date(s)) • Acceptability/non-acceptability letter(s) (indicate date(s)) 	May 28, 2009, September 22, 2009 June 1, 2009
<ul style="list-style-type: none"> ❖ Labeling reviews (indicate dates of reviews and meetings) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP <input checked="" type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁴/Memo of Filing Meeting) (indicate date of each review) 	October 17, 2009
<ul style="list-style-type: none"> • NDAs only: Exclusivity Summary (signed by Division Director) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons) 	
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • PeRC (indicate date of mtg; approvals only) 	<input type="checkbox"/> Not applicable 5/27/09, no minutes
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (indicate date of mtg; approvals only) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> • Regulatory Briefing (indicate date of mtg) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (indicate date of mtg) 	<input type="checkbox"/> No mtg February 26, 2009
<ul style="list-style-type: none"> • EOP2 meeting (indicate date of mtg) 	<input type="checkbox"/> No mtg

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None November 6, 2009
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	November 6, 2009
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	Included in MO review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Included in MO review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None May 18, 2009; June 30, 2009
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested Included
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None July 30, 2009; October 27, 2009; June 15, 2009
Clinical Pharmacology <input type="checkbox"/> None	

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/26/09

• Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None March 24, 2009; October 16, 2009; October 27, 2009; November 9, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None May 14, 2009; June 22, 2009; October 27, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
• Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) (indicate date for each review)	<input type="checkbox"/> None April 13, 2009
• ONDQA Biopharmaceutics review (indicate date for each review)	
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	
<input checked="" type="checkbox"/> Review & FONSI (indicate date of review)	March 27, 2009
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: September 21, 2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	<p>Date completed:</p> <p><input type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p> <p>Date completed:</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Accepted <input type="checkbox"/> Hold</p>
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<p><input type="checkbox"/> Completed</p> <p><input type="checkbox"/> Requested</p> <p><input checked="" type="checkbox"/> Not yet requested</p> <p><input type="checkbox"/> Not needed</p>

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: This study is a pharmacoepidemiologic study to provide data on the patterns of concomitant use of Lysteda with hormonal contraceptives.

PMR/PMC Schedule Milestones: Final protocol Submission Date: January 30, 2010
Study/Clinical trial Completion Date: July 30, 2012
Final Report Submission Date: January 30, 2013
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A PMC is appropriate for this issue because women using hormonal contraceptives were excluded from the clinical trials supporting approval of Lysteda. Given that both products are indicated for women of reproductive age, and that hormonal contraceptives are often used off-label to manage heavy menstrual bleeding, it is unknown to what extent the two products will be used concomitantly.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Due to the exclusion of women on hormonal contraception from the Lysteda trials, it is unknown whether the population of women using both products concomitantly is large enough to study, should further study be needed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study to be conducted is a pharmacoepidemiologic study that will be based on drug use information (e.g., available in a claims database). The primary objective will be to assess the patterns of concomitant use of Lysteda and hormonal contraception, including assessment of the ages of women using both products as compared to women using Lysteda alone.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Application
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Submission
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Submitter Name

Product Name

NDA-22430

ORIG-1

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Lysteda

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/s/

JENNIFER L MERCIER
11/10/2009

SCOTT E MONROE
11/10/2009



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: October 29, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Lysteda: Information Request #12 Labeling re: adverse reactions	

Total no. of pages including cover: 20

Dear Sabrina,

Pending receipt of your response to our Information Request #11 dated October 28, 2009, thus far, attached are the labeling recommendations from the Division containing the language on the adverse events, as discussed during the teleconference with you and your firm on October 28, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Application
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Type/Number

Submitter Name

Product Name

NDA-22430

ORIG-1

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Lysteda

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/s/

NENITA I CRISOSTOMO
10/29/2009



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: October 28, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Lysteda: Information Request #11 – Anaphylaxis	

Total no. of pages including cover: 3

Dear Sabrina,

As conveyed to you over the phone this morning, attached is the list of Information Requests regarding adverse reactions to Lysteda.

For our immediate review, while enroute for official submission, please provide your response via email to me as soon as possible.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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INFORMATION REQUEST #11

CLINICAL

Anaphylaxis

October 28, 2009

NDA 22-430 Lysteda (tranexamic acid) tablets

- 1) In Study 304, Subject 724-1009 withdrew from the study due to the adverse events (AE) of shortness of breath and throat tightening associated with facial flushing.
 - a. Provide detailed information as to the number of cycles and drug/dose she was exposed to in Study 301 or 303 prior to entering Study 304, whether she had any similar adverse events in the earlier study, the temporal relationship between the onset of the AE and dosing, and how the AE was managed (medications used, etc).
 - b. In addition, provide medical records from the emergency room (ER) visit on this subject.
 - c. Why was this not considered a serious adverse event (SAE)?
- 2) We request fully detailed narratives on any other subjects who experienced any level of allergic, hypersensitivity or anaphylactic reactions to Lysteda in the trials, regardless of whether they are considered SAEs.
- 3) Provide any information available to you regarding the extent of global postmarketing reports of severe allergic, hypersensitivity or anaphylactic reactions to tranexamic acid (whether given orally or intravenously).

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Type/Number

Submitter Name

Product Name

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NENITA I CRISOSTOMO

10/28/2009



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: October 26, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Lysteda: Information Request #10 Labeling—FDA Recommendations #4	

Total no. of pages including cover:

Dear Sabrina,

Attached are the labeling recommendations from the Division in response to your emailed label on October 23, 2009. As discussed with you over the phone a minutes ago, please accept our recommendations, and, if you have any further edits, please mark only your changes on a clean copy and email your version back to me by the morning of October 27, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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 § 552(b)(5) Deliberative Process

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NENITA I CRISOSTOMO
10/26/2009



**Food and Drug Administration
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FACSIMILE TRANSMITTAL SHEET

DATE: October 26, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Lysteda: Information Request #10 Labeling—FDA Recommendations #4	

Total no. of pages including cover:

Dear Sabrina,

Attached are the labeling recommendations from the Division in response to your emailed label on October 23, 2009. As discussed with you over the phone a minutes ago, please accept our recommendations, and, if you have any further edits, please mark only your changes on a clean copy and email your version back to me by the morning of October 27, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: **YES** **NO**

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 § 552(b)(5) Deliberative Process

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NENITA I CRISOSTOMO
10/26/2009



**Food and Drug Administration
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FACSIMILE TRANSMITTAL SHEET

DATE: October 23, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Lysteda: Information Request #9 Labeling—FDA Recommendations #3	

Total no. of pages including cover:

Dear Sabrina,

As discussed during our October 22, 2009, teleconference with you following our receipt of your emailed version of the label, attached are the labeling recommendations from the Division. The new comments since the teleconference are highlighted in yellow ink.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

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10/23/2009



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FACSIMILE TRANSMITTAL SHEET

DATE: October 19, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Lysteda: Labeling—FDA Recommendations #2	

Total no. of pages including cover:

Dear Sabrina,

As discussed during our October 15, 2009, teleconference with you, attached are the labeling that contains the Division's recommendations. We remind you that we would like to have final agreed-upon labeling by next Monday, October 26, 2009. Therefore, if you have any revisions to our proposed labeling, please make them available to us as soon as possible this week so that we have time for any further negotiations needed.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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INFORMATION REQUEST #8

LABELING RECOMMENDATIONS #2

October 19, 2009

NDA 22-430 Lysteda (tranexamic acid) tablets

The FDA label review has now been done at the level of the signatory authority, and the major changes in this label include the following:

1. Revision of the indication to exclude ~~_____~~ These are still discussed and data provided in the Clinical Studies section of the label, but they are not to be part of the actual indication. **b(4)**
2. Acceptance of your proposal to remove use with hormonal contraceptives as a contraindication. We agree that this may be a Warning, but we have strengthened the language, and would not find any softening of this tone acceptable. As we discussed on October 15, 2009, along with our agreement to make this rise only to the level of a Warning, we would request that you commit to providing us with postmarketing use data on how extensively LYSTEDA is used by women who also use hormonal contraception.
3. Acceptance of your proposal to remove ~~_____~~ **b(4)**
4. Extensive revisions of Table 2 on Clinical Trial adverse events. We have calculated AE rates according to your Tables 61 and 49, and have considered ALL AEs, not only those felt to be associated by the investigator. Because this is placebo-controlled data, we believe an excess of events in the LYSTEDA arm is a fair indication of likely drug-relatedness. Given the very short time in which we have to work, if you propose any changes to this table, you will need to provide us with very clear data tables and explanations as to how you arrive at different numbers than we did.
5. Clinical studies section has been extensively revised. Only high level description of the endpoints are included; specifically, we do not discuss the MIQ instrument, which has not been formally reviewed as to validity by FDA's SEALD team. We believe the level of information provided is sufficient for healthcare providers to evaluate the evidence of efficacy. The numbers we report in the efficacy tables are from our Statistician's review; as noted in the Adverse Reactions section, if you disagree, you will need to provide with easily reviewable data and explanations to support your alternative proposal. We like your (now) Figure 1, and recommend some minor modifications to increase its clarity.
6. Patient labeling has been revised by the Division responsible for reviewing the readability and clarity of patient labeling.

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_____ § 552(b)(5) Deliberative Process

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Product Name

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10/19/2009



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FACSIMILE TRANSMITTAL SHEET

DATE: October 19, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Clinical Information Request: Postmarketing Commitment—Concomitant use of Lysteda with hormonal contraceptives	

Total no. of pages including cover: 3

Dear Sabrina,

As discussed during our October 15, 2009, teleconference with you, attached is a Clinical Information Request regarding the need for postmarketing data on the concomitant use of Lysteda with hormonal contraceptives. Please submit your response on or before the close of business on October 22, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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INFORMATION REQUEST #7

CLINICAL Postmarketing Commitment

October 19, 2009

NDA 22-430 Lysteda (tranexamic acid) tablets

As discussed during our October 15, 2009, teleconference with your firm, there are no data on the patterns of concomitant use of Lysteda with hormonal contraceptives. Given that both products are indicated for women of reproductive age, and that hormonal contraceptives are often used off-label to manage heavy menstrual bleeding, it is unknown to what extent the two products will be used concomitantly. Because women using hormonal contraceptives were excluded from the clinical trials supporting the approval of Lysteda, it is not known whether the population of women using both products concomitantly is large enough to study, should further study be warranted. Therefore, a postmarketing commitment is appropriate for this issue.

We are seeking your agreement to the following phase 4 study.

Conduct a pharmacoepidemiologic study based on drug use information to assess the patterns of concomitant use of Lysteda and hormonal contraception, including assessment of the ages of women using both products as compared to women using Lysteda alone.

Protocol Submission:	January 30, 2010
Study/Clinical Completion:	July 30, 2012
Final Report Submission:	January 30, 2013

We also ask that you provide an interim report following collection of the first year of data.

Please submit your written response on or before the close of business on October 22, 2009.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22430

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Lysteda

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NENITA I CRISOSTOMO
10/19/2009

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22-430 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Lysteda Established/Proper Name: tranexamic acid Dosage Form: tablet Strengths: 650 mg		
Applicant: Xanodyne Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: January 30, 2009 Date of Receipt: January 30, 2009 Date clock started after UN:		
PDUFA Goal Date: July 30, 2009 Priority Review	Action Goal Date (if different): July 30, 2009	
Filing Date: March 31, 2009	Date of Filing Meeting: March 4, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3S		
Proposed indication(s)/Proposed change(s): Treatment of menorrhagia (heavy menstrual bleeding) and amelioration of associated limitations of activities		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 68,096				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		✓		Document Room staff is notified for both IND and NDA
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>		✓		Document Room staff is notified
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓																		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		✓																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>		✓																		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		✓																		
If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		✓																		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			✓																	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	✓																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	✓			
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>		✓		

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance ¹ ? If not, explain (e.g., waiver granted).	✓			No error is reported by EDR
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	✓			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>		✓		
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	

If yes, BLA #				
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Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	✓			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? <i>Forms must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	✓			
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>) <i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i> <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	✓			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			✓	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	✓			PeRC Meeting is scheduled for May 27, 2009
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		✓		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	✓			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	✓			
<p><u>BPCA (NDAs/NDA efficacy supplements only):</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		✓		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	✓			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	✓			
Is the PI submitted in PLR format?	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			Sent April 3, 2009
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			Sent March 16, 2009
REMS consulted to OSE/DRISK?			✓	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	✓			Sent directly by sponsor, along with the Trade Name review request
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	✓			1. OSE AERS Search – 3/16/09 2. QTIRT – 3/17/09 3. DSI – 4/3/09 4. Ophthalmology – 5/22/09 & 9/15/09

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): September 20, 2004 <i>If yes, distribute minutes before filing meeting</i>	✓			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): February 26, 2008 – Nonclinical & CMC October 31, 2008 – Clinical <i>If yes, distribute minutes before filing meeting</i>	✓			
Any Special Protocol Assessments (SPAs)? Date(s): June 24, 2005 June 30, 2005 September 28, 2006 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	✓			

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 4, 2009

BLA/NDA/Supp #: NDA 22-430

PROPRIETARY NAME: Lysteda

ESTABLISHED/PROPER NAME: tranexamic acid

DOSAGE FORM/STRENGTH: tablets, 650 mg

APPLICANT: Xanodyne Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of menorrhagia and amelioration of associated limitations of activities

BACKGROUND: This new drug application is submitted as a 505(b)(2), received January 30, 2009, supported by the investigational new drug (IND) application, IND 68,096, relying on literature data and the Agency's findings of safety for Cyklokapron[®]. It is granted a Priority review with a PDUFA Goal date of July 30, 2009. Tranexamic acid is a lysine analog that reversibly blocks lysine binding sites on plasminogen and thereby prevents the degradation of fibrin by plasmin. An intravenous (IV) formulation (Cyklokapron[®]) of tranexamic acid is currently marketed in the US. Cyklokapron[®] was approved in 1986 as an orphan drug for hemophilia patients to reduce/prevent bleeding during and following tooth extraction.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nenita Crisostomo	Y
	CPMS/TL:	Jennifer Mercier	Y
Cross-Discipline Team Leader (CDTL)	Lisa Soule, M.D.		Y
Clinical	Reviewer:	Daniel Davis, M.D.	Y
	TL:	Lisa Soule, M.D.	Y

Clinical Pharmacology	Reviewer:	Hyunjin Kim	Y
	TL:	Myong-Jin Kim	Y
Biostatistics – Efficacy	Reviewer:	Xin Fang	Y
	TL:	Mahboob Sobhan	Y
Biostatistics – Safety	Reviewer:	Olivia Lau	Y
	TL:	Paul Schuette	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Hatfield, Ph.D.	Y
	TL:	Lynnda Reid, Ph.D.	Y
Product Quality (CMC)	Reviewer:	Gene Holbert, Ph.D.	Y
	TL:	Donna Christner, Ph.D.	Y
OSE/DMEPA (proprietary name)	Reviewer:	Anne Crandall, Pharm.D.	Y
	TL:	Melina Griffis, R.Ph.	N
OSE/DRISK (PPI)	Reviewer:	Robin Duer, R.N., M.B.A.	Y
	TL:	Jodi Duckhorn, M.A.	N
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay, Ph.D.	Y
	TL:	Constance Lewin, M.D., M.P.H.	N

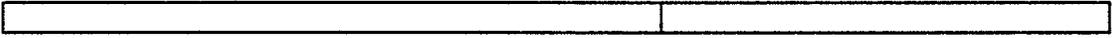
DDMAC (PI)	Janice Maniwang, Pharm.D., M.B.A. Carrie Newcomer, Pharm.D.	Y N
Other attendees		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p><u>Clinical Pharmacology</u></p> <ol style="list-style-type: none"> 1. Your proposed dosage adjustment in patients with renal impairment is based on serum creatinine concentration and estimated glomerular filtration rate (GFR). This will be a review issue. 2. The robustness of the tranexamic acid modified release formulation in the presence of various alcohol concentrations (0, 5%, 10%, 20%, and 40%) as well as in different pH levels will be reviewed. <p><u>Chemistry</u></p> <ol style="list-style-type: none"> 1. Clarify if (1) impurities A, B, C, and D are only drug substance process impurities and are therefore not controlled in the drug product or if (2) these are also degradation products and are included in the drug product "Related Substances" specification under "Individual Unknowns." 2. Submit a copy of the blister card. Clarify whether the high density polyethylene (HDPE) bottles will be packaged in cartons; if so, carton labels should be provided. 3. Please be aware that "Modified Release Tablets" is not a recognized dosage form for purposes of labeling. "Extended Release Tablets" may be more appropriate for your product, but the final determination will be made during the NDA review and will be conveyed with other carton and container label comments. 4. Provide the individual dissolution data points in tabular form for the following graphs in Section 	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
--	--

<p>3.2.P.2. In addition, state what dissolution method was used.</p> <ul style="list-style-type: none"> • Figure 2 on page 12 • Figure 8 on page 21 • Figure 9 on page 22 	
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Reviewer will provide later as an Information Request</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter



<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Nenita Crisostomo, R.N. – Regulatory Health Project Manager	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Other: Consults: DSI, OSE, Cardio-renal (QTIRT), DDMAC, PeRC

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

/s/

NENITA I CRISOSTOMO
10/17/2009



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: September 22, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Clinical Information Request: Updated Information--Studies 302 and 304	

Total no. of pages including cover: 3

Dear Sabrina,

Attached are Clinical Information Requests for additional information for Studies 302 and 304. Please provide Items 1, 3, 4, and 5 no later than by 12 noon on September 28, 2009, and provide Items 2 and 6 no later than close of business on October 1, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: YES NO

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INFORMATION REQUEST #6

CLINICAL

September 22, 2009

NDA 22-430 Lysteda™ (tranexamic acid) tablets

To facilitate our ongoing review of NDA 22-430, we are requesting the following additional information for Studies 302 and 304. We assume that both studies are now completed, and we would like the updated information to reflect final data from these studies if possible.

1. Provide the following listings to include all new cases/events not previously reported in either your original submission or your Safety Update of April 2009:
 - a. New deaths
 - b. New serious adverse events (SAEs)
 - c. New premature terminations for all causes (specify cause)
 - d. New premature discontinuations for adverse events (specify AE)
2. Provide narratives for any new deaths, SAEs, and discontinuations due to AEs.
3. Provide an updated summary of exposure to tranexamic acid. The summary should provide exposure separately for each of Studies 302 and 304 based on numbers of subjects completing 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, and 27 months of treatment, respectively. Also provide a composite summary of exposure to tranexamic acid combined across the four Phase 3 studies using the same time intervals as requested for each of Studies 302 and 304.
4. Provide Updates of Tables S4 (Study 302) and S5 (Study 304) that were included in your Safety Update.
5. Provide updates (recomputed tables) for the following tables previously provided in your Safety Update of April 2009:
 - a. For Study 304: Table 1 (Subject completion/disposition), Table 2 (Treatment emergent AEs) and Table 5 (Treatment emergent SAEs)
 - b. For Study 302: Table 16 (Subject completion/disposition), Table 17 (Treatment emergent AEs) and Table 20 (Treatment emergent SAEs)
6. Provide a series of Tables displaying disposition of subjects in Studies 302 and 304 for each 3-month treatment interval. The format of the requested tables should be similar to that of Table 1 from the Safety Update with the addition of a category called "On Treatment" to be placed between the categories of "Completed" and "Withdrawn" in Table 1 of the Safety Update.

Please provide Items 1, 3, 4, and 5 no later than by 12 noon on September 28, 2009, and provide Items 2 and 6 no later than close of business on October 1, 2009.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22430

ORIG-1

XANODYNE
PHARMACEUTICS
INC

TRANEXAMIC ACID 650MG
MODIFIED RELEASE T

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/s/

NENITA I CRISOSTOMO
09/22/2009

September 15, 2009



Scott Monroe, MD
Division Director, Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

**RE: NDA 22-430, Amendment 0017
Lysteda™ (tranexamic acid) tablets
Response to CMC/DMEPA Information Request #4: Carton Labels; and
Response to Clinical Information Request #5: PREA Postmarketing Commitment**

Dear Dr. Monroe:

Xanodyne Pharmaceuticals, Inc. is submitting Amendment 0017 to NDA 22-430 for Lysteda (tranexamic acid) tablets. This Amendment contains our response to the CMC/DMEPA Information Request #4: Carton Labels and the Clinical Information Request #5: PREA Postmarketing Commitment, both dated September 1, 2009.

The Division's requested changes have been incorporated into the carton and container labels. However, we retained the word "tablets" rather than "tablet" on the labels in an effort to be consistent with the packaging of the product. The internal control number on the 30 count and 500 count bottle labels was relocated in order to present consistent layout across all retail bottle configurations. In addition, the internal control number on all packaging has been updated to reflect the final tracking numbers. The revised labeling files listed below are being submitted as "replace" files in the eCTD.

- 6-ct-lbl.pdf
- 30-ct-lbl.pdf
- 100-ct-lbl.pdf
- 500-ct-lbl.pdf
- carton-30-ct.pdf
- blister.pdf

In this Amendment, we are also formally agreeing to the Division's suggestions contained in the September 1, 2009 letter. We agree to conduct a pharmacokinetic study on healthy female subjects, 12-17 years old, with evidence of heavy menstrual bleeding. The protocol will be submitted by the end of February 2010, the study will start by the end of September 2010 and the final study report will be submitted to the Division by the end of March 2012.

The contents of this submission are certified to be virus free [NOD32, program version 3806, with virus definition date of (20090915) NT]. If you should require further information, please contact me via email (sgirty@xanodyne.com) or by telephone at (859) 342-2088.

Sincerely,

Sabrina R. Girty, Esq.
Associate Director, Regulatory Affairs

cc: Nenita Crisostomo (cover letter by email)

Xanodyne Pharmaceuticals, Inc. | ph (877) 926-6396
One Riverfront Place | fax (859) 371-6391
Newport, KY 41071-4563 | www.xanodyne.com

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 1, 2009

TO: Nenita Crisostomo, Regulatory Project Manager
Dan Davis, M.D., Medical Officer
Division of Reproductive and Urologic Drugs Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-430

APPLICANT: Xanodyne Pharmaceuticals, Inc.

DRUG: Lysteda (tranexamic acid)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of heavy bleeding and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure and physical activities

CONSULTATION REQUEST DATE: April 2, 2009

DIVISION ACTION GOAL DATE: October 30, 2009

PDUFA DATE: October 30, 2009

I. BACKGROUND:

The conduct of the following four protocols was inspected:

#XP12B-MR-301, entitled "A Randomized, Double- Blind, Placebo Controlled, Parallel Group, Multicenter Study to Evaluate Efficacy and Safety of 0.65 G and 1.3 G Oral Doses of XP12B-MR TID Administered During Menstruation for the Treatment of Menorrhagia", and

#XP12B-MR-302, entitled "A Long Term, Open Label, Multicenter Study to Evaluate the Safety of a 1.3 G Oral Dose of a New Modified-Release Tranexamic Acid Formulation Administered Three Times Daily for up to 5 Days During the Menstrual Cycle in Women with Heavy Menstrual Bleeding Associated with Menorrhagia", and

#XP12B-MR-303, Entitled "A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multicenter Study to Evaluate Efficacy and Safety of a 1.3 G Oral Dose of XP12B-MR TID Administered During Menstruation for the Treatment of Menorrhagia", and

#XP12B-MR-304, entitled A Multi-Center, Open Label Extension Study to Evaluate the Safety of a 1.3 G Oral Dose of XP12B-MR TID Administered During Menstruation for the Treatment of Menorrhagia"

The primary safety or efficacy endpoints for these studies were as follows:

Protocol #XP12B-MR-301

Menstrual blood loss (MBL) during the entire menstrual period as assessed by the alkaline hematin method. The primary efficacy variable was assessed for pretreatment menstrual periods 1 and 2 (Visits IB and LC) and for treatment periods 1 (Visit 3), 2 (Visit 4), and 3 (Visit 5).

Protocol XPI2B-MR-302

The primary objective of this study was to determine the safety of a 1.3 g dose of XPI2B-MR administered 3 times daily for up to 5 days (maximum of 15 doses) for the reduction of blood loss in women with heavy menstrual bleeding.

Protocol #XPI2B-MR-303

MBL during the entire menstrual period as assessed by the alkaline hematin method. The primary efficacy variable was assessed for pretreatment menstrual periods 1 and 2 (Visits IB and 1C) and for treatment periods 1 (Visit 3), 2 (Visit 4), 3 (Visit 5), and 6 (Visit 8).

Protocol #XPI2B-MR-304

The primary objective of this study was to assess the safety of 3.9 g/day of a modified-release formulation (MR) of tranexamic acid (XPI2B-MR) administered orally three times daily for up to 5 days (maximum of 15 doses) during each menstrual period in women diagnosed with heavy menstrual bleeding.

The clinical sites of Drs. Lukes, Baker, and Mabey were selected for inspection because they were representative of the sites in general. Also, _____ received \$75,000 in consultation fees from the sponsor.

b(6)

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site #746 Andrea Lukes, M.D. Women's Wellness Center 249 E Highway 54, Suite 330 Durham, NC 27713	MR-301 and MR-304/ 15 (3 month trial)/ 7 (9 month extension trial)/	29 June-2 Jul 2009	NAI.
Site #602, Jeffrey Baker, M.D. 2327 Coronado St. Idaho Falls, ID 83404	MR-303/ 18 (6 month trial)/ 15 (9 month extension trial)/	9-12 Jun 2009	VAI.
Site #524 R Garn Mabey, Jr., M.D. 2881 N. Tenaya Way Las Vegas, NV 89128	MR-302/ 44 (6 month trial)/ 6 (month extension trial)/	1-9 Jun 2009	VAI.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

1. Andrea Lukes, M.D.
Women's Wellness Center
249 E Highway 54, Suite 330
Durham, NC 27713

- a. **What was inspected:** At this site, two studies were conducted: Protocol #XP12B-MR-301 with 15 subjects enrolled and 14 completing the study, and #XP12B-MR-304 with seven subjects enrolled and five subjects completing the study. The records of seven subjects from each of these protocols were audited. Records reviewed for both protocols included, but were not limited to, consent forms, randomization procedures, primary efficacy endpoints,

protocol deviations, concomitant medications, early discontinuations, adverse events, laboratory reports, and test article accountability.

- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

2. Jeffrey Baker, M.D.
2327 Coronado St.
Idaho Falls, ID 83404

- a. **What was inspected:** At this site, two studies were conducted: XP12B-MR-303 with 18 subjects enrolled and nine subject records reviewed and XP12B-MR-304 with 18 subjects enrolled and ten records reviewed. All consent forms were reviewed. Other records reviewed included, but were not limited to, IRB correspondence, concomitant medications, adverse events, laboratory results, and study drug compliance.
- b. **General observations/commentary:** A Form FDA 483 was issued. Review of the records revealed that Subject 6023035 was enrolled in Study 303 despite a Pap smear result indicating the presence of atypical squamous cells of undetermined significance (ASC-US). This subject completed both Studies 303 and 304. Also, protocol-required Pap smears were not performed for Subjects 6023019, 6023011, and 7771002 at Visit 4 for Study 304
- c. **Assessment of data integrity:** The deviations noted immediately above would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

3. R. Garn Mabey, Jr., M.D.
2881 N. Tenaya Way
Las Vegas, NV 89128

- a. **What was inspected:** Study XP12B-MR-302 was conducted at this site. At this site, 44 subjects were enrolled and 12 subjects completed the study. The records of 20 subject were reviewed. Documentation reviewed included, but were not limited to, Informed Consent Forms (ICFs), Case Report Forms (CRFs), source documentation, drug accountability records, IRB correspondence, monitoring records, laboratory reports, concomitant medication records, and adverse events records.
- b. **General observations/commentary:** A Form FDA 483 was issued. Review of the records revealed that Subjects 2014, 2016, and 2022, each took four doses of the test article per day on various dates in violation of the protocol-specified maximum of three doses per day. Dr. Mabey responded satisfactorily in writing to the remaining observations on the Form FDA 483.

- c. **Assessment of data integrity:** The review division may wish to consider excluding data from Subjects 2014, 2016, and 2022, for the reason noted immediately above; otherwise, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites were inspected. The data generated by the clinical sites of Drs. Lukes and Baker appear acceptable in support of the respective application. The review division may wish to consider excluding data from Dr. Mabey's site for Subjects 2014, 2016, and 2022, for the reason noted immediately above; otherwise, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

ROY A BLAY
09/03/2009

TEJASHRI S PUROHIT-SHETH
09/03/2009



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: September 1, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-	Phone number: 301-796-0875
Subject: NDA 22-430 Information Request #4 for Chemistry, DMEPA: Carton Labels	

Total no. of pages including cover: 4

Dear Sabrina,

We are currently reviewing your submission dated June 23, 2009, containing your revised carton labeling. Listed below are our additional recommendations. Please submit your response on or before 12:00 PM on September 7, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed:

YES

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INFORMATION REQUEST #4

**CHEMISTRY, MANUFACTURING, AND CONTROLS
DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS**

September 1, 2009

NDA 22-430 Lysteda™ (tranexamic acid) tablets

1. The size of the numerical strength designation should be increased.
2. The word "tablet" should be outside the parenthesis.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22430	ORIG 1	XANODYNE PHARMACEUTICS INC	TRANEXAMIC ACID 650MG MODIFIED RELEASE T

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/s/

NENITA I CRISOSTOMO
09/01/2009



NDA 22-430

Xanodyne Pharmaceuticals, Inc.
Attention: Sabrina R. Girty, Esq.
Associate Director, Regulatory Affairs
One Riverfront Place
Newport, KY 41071-4563

Dear Ms. Girty:

Please refer to your new drug application (NDA) dated and received January 30, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Lysteda™ (tranexamic acid tablets).

We also refer to your clinical development plans for the adolescent population, age 12-17 years old, following the approval of tranexamic acid.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. We are seeking your agreement to the following suggestions for the phase 4 study, as enclosed. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at 301-796-0875.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Phase 4 Study: Postmarketing Commitment

Conduct a pharmacokinetic study to be performed on healthy female subjects, 12-17 years old, with evidence of heavy menstrual bleeding.

Protocol Submission:	February 2010
Study Start:	September 2010
Final Report Submission:	March 2012

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/s/

JENNIFER L MERCIER
09/01/2009

Crisostomo, Nenita

From: Greeley, George
Date: Monday, June 22, 2009 4:23 PM
To: Crisostomo, Nenita
Cc: Stowe, Ginneh D.
Subject: NDA 22-430 Lysteda

Importance: High

Hi Nita,

The Lysteda (tranexamic acid) partial waiver/deferral and plan was reviewed by the PeRC PREA Subcommittee on May 27, 2009. The Division recommended a partial waiver from 0-12 years because necessary studies would be impossible or highly impracticable because too few children with disease/condition to study and a deferral from 12-17 years until this product has been determined to be safe and effective for women 18 years and older for the proposed indication. The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

In addition, the PeRC has requested that the pediatric page be modified to reflect a waiver from 0-11 years and that you also uncheck the box under "not meaningful therapeutic benefit".

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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1. REQUEST FOR DEFERRAL - PEDIATRIC STUDIES

Under the pediatric rule (21 CFR 201.23(a)), FDA requires applicants to conduct a pediatric assessments for drug products and indications contained in newly filed applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Under the rule, FDA also has the authority to require pediatric studies on an approved drug product if there is substantial use in the pediatric population or the product would provide a meaningful therapeutic benefit and the absence of adequate labeling could pose significant risk.

Xanodyne Pharmaceuticals, Inc. is developing tranexamic acid with a new modified-release (MR) oral dose formulation (XP12B-MR), new tablet strength (650 mg), and new dosage regimen (2 tablets administered three times daily) for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities. The Sponsor is submitting this NDA as a 505(b)(2) application.

Tranexamic acid has been marketed for more than three decades in Asia, Australia, Europe, and Canada for the treatment of hemorrhage or risk of hemorrhage in increased fibrinolysis or fibrinogenolysis (including thrombolytic overdose) and for the treatment of menorrhagia. In the US, oral and intravenous (IV) tranexamic acid was approved in 1986 to treat patients with hemophilia for short-term use (2 to 8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. Tranexamic acid is currently not approved for the treatment of menorrhagia in the US.

On 20 September 2004, an End-of-Phase 2 meeting was held between the FDA and Xanodyne to discuss the development of tranexamic acid modified-release tablets for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities (see 1.6.3 Correspondence Regarding Meetings FDA meeting minutes dated 20 October 2004). During this meeting, Xanodyne requested a pediatric waiver for children < 12 years of age (see 1.9.2 Request for Waiver) and a deferral for children 12 – 17 years of age. FDA indicated that efficacy in pediatric patients needs to be supported with a clinical study that enrolls adolescents. FDA also indicated that this study could be conducted as a Phase 4 commitment during the post-approval period.

On 31 October 2008, a pre-NDA meeting was held between the FDA and Xanodyne (see 1.6.3 Correspondence Regarding Meetings FDA meeting minutes dated 26 November 2008). During this meeting, FDA reiterated the need for a clinical study with tranexamic acid modified-release tablets that enrolls adolescents. FDA indicated that a pharmacokinetic study demonstrating acceptable dosing in the adolescent population would fulfill the pediatric requirement for this development program. A clinical development plan for this study is provided in 1.9.6 Other Correspondence Regarding Pediatric Exclusivity or Study Plans.

Xanodyne Pharmaceuticals, Inc. requests the deferral of this pediatric study until after the product is approved.

1. REQUEST FOR WAIVER - PEDIATRIC STUDIES

Under the pediatric rule (21 CFR 201.23(a)), FDA requires applicants to conduct a pediatric assessments for drug products and indications contained in newly filed applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Under the rule, FDA also has the authority to require pediatric studies on an approved drug product if there is substantial use in the pediatric population or the product would provide a meaningful therapeutic benefit and the absence of adequate labeling could pose significant risk.

Xanodyne Pharmaceuticals, Inc. is developing tranexamic acid with a new modified-release (MR) oral dose formulation (XP12B-MR), new tablet strength (650 mg), and new dosage regimen (2 tablets administered three times daily) for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities. The Sponsor is submitting this NDA as a 505(b)(2) application.

Tranexamic acid has been marketed for more than three decades in Asia, Australia, Europe, and Canada for the treatment of hemorrhage or risk of hemorrhage in increased fibrinolysis or fibrinogenolysis (including thrombolytic overdose) and for the treatment of menorrhagia. In the US, oral and intravenous (IV) tranexamic acid was approved in 1986 to treat patients with hemophilia for short-term use (2 to 8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. Tranexamic acid is currently not approved for the treatment of menorrhagia in the US.

Because tranexamic acid modified-release tablets is indicated for women of reproductive age and is not intended for pediatric use in children < 12 years of age, Xanodyne requests a full pediatric waiver for children in this age group. FDA has indicated in both the End-of-Phase 2 meeting (see 1.6.3 Correspondence Regarding Meetings FDA meeting minutes dated 20 October 2004) and pre-NDA meeting (see 1.6.3 Correspondence Regarding Meetings FDA meeting minutes dated 26 November 2008), that a clinical study with tranexamic acid modified-release tablets would be required that enrolls adolescents only (see 1.9.1 Request for Deferral).



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-430

PDUFA GOAL DATE EXTENSION

Xanodyne Pharmaceuticals, Inc.
Attention: Sabrina R. Girty, Esq.
Associate Director, Regulatory Affairs
One Riverfront Place
Newport, KY 41071-4563

Dear Ms. Girty:

Please refer to your January 30, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lysteda (tranexamic acid) Tablets, 650 mg.

Your submission, dated and received June 30, 2009, constituted a major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 30, 2009. We plan to communicate proposed labeling and any post-marketing commitment requests by October 9, 2009.

If you have questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
7/16/2009 12:46:38 PM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: June 17, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Clinical/DMEPA Information Request #4: Carton Labeling	

Total no. of pages including cover: 2

Dear Sabrina,

Attached are the Division's recommendations to your carton labeling. Please submit your response, along with mock labels, on/before close of business on June 22, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: **YES** **NO**

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INFORMATION REQUEST #4

CLINICAL/CMC/DMEPA CARTON LABELS

June 17, 2009

NDA 22-430 Lysteda (tranexamic acid)

We are currently reviewing your carton labeling and in conjunction with the Division of Medication Error Prevention and Analysis, we have identified the following areas of needed improvement.

A. Blister Label

1. Increase the font size of the strength so that it is more prominently displayed.
2. Revise the prominence of the established name to ensure that it is half the size of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2) that will improve the prominence of the established name.

B. Container Label and Carton Labeling

1. Increase the prominence and font size of the product strength, '650 mg.' Additionally, the strength is located in the corner in close proximity to the net quantity. The strength should be relocated so that it immediately follows the proprietary and established names on the primary display panel. The relocation and increase in size of the strength may require more room on the primary display panel, which can be provided by deleting the star symbol that is currently located to the upper right of the name.
2. Revise the prominence of the established name to ensure that it is half the size of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2) that will improve the prominence of the established name.
3. Change the statement regarding maximum amount allowed per 24 hour period to read, 'Do not exceed 6 tablets in a 24 hour period.'

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/s/

Nenita Crisostomo
6/17/2009 05:48:14 AM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: June 15, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Clinical/DMEPA Information Request #4: Carton Labeling	

Total no. of pages including cover: 2

Dear Sabrina,

Attached are the Division's recommendations to your carton labeling. Please submit your response, along with mock labels, on/before close of business on June 19, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: **YES** **NO**

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INFORMATION REQUEST #4

CLINICAL/DMEPA

May 16, 2009

NDA 22-430 Lysteda (tranexamic acid)

We are currently reviewing your carton labeling and in conjunction with the Division of Medication Error Prevention and Analysis, we have identified the following areas of needed improvement.

A. Blister Label

1. Increase the font size of the strength so that it is more prominently displayed.
2. Revise the prominence of the established name to ensure that it is half the size of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2) that will improve the prominence of the established name.

B. Container Label and Carton Labeling

1. Increase the prominence and font size of the product strength, '650 mg.' Additionally, the strength is located in the corner in close proximity to the net quantity. The strength should be relocated so that it immediately follows the proprietary and established names on the primary display panel. The relocation and increase in size of the strength may require more room on the primary display panel, which can be provided by deleting the star symbol that is currently located to the upper right of the name.
2. Revise the prominence of the established name to ensure that it is half the size of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2) that will improve the prominence of the established name.
3. Change the statement regarding maximum amount allowed per 24 hour period to read, 'Do not exceed 6 tablets in a 24 hour period.'

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/s/

Nenita Crisostomo
6/16/2009 05:20:25 PM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: June 5, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875

Subject: NDA 22-430 Clinical Information Request #3: Prevalence of Heavy Menstrual Bleeding in Adolescence

Total no. of pages including cover: 2

Dear Sabrina,

Please provide data on the prevalence of heavy menstrual bleeding (menstrual blood loss of > 80 ml) in the adolescent population. If data are available, these rates should be provided for year of age from 12 to 17 years old. Submit your response on or before 12:00 Noon, on June 19, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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/s/

Nenita Crisostomo
6/5/2009 11:04:54 AM
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NDA 22-430

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

Xanodyne Pharmaceuticals, Inc.
One Riverfront Place
Newport, Kentucky 41071-4563

ATTENTION: Sabrina R. Girty
Associate Director, Regulatory Affairs

Dear Ms. Girty:

Please refer to your New Drug Application dated January 30, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tranexamic Acid Modified-Release Tablets, 650mg.

We also refer to your March 2, 2009 correspondence, received March 4, 2009 requesting review of your proposed proprietary name, Lysteda. We have completed our review of the proposed proprietary name, Lysteda and have concluded that it is acceptable.

Lysteda will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If any of the proposed product characteristics as stated in your March 2, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application contact the Office of New Drugs (OND), Neni Crisostomo, Regulatory Project Manager at 301-796-0875.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Carol Holquist
6/1/2009 08:22:43 AM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: May 29, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Chemistry Information Request #3	

Total no. of pages including cover: 3

Dear Sabrina,

Please submit your response to the Information Request below on/before 12:00 PM on June 4, 2009.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed:

YES

NO

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INFORMATION REQUEST #3

CHEMISTRY, MANUFACTURING, AND CONTROLS

May 29, 2009

NDA 22-430 Lysteda™ (tranexamic acid)

1. HPLC retention time alone is not a sufficient test for identity. ICH Q6A states that "Identification solely by a single chromatographic retention time, for example, is not regarded as being specific" (ICH Q6A 3.2.2. (b) identification). A second identification test, such as UV by diode array detection, should be added.
2. The residual solvents to be monitored are not specified. Provide a list of residual solvents to be monitored in the drug product.
3. Clarify who performs USP testing of the packaging components.
4. Clarify what the difference is between MF 949 and MF 1036A/B.
5. Your formulation does not fit the description of a delayed release tablet (enteric coated) and it is not an extended release tablet because the dosing is three times a day. We have determined that the correct dosage form is "tablet". Please change your labeling accordingly.

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/s/

Nenita Crisostomo
5/29/2009 04:52:57 PM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: May 14, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Clinical Information Request #2: Foreign Labeling	

Total no. of pages including cover: 2

Dear Sabrina,

Please submit foreign labeling, in the English version, for the tranexamic acid formulations marketed in United Kingdom or Sweden, Canada, and Australia at/before 12:00 A.M. on May 18, 2009. If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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/s/

Nenita Crisostomo
5/14/2009 12:06:12 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: April 17, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Xanodyne Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Responses to Sponsor's Inquiry—Plans for Electronic Submission of Safety Update	

Total no. of pages including cover: 3

Comments:

Dear Sabrina,

Attached below are our responses to your email dated April 14, 2009, requesting responses to your questions regarding the electronic submission of the Safety Update.

If you have any further questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: **YES** **NO**

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INFORMATION REQUEST #3
Responses to April 14, 2009, email inquiries

STATISTICAL SAFETY

April 17, 2009

NDA 22-430 Lysteda (tranexamic acid)

Question 1:

We plan to submit the datasets with data through February 28, 2009 as "append" datasets in the eCTD since we are not submitting all of the -302, -304 and ISS datasets in the Safety Update. Is it acceptable to submit the Safety Update datasets as "append" files?

FDA RESPONSE: Yes.

Question 2:

We plan to submit the define files for the datasets as "append" files in the eCTD since only a sub-set of the -302, -304 and ISS datasets are being updated in the Safety Update. We also plan to submit define files that only list the datasets being included in the Safety Update. We will not list the other datasets that were not updated in the Safety Update in the define files. Does the Division agree that the define files should only describe the datasets that have been updated in the Safety Update (listed below)?

FDA RESPONSE: No. Use define files that contain all datasets (including datasets not being updated in the Safety Update). Include hypertexted links from the updated define file to datasets submitted in a prior sequence. If linking to a dataset submitted in a prior sequence, please make sure that the link points to the most recent version of the submitted data.

Question 3:

If the answer to Question #2 is that the Division would prefer that the define files contain all datasets (including datasets not being updated in the Safety Update), does the Division agree that we should provide hypertext links from the updated define files to the datasets submitted in a prior sequence? (Rather than re-submit unchanged datasets in the Safety Update.)

FDA RESPONSE: Yes, please see response to Question 2.

Additional comments regarding the datasets listed below:

- In addition to the study tabulation domains listed below, please include the cm.xpt, oe.xpt, and lb.xpt tabulation data sets for studies -302 and -304.
- Note that the updated ISS analysis files should reflect any data collected through February 28, 2009. If necessary, the study tabulation data sets for studies -302 and -304 should also be updated to reflect the updated study tabulation data (used to construct the updated ISS analysis files). For example, if the updated ISS ophexam.xpt datasets contains updated information on subjects enrolled in studies -302 and -304, then the relevant oe.xpt study tabulation datasets should also be updated.

Study -302 Tabulation Datasets (5)

ae.xpt
ds.xpt
ex.xpt

dm.xpt
suppqual.xpt

Study -302 Analysis Datasets (2)

ae.xpt
term.xpt

Study -304 Tabulation Datasets (5)

ae.xpt
ds.xpt
ex.xpt
dm.xpt
suppqual.xpt

Study -304 Analysis Datasets (2)

ae.xpt
term.xpt

ISS Analysis Datasets (7)

demo.xpt
cusage.xpt
studypop.xpt
ophexam.xpt
ae.xpt
lab.xpt
dusage.xpt

From: Sabrina Girty [mailto:sgirty@xanodyne.com]
Sent: Tuesday, April 14, 2009 5:36 PM
To: Crisostomo, Nenita
Cc: Sabrina Girty
Subject: NDA 22-430 Safety Update Questions

Dear Nita,

We are preparing our 90 day Safety Update for the Tranexamic Acid NDA 22-430. Part of our Safety Update will include updated study -302 and study -304 datasets which will contain the additional data that has occurred through our safety data cut-off date (which was February 28, 2009). The set of -302 and -304 datasets that will be included in the Safety Update comply with Division's request from the October 31, 2008 Pre-NDA meeting. Note however that not all -302 and -304 datasets will be submitted in the Safety Update, only those agreed upon during the Pre-NDA meeting (listed below) will be included in the Safety Update.

In addition, we will be including the 7 updated ISS Analysis Datasets with data through the safety data cut-off date in the Safety Update. This meets the Division's Statistical Safety Information Request #1 (dated March 6, 2009). We have three questions for the Safety Statistician described below. It would be very helpful to receive guidance from the Safety Statistician as soon as possible so that upcoming Safety Update meets the Division's expectations. If it would be helpful, we would be happy to schedule a brief teleconference with you and the Safety Statistician to discuss our questions at your convenience.

Question 1:

We plan to submit the datasets with data through February 28, 2009 as "append" datasets in the eCTD since we are not submitting all of the -302, -304 and ISS datasets in the Safety Update. Is it acceptable to submit the Safety Update datasets as "append" files?

Question 2:

We plan to submit the define files for the datasets as "append" files in the eCTD since only a sub-set of the -302, -304 and ISS datasets are being updated in the Safety Update. We also plan to submit define files that only list the datasets being included in the Safety Update. We will not list the other datasets that were not updated in the Safety Update in the define files. Does the Division agree that the define files should only describe the datasets that have been updated in the Safety Update (listed below)?

Question 3:

If the answer to Question #2 is that the Division would prefer that the define files contain all datasets (including datasets not being updated in the Safety Update), does the Division agree that we should provide hypertext links from the updated define files to the datasets submitted in a prior sequence? (Rather than re-submit unchanged datasets in the Safety Update.)

Study -302 Tabulation Datasets (5)

ae.xpt
ds.xpt
ex.xpt
dm.xpt
supqual.xpt

Study -302 Analysis Datasets (2)

ae.xpt
term.xpt

Study -304 Tabulation Datasets (5)

ae.xpt
ds.xpt
ex.xpt
dm.xpt
supqual.xpt

Study -304 Analysis Datasets (2)

ae.xpt
term.xpt

ISS Analysis Datasets (7)

demo.xpt
cusage.xpt
studypop.xpt
ophtexam.xpt
ae.xpt
lab.xpt
dusage.xpt

We greatly appreciate your feedback on these questions. I will give you a quick follow-up call tomorrow to see if you think we should schedule a teleconference to discuss our questions.

Kind regards,

Sabrina

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/s/

Nenita Crisostomo
4/17/2009 04:16:46 PM
CSO

REQUEST FOR CONSULTATION

TO: Division of Drug Marketing, Advertising and Communications
Attention: Wayne Amchin, Paul Loebach, Janice Maniwang, Cynthia Collins

FROM: Div. of Reproductive and Urologic Products, HFD-580
Nenita Crisostomo, Project Manager
Ph: 301-796-0875

DATE April 3, 2009	IND NO.	NDA NO. 22-430	TYPE OF DOCUMENT Labeling for new NDA	DATE OF DOCUMENT January 30, 2009
-----------------------	---------	-------------------	--	--------------------------------------

NAME OF DRUG Lysteda (tranexamic acid)	PRIORITY CONSIDERATION PRIORITY REVIEW	CLASSIFICATION OF DRUG Antifibrinolytic drug	DESIRED COMPLETION DATE June 3, 2009
---	---	---	---

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input checked="" type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the label for this new 505(b)(2) NDA. The submission is fully electronic in eCTD format. This application is on a Priority Review clock with a PDUFA Goal Date of July 30, 2009. If you have any questions, please feel free to contact me.

Thank you,
Nita

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Nenita Crisostomo
4/3/2009 03:34:23 PM

DSI CONSULT: Request for Clinical Inspections

Date: April 2, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Roy Blay, Ph.D., Reviewer
Good Clinical Practice Branch I
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Daniel Davis, M.D. – Clinical Reviewer
Lisa Soule, M.D. – Clinical Team Leader

From: Nenita Crisostomo, R.N., Regulatory Health Project Manager, HFD-580

Subject: **Request for Clinical Site Inspections**
NDA 22-430 Lysteda (tranexamic acid)

I. General Information

Application#: NDA-22-430
Applicant/Applicant contact information (to include phone/email):
Sponsor: Xanodyne Pharmaceuticals, Inc.
Contact Person: Sabrina Girty, Esq.
Phone #: 859-342-2088
Fax #: 859-371-6391
email: sgirty@xanodyne.com

Drug Proprietary Name: Lysteda (tranexamic acid)
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Priority
Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of heavy bleeding and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure and physical activities

PDUFA: July 30, 2009
Action Goal Date: July 30, 2009
Inspection Summary Goal Date: June 26, 2009

DSI Consult
version: 5/08/2008

II. Protocol/Site Identification

MR-301 is a blinded three arm (two active doses), 3-month trial to assess the safety and efficacy of tranexamic acid to reduce menstrual blood loss (MBL) when administered for 5 days during menstruation compared to placebo. This trial determined that the higher dose would be used in trials 303, and the extension trials 302 (27 months) and 304 (9 months).

MR-303 is a blinded two arm (one active treatment), 6-month trial to assess the safety and efficacy of tranexamic acid to reduce menstrual blood loss (MBL) when administered for 5 days during menstruation compared to placebo.

MR-302 is an open-label 27-month trial to assess the safety of tranexamic acid when used for a longer period of time (up to 27 menstrual cycles). This was a much larger trial enrolling 720 women at 62 sites. Strict efficacy data was not collected I this trial.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #746 Andrea Lukes Women's Wellness Center 249 E Highway 54, Suite 330 Durham, NC 27713	Trial MR-301 and 304	Enrolled 15 women in a 3-month trial & 7 women continued in a 9-month extension trial	Heavy Menstrual Bleeding
Site #602, Jeffrey Baker 2327 Coronado St. Idaho Falls, ID 83404	Trial MR-303 and 304	Enrolled 18 women in a 6-month trial and 15 women continued in the 9-month extension trial.	Heavy Menstrual Bleeding
Site #524 R Garn Mabey, Jr. 2881 N. Tenaya Way Las Vegas, NV 89128	Trial MR-302	Enrolled 44 women in the 27-month open label extension trial.	Heavy Menstrual Bleeding

III. Site Selection/Rationale

Rationale for DSI Audits:

The rationale is that this is a new indication with no prior approved drugs for this indication. The NDA will be given a priority review and we feel that inspection of 2 or 3 sites is reasonable. There is no specific safety or efficacy concern at any of the sites.

At site ~~the~~ the investigator's financial disclosure stated that ~~we~~ received \$75,000 in consulting fees from the sponsor. b(6)

Sites 602 and 603 do not both need to be visited; if the Michigan site is easier to inspect than the Idaho site, then that is fine.

Domestic Inspections:

Reasons for inspections:

- Sites 602/603 and 524: Enrollment of large numbers of study subjects
- High treatment responders (specify):
 - Significant primary efficacy results pertinent to decision-making
 - There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Site _____ Other: Financial disclosure **b(6)**

International Inspections: Not applicable

IV. Tables of Specific Data to be Verified (if applicable)

There are none at this time.

Should you require any additional information, please contact Nenita Crisostomo, R.N., at 301-796-0875 or Daniel Davis, M.D. at 301-796-0880.

Concurrence:

 Lisa Soule, M.D. Medical Team Leader

 Daniel Davis, MD Medical Reviewer

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/s/

Nenita Crisostomo
4/3/2009 03:05:42 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-430

FILING COMMUNICATION

Xanodyne Pharmaceuticals, Inc.
Attention: Sabrina R. Girty, Esq.
One Riverfront Place
Newport, KY 41071-4563

Dear Ms. Girty:

Please refer to your new drug application (NDA) dated and received January 30, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Lysteda™ (tranexamic acid tablets).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is July 30, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any post-marketing commitment requests by July 9, 2009.

During our filing review of your application, we identified the following potential review issues.

Clinical Pharmacology

1. Your proposed dosage adjustment in patients with renal impairment is based on serum creatinine concentration and estimated glomerular filtration rate (GFR). This will be a review issue.
2. The robustness of the tranexamic acid modified release formulation in the presence of various alcohol concentrations (0, 5%, 10%, 20%, and 40%) as well as in different pH levels will be reviewed.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information.

Chemistry

1. Clarify if (1) impurities A, B, C, and D are only drug substance process impurities and are therefore not controlled in the drug product or if (2) these are also degradation products and are included in the drug product "Related Substances" specification under "Individual Unknowns."
2. Submit a copy of the blister card. Clarify whether the high density polyethylene (HDPE) bottles will be packaged in cartons; if so, carton labels should be provided.
3. Please be aware that "Modified Release Tablets" is not a recognized dosage form for purposes of labeling. "Extended Release Tablets" may be more appropriate for your product, but the final determination will be made during the NDA review and will be conveyed with other carton and container label comments.
4. Provide the individual dissolution data points in tabular form for the following graphs in Section 3.2.P.2. In addition, state what dissolution method was used.
 - Figure 2 on page 12
 - Figure 8 on page 21
 - Figure 9 on page 22

Respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and deferral of pediatric studies for this application. We will notify you whether your request is granted or denied following our evaluation.

NDA 22-430

Page 3

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.

Director

Division of Reproductive and Urologic Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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/s/

Scott Monroe

3/31/2009 02:37:36 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: March 27, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Statistical Safety Information Request #2: Safety Data	

Total no. of pages including cover: 2

Comments:

Dear Sabrina,

Please submit your response to the attached Information Request on/before 12:00 P.M. March 31, 2009. If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: YES NO

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INFORMATION REQUEST #2

STATISTICAL SAFETY

March 27, 2009

NDA 22-430 Lysteda (tranexamic acid)

According to the study reports, there should be data for 304 subjects from study -301 and 196 subjects from study -303. In the revised cusage.xpt and ophexam.xpt files submitted on March 20, 2009, there are data for 235 subjects from -301 and 147 subjects from -303.

Are there any cycle drug usages or ophthalmic exam data available for the subjects not included in the existing cusage.xpt and ophexam.xpt data files? If so, please provide data for these subjects (in the same format as the files submitted on March 20, 2009).

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/s/

Nenita Crisostomo
3/27/2009 03:15:03 PM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: March 25, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Roy Blay, Ph.D., Reviewer
Good Clinical Practice Branch I
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Daniel Davis, M.D. – Clinical Reviewer
Lisa Soule, M.D. – Clinical Team Leader

From: Nenita Crisostomo, R.N., Regulatory Health Project Manager, HFD-580

Subject: **Request for Clinical Site Inspections**
NDA 22-430 Lysteda (tranexamic acid)

I. General Information

Application#: NDA-22-430
Applicant/Applicant contact information (to include phone/email):
Sponsor: Xanodyne Pharmaceuticals, Inc.
Contact Person: Sabrina Girty, Esq.
Phone #: 859-342-2088
Fax #: 859-371-6391
email: sgirty@xanodyne.com

Drug Proprietary Name: Lysteda (tranexamic acid)
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Priority
Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of heavy bleeding and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure and physical activities

PDUFA: July 30, 2009
Action Goal Date: July 30, 2009
Inspection Summary Goal Date: June 26, 2009

DSI Consult
version: 5/08/2008

II. Protocol/Site Identification

MR-301 is a blinded three arm (two active doses), 3-month trial to assess the safety and efficacy of tranexamic acid to reduce menstrual blood loss (MBL) when administered for 5 days during menstruation compared to placebo. This trial determined that the higher dose would be used in trials 303, and the extension trials 302 (27 months) and 304 (9 months).

MR-303 is a blinded two arm (one active treatment), 6-month trial to assess the safety and efficacy of tranexamic acid to reduce menstrual blood loss (MBL) when administered for 5 days during menstruation compared to placebo.

MR-302 is an open-label 27-month trial to assess the safety of tranexamic acid when used for a longer period of time (up to 27 menstrual cycles). This was a much larger trial enrolling 720 women at 62 sites. Strict efficacy data was not collected I this trial.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #746 Andrea Lukes Women's Wellness Center 249 E Highway 54, Suite 330 Durham, NC 27713	Trial MR-301	Enrolled 15 women in a 3-month trial & 7 women continued in a 9-month extension trial	Heavy Menstrual Bleeding
Site #602, Jeffrey Baker 2327 Coronado St. Idaho Falls, ID 83404	Trial MR-303	Enrolled 18 women in a 6-month trial and 15 women continued in the 9-month extension trial.	Heavy Menstrual Bleeding
Site #524 R Garn Mabey, Jr. 2881 N. Tenaya Way Las Vegas, NV 89128	Trial MR-302	Enrolled 44 women in the 27-month open label extension trial.	Heavy Menstrual Bleeding
Site #603 Roger Beyer 505 Haven St., Suite 204 Paw Paw, MI 49079	Trial MR-303	Enrolled 14 women in a 6-month trial and 6 women continued in the 9-month extension trial.	Heavy Menstrual Bleeding

III. Site Selection/Rationale

Rationale for DSI Audits:

The rationale is that this is a new indication with no prior approved drugs for this indication. The NDA will be given a priority review and we feel that inspection of 2 or 3 sites is reasonable. There is no specific safety or efficacy concern at any of the sites.

At site — the investigator's financial disclosure stated that — received \$75,000 in consulting fees from the sponsor.

b(6)

Sites 602 and 603 do not both need to be visited; if the Michigan site is easier to inspect than the Idaho site, that is fine.

Domestic Inspections:

Reasons for inspections:

- Sites 602/603 and 524: Enrollment of large numbers of study subjects
- High treatment responders (specify):
 - Significant primary efficacy results pertinent to decision-making
 - There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Site Other: Financial disclosure b(6)

International Inspections: Not applicable

IV. Tables of Specific Data to be Verified (if applicable)

There are none at this time.

Should you require any additional information, please contact Nenita Crisostomo, R.N., at 301-796-0875 or Daniel Davis, M.D. at 301-796-0880.

Concurrence: (as needed)

Lisa Soule, M.D. Medical Team Leader

Daniel Davis, MD Medical Reviewer

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/s/

Nenita Crisostomo
3/30/2009 06:03:57 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: March 27, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Statistical Safety Information Request #2: Safety Data	

Total no. of pages including cover: 2

Comments:

Dear Sabrina,

Please submit your response to the attached Information Request on/before 12:00 P.M. March 31, 2009. If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

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Document to be mailed: YES NO

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INFORMATION REQUEST #2

STATISTICAL SAFETY

March 27, 2009

NDA 22-430 Lysteda (tranexamic acid)

According to the study reports, there should be data for 304 subjects from study -301 and 196 subjects from study -303. In the revised cusage.xpt and ophexam.xpt files submitted on March 20, 2009, there are data for 235 subjects from -301 and 147 subjects from -303.

Are there any cycle drug usages or ophthalmic exam data available for the subjects not included in the existing cusage.xpt and ophexam.xpt data files? If so, please provide data for these subjects (in the same format as the files submitted on March 20, 2009).

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/s/

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**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: March 20, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Clinical Information Request #1: Clinical Sites	

Total no. of pages including cover: 2

Dear Sabrina,

Please submit your response to the Information Request below on/before 12:00 P.M. on or before March 23, 2009. If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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INFORMATION REQUEST #1

CLINICAL

March 20, 2009

NDA 22-430 Lysteda™ (tranexamic acid)

1. Provide the number of patients enrolled in each study for all study sites that enrolled at least one patient.
2. Were the investigators assigned to more than one trial?

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Nenita Crisostomo
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FACSIMILE TRANSMITTAL SHEET

DATE: March 18, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 QT/IRT Information Request #2: Highlights of Clinical Pharmacology	

Total no. of pages including cover: 3

Dear Sabrina,

Please submit your response to the attached Information Request as soon as possible, or at the latest, before close of business on March 20, 2009. If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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INFORMATION REQUEST #2

THE INTERDISCIPLINARY REVIEW TEAM FOR QT STUDIES

March 18, 2009

NDA 22-430 Lysteda™ (tranexamic acid)

Please complete the following table and submit officially on or before close of business on March 20, 2009:

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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/s/

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FACSIMILE TRANSMITTAL SHEET

DATE: March 18, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 QT/IRT Information Request #1: ECG Raw data	

Total no. of pages including cover: 3

Dear Sabrina,

Please submit your response to the Information Request below on/before close of business on March 25, 2009. If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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INFORMATION REQUEST #1

THE INTERDISCIPLINARY REVIEW TEAM FOR QT STUDIES

March 18, 2009

NDA 22-430 Lysteda™ (tranexamic acid)

Please submit ECG raw data for this study that includes the following:

1. subject ID
2. treatment
3. period
4. ECG date
5. ECG time (up to second)
6. nominal day
7. nominal time
8. replicate number
9. heart rate HR
10. intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.)
11. Lead
12. ECG ID (link to waveform files if applicable)

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/s/

Nenita Crisostomo
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REQUEST FOR CONSULTATION

TO (Office/Division):
 Division of Cardiovascular and Renal Products
 QT Interdisciplinary Review Team
 Attn: Devi Kozeli, RAC
 Assistant to the Division Director

FROM (Name, Office/Division, and Phone Number of Requestor):
 Nenita Crisostomo, R.N. --Regulatory Health Project Manager
 Division of Reproductive and Urologic Products
 Ph: 301-796-0875

DATE March 17, 2009	IND NO.	NDA NO. 22-430	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT January 30, 2009
------------------------	---------	-------------------	-----------------------------	--------------------------------------

NAME OF DRUG Lysteda (tranexamic acid)	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Uterine Acting Agent	DESIRED COMPLETION DATE May 1, 2009
---	------------------------------------	--	--

NAME OF FIRM: Xanodyne Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <i>New NDA</i> |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:
 We are requesting your review of the QT study in this new NDA submitted in EDR, fully electronic, in eCTD format:
 \CDSESUB1\EVSPROD\NDA022430\0002. The NDA is designated a Priority Review and therefore, the PDUFA Goal Date is
 July 30. If you have any questions, please feel free to contact me.

Thank you,
 Nita

CC: NDA 22430

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DARRTS <input checked="" type="checkbox"/> EMAIL <input checked="" type="checkbox"/> DFS <input type="checkbox"/> HAND
------------------------	---

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER
--	---

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/s/

Nenita Crisostomo
3/17/2009 03:30:57 PM

REQUEST FOR CONSULTATION

TO (Division/Office):

Office of Surveillance and Epidemiology
Attention: Cheryle Milburn
Regulatory Health Project Manager

FROM:

Division of Reproductive and Urologic Products
Nenita Crisostomo, R.N. – Regulatory Health Project Manager
Ph. 301-796-0875

DATE
March 16, 2009

IND NO.

NDA NO.
22-430

TYPE OF DOCUMENT
AERS search during review of
new drug application

DATE OF DOCUMENT
January 30, 2009

NAME OF DRUG
Lysteda™ (tranexamic acid)

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
antifibrinolytic

DESIRED COMPLETION DATE
May 10, 2009

NAME OF FIRM: Xanodyne Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): AERS Search |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

For this product, we would like an AERS search particularly focusing on VTE and ophthalmologic adverse events (AEs). The only product marketed in the US is the IV formulation (Cyklokapron Injection), but if you should find any data from foreign markets on the oral formulation (Cyklo-f and Cyklokapron are two brand names), we would also like that data reported. As we continue our review, we may request additional AEs of interest, but at this point, these are the top concerns. This application is under a Priority Review, and therefore, the PDUFA Goal date is July 30, 2009. If you have any questions, please feel free to contact me.

Thank you, Nita Crisostomo

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

- DFS EMAIL HAND

SIGNATURE OF RECEIVER

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/s/

Nenita Crisostomo
3/16/2009 09:35:34 PM

REQUEST FOR CONSULTATION

TO (Division/Office)
Office of Surveillance and Epidemiology
Attention: **Cheryle Milburn**
Regulatory Health Project Manager

FROM:
Division of Reproductive and Urologic Products
Nenita Crisostomo, R.N. – Regulatory Health Project Manager
Ph. 301-796-0875

DATE March 16, 2009	IND NO.	NDA NO. 22-430	TYPE OF DOCUMENT Patient Package Insert for new NDA	DATE OF DOCUMENT January 30, 2009
------------------------	---------	-------------------	---	--------------------------------------

NAME OF DRUG Lysteda™ (tranexamic acid)	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG antifibrinolytic	DESIRED COMPLETION DATE May 10, 2009
--	------------------------------------	--	---

NAME OF FIRM: Xanodyne Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): review of PPI of new NDA |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
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 CASE REPORTS OF SPECIFIC REACTIONS (List below)
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 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the labeling located in EDR \\CDSESUB1\EVSPROD\NDA022430\0000 in eCTD format. We understand that the Physician Insert and carton labeling will be reviewed along with the review of the Trade Name proposal as submitted directly to you on March 2, 2009. This application is under a Priority Review, and therefore, the PDUFA Goal date is July 30, 2009. If you have any questions, please feel free to contact me.
Thank you, Nita Crisostomo

SIGNATURE OF REQUESTER

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/s/

Nenita Crisostomo
3/16/2009 09:04:56 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: March 12, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Chemistry Information Request #2: Manufacturing site information and LOA	

Total no. of pages including cover: 3

Dear Sabrina,

Please submit your response to the Information Request below on/before 12:00 PM on March 16, 2009.

Clarify if the API will be used for commercial distribution. If so, information on the manufacturing site and a letter of authorization (LOA) to reference the Drug Master File (DMF) for CMC information should be provided.

b(4)

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed:

YES

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2130. Thank you.

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/s/

Nenita Crisostomo
3/12/2009 03:32:55 PM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: March 12, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875

Subject: NDA 22-430 Clinical Pharmacology Information Request #1

Total no. of pages including cover: 3

Dear Sabrina,

Please submit your response to the Information Request below on/before 10:00 A.M. on or before March 16, 2009. If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: **YES** **NO**

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INFORMATION REQUEST #1

CLINICAL PHARMACOLOGY

March 12, 2009

NDA 22-430 Lysteda™ (tranexamic acid)

1. Provide the demographic information including sex, age, and weight of the patients enrolled in the study (Anderson L. et al., Urological Research 6, 83-88, 1978) to calculate those patients' creatinine clearance.
2. Provide the information or equation used to estimate Glomerular Filtration Rate (GFR) from serum creatinine in Section 8.6 (Renal Impairment section) of your proposed label.

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/s/

Nenita Crisostomo
3/12/2009 02:47:35 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: March 6, 2009

To: Sabrina R. Girty, Esq. Associate Director, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Reproductive and Urologic Products
Fax number: 859-371-6391	Fax number: 301-796-9897
Phone number: 859-342-2088	Phone number: 301-796-0875
Subject: NDA 22-430 Statistical Safety Information Request #1: Safety Data	

Total no. of pages including cover: 5

Comments:

Dear Sabrina,

Please submit your response to the attached Information Request on/before 10:00 A.M. on or before March 23, 2009. If you have any questions, please do not hesitate to contact me.

Best Regards,

Nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed:

YES

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2130. Thank you.

INFORMATION REQUEST #1

STATISTICAL SAFETY

March 6, 2009

NDA 22-430 Lysteda (tranexamic acid)

I. Questions to the sponsor

- (A) Were any subjects in studies -301, -302, or -303 enrolled in more than one study? If so, please identify these subjects.
- (B) Please identify any investigational sites in study -301, -302, and -303 that enrolled subjects in more than one study. For example, the physical location designated site 7xx in study -301 corresponds to site 6xx in study -303.
- (C) For study -303, are any adverse events or labs data available for subjects on placebo in cycles 4, 5, or 6? Please include these data in the integrated adverse event and labs datasets described in sections II.C and II.D below.

II. Data requested to facilitate review

For the safety analysis of tranexamic acid (NDA 22-430), we request the sponsor correct the following problems in the submitted data. These corrections are crucial if the review is to be completed in a timely and efficient manner. Please produce the following data sets as soon as possible and by no later than March 23, 2009:

1. Revised ISS demo.xpt file with a USUBJID as defined in (A) below, and the following additional variables:
 - SAFETY flag that indicates if subjects were randomized, received at least one dose of the study drug, and completed at least one follow-up visit
 - HEIGHT in cm
 - WEIGHT in kg
2. Revised ISS cusage.xpt file (with USUBJID as in (II.A) below)
3. Revised ISS studypop.xpt file (with USUBJID as in (II.A) below)
4. Revised ISS ophexam.xpt file (described in (II.B) with USUBJID as in (II.A) below)
5. Integrated adverse events data set (defined in (II.C) with USUBJID as in (II.A) below)
6. Integrated labs data set (as defined in (II.D) with USUBJID as in (II.A) below)
7. Integrated drug usage data set (as defined in (II.E) with USUBJID as in (II.A) below)

Please note that the first three items above are almost identical to the ISS data sets already submitted. For the integrated AE and labs data, many of the variables requested below are available separately in existing data sets, but need to be included in an integrated data set. Items in italics below indicate that the definition of the term differs from that given in the ISS define.xml file already submitted. In addition, when submitting the safety update for studies -302 and -304, please resubmit all seven of the data sets enumerated above with all subjects from all four Phase 3 studies.

The specific components of this request are as follows:

- (A) The USUBJID variable should represent the study.site.subject number for each subject. If a subject was enrolled in more than one trial (e.g., -301 and -304), the study number should correspond to the number of the first study in which she enrolled. The site number should also be consistent from study to study, such that the physical location designated Center 101 in study 301 should also be Center 101 in study 304. The USUBJID variable should be identical between the study tabulation, study-level analysis, and ISS analysis data sets.
- (B) The ISS ophthexam.xpt file should have one row per subject-visit. Each row should contain all observations collected from the subject for that cycle visit. The following is an example of the structure of the current ophthexam.xpt file:

USUBJID	STUDYID	LVISACU	RVISACU	CYCLECNT
301.701.101	XP12B-MR-301	20/30		3
301.701.101	XP12B-MR-301		20/25	3

In the current file, the observations for one subject at one time point are split between two rows for the left and right eye. These data may be consolidated into one row for that subject-time point as follows:

USUBJID	STUDYID	LVISACU	RVISACU	CYCLECNT
301.701.101	XP12B-MR-301	20/30	20/25	3

If the subject also had other measurements taken at the same ophthalmic examination, these should also be included by adding variables in the same row above. The revised ISS ophthexam.xpt files should contain one row per subject-visit, and should contain the following variables:

- **USUBJID** (no missing values) As described in (II.A) above.
- **STUDYID** (no missing values) The first study in which the subject was enrolled (one of -301, -302, or -303)
- **TRTMNT** Treatment to which the subject was assigned during studies -301, -302, or -303
- **TRT304** The treatment to which the subject was assigned in study -304 (leave blank for subjects in study -302).
- **STEXP** Flag for short-term exposure group
- **LTEXP** Flag for long-term exposure group
- **CYCLECNT** The cycle during which the examination occurred. For subjects in study -304, use the total number of cycles since treatment assignment, including cycles from studies -301 or -303 if the subject was assigned to any dose of tranexamic acid in those studies. If a subject completed study -303 on the placebo arm (6 cycles), enrolled in study -304, and had measurements 4 weeks after enrolling in study -304, then CYCLECNT = 4 for that row.
- **LVISACU** Visual acuity in the left eye
- **RVISACU** Visual acuity in the right eye
- **IPLEFT** Intraocular pressure in the left eye
- **IPRIGHT** Intraocular pressure in the right eye
- **RETEXAM** Retinal exam
- **COLVIS** Color vision

Please include baseline measurements using CYCLECNT = 0.

- (C) For the lt_ae.xpt and st_ae.xpt adverse events data in the ISS: Please integrate these data into one file, with one entry per adverse event for subjects enrolled in all four of the Phase 3 studies. Events that are currently in both the lt_ae.xpt and st_ae.xpt files should be included only once in the integrated data. In addition, the adverse events that occurred during cycles 4-6 for subjects on placebo in study -303 were

omitted from both the lt_ae.xpt and st_ae.xpt files and should be included in the integrated AE data. The integrated data should include the following variables for every adverse event entry:

- **USUBJID** (no missing values) As described in (II.A) above.
- **STUDYID** (no missing values) The first study in which the subject was enrolled (one of -301, -302, or -303)
- **TRTMNT** Treatment to which the subject was assigned during studies -301, -302, or -303
- **TRT304** The treatment to which the subject was assigned in study -304 (leave blank for subjects in study -302). If the subject was assigned to treatment in study -304, but the adverse event occurred during studies -301 or -303 (e.g., prior to the beginning of study -304), then TRT304 should still be the treatment to which the subject was assigned in study 304.
- **IN304** Flag for whether the adverse event occurred during study -304.
- **STEXP** Flag for short-term exposure group
- **LTEXP** Flag for long-term exposure group
- **CYCLECNT** The cycle during which the adverse reaction was observed, with negative values indicating that they occurred prior to the first dose of the study drug. For subjects in study -304, use the total number of cycles since treatment assignment, including cycles from studies -301 or -303 if the subject was assigned to any dose of tranexamic acid in the earlier studies. If a subject completed study -303 on the active treatment arm (6 cycles), enrolled in study -304, and experienced an adverse event 4 weeks after enrolling in study -304, then CYCLECNT = 10 for this adverse event.
- **SPDATE** Stop date of adverse event
- **STDATE** Start date of adverse event
- **DURATION** Duration of AE in days
- **AEOUT** Outcome of adverse event
- **AEACN** Action taken in response to the AE
- **AESER** Flag for serious adverse event
- **VERBATIM** Verbatim term for the adverse event
- **PREFTERM** Dictionary-derived term (coded in MedDRA version 7.1)
- **SOC** System organ class (using primary axis from MedDRA 7.1)
- **ONSETINT** Onset / interval (if value is derived, describe derivation in comment section of define.xml)
- **RELDAY** Relationship day from the first dose
- **TE_FLAG** Treatment emergent flag
- **D_FLAG** During dosing flag
- **P_FLAG** During period flag

If any additional FLAG variables are included in the integrated AE data set (e.g., FLAG1, FLAG2, TEAE1, TEAE2, PRIOR1, PRIOR2, etc), these flags should be defined in the comments section of the ISS define.xml file.

- (D) For the st_lab.xpt and lt_lab.xpt analysis data in the ISS: Please integrate these data into one file, with one entry per subject per time point. Measurements that are included in both the st_lab.xpt and lt_lab.xpt files should be included only once in the integrated data. If available, please include the labs for placebo subjects obtained during cycle 6 of study -303 as these measurements were omitted from both the st_lab.xpt and lt_lab.xpt files. The integrated labs data should include *all of the laboratory variables currently included* in the st_labs.xpt and lt_labs.xpt files, and the following additional variables:

- *USUBJID* (no missing values) As described in (II.A) above.
- *STUDYID* (no missing values) The first study in which the subject was enrolled (one of -301, -302, or -303)
- *TRTMNT* Treatment to which the subject was assigned during studies -301, -302, or -303
- *TRT304* Treatment to which the subject was assigned in study -304 (leave blank for subjects in study -302)
- *IN304* Flag for whether the lab measurement was taken during study -304
- *STEXP* Flag for short-term exposure group
- *LTEXP* Flag for long-term exposure group
- *CYCLECNT* The cycle during which the lab measurements were taken.

In addition, the define.xml file for the integrated labs data should include the units associated with each lab measurement in the Comments section.

(E) An integrated drug usage data set, incorporating subjects in both *dusage39.xpt* and *dusag195.xpt*. In addition to the variables currently included, please add

- *USUBJID* (no missing values) As described in (A) above.
- *STUDYID* (no missing values) The first study in which the subject was enrolled (one of -301, -302, or -303)
- *TRTMNT* Treatment to which the subject was assigned during studies -301, -302, or -303
- *TRT304* Treatment to which the subject was assigned in study -304 (leave blank for subjects in study -302)
- *PDOSE* Dose per tablet taken (either 1.95 or 3.9, with units in grams)

III. SDTM and ADaM compliance issues

Please resubmit all data with a *USUBJID* variable that conforms to the definition give in (II.A). In particular, please follow the recommendations below:

(A) For the individual study tabulation data: Since study -304 is an open-label extension study for subjects enrolled in studies -301 and -303, the *USUBJID* assigned to subjects in the study data for study -304 should have *USUBJID* identical to that used to identify the subject in the first study in which they enrolled (studies -301 and -303). Please re-submit all study tabulation data associated with study -304 with a *USUBJID* that meets this definition.

(B) For the analysis data sets (including ISS analysis data sets): There is no *USUBJID* variable in the analysis data sets. Please re-submit **all** analysis data sets with a *USUBJID* variable that matches the *USUBJID* variable assigned to particular subjects in the individual study tabulation data.

These revised data sets may be submitted after the 7 data sets enumerated above, but the *USUBJID* should be provided in every data set in the submission, and should identify subjects consistently throughout the individual study tabulation data, individual study analysis data, and analysis data submitted with the ISS.

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/s/

Nenita Crisostomo
3/6/2009 05:09:07 PM
CSO



NDA 22-430

INFORMATION REQUEST LETTER

Xanodyne Pharmaceuticals, Inc.
Attention: Sabrina R. Girty, Esq.
Associate Director, Regulatory Affairs
One Riverfront Place
Newport, KY 41071-4563

Dear Ms. Girty:

Please refer to your January 30, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lysteda™ (tranexamic acid), modified-release tablets, 650 mg.

We are reviewing the Environmental Analysis section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

On page 4 of the Environmental Assessment dated October 28, 2008 (submitted January 30, 2009), the following paragraph states:

"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."

- 1. Provide support for the statement, "Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system."**
- 2. In addition, provide any available information (e.g., publications, surveys) on the percentage of drugs that may be disposed of by patients in the home.**

To facilitate prompt review of your response, please provide courtesy copies of your official submission to Jeannie David, Regulatory Health Project Manager in the Office of New Drug Quality Assessment for issues related to Chemistry, Manufacturing and Controls (jeannie.david@fda.hhs.gov; fax 301-796-9877) and Nenita Crisostomo, R.N., Regulatory Health Project Manager (nenita.crisostomo@fda.hhs.gov) who remains the main contact for the overall application.

If you have any questions regarding this letter, please call Jeannie David, Regulatory Health Project Manager, at 301-796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
2/27/2009 02:43:52 PM
Chief, Branch III



NDA 22-430

NDA ACKNOWLEDGMENT

Xanodyne Pharmaceuticals, Inc.
Attention: Sabrina R. Girty, Esq.
Associate Director, Regulatory Affairs
One Riverfront Place
Newport, KY 41071-4563

Dear Ms. Girty:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Lysteda™ (tranexamic acid) modified-release tablets

Date of Application: January 30, 2009

Date of Receipt: January 30, 2009

Our Reference Number: NDA 22-430

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 31, 2009, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.

Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please call me at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Nenita Crisostomo
2/26/2009 10:23:06 PM

REQUEST FOR CONSULTATION

(Office/Division): Raanan (Ron) Bloom, OPS/PARS, 301-796-2185

FROM (Name, Office/Division, and Phone Number of Requestor): Donna Christner, Ph.D., Division of Pre-Marketing Assessment II, Office of New Drug Quality Assessment, through Jeannie David, Regulatory Proj. Mgr, 301-796-4247

DATE
February 17, 2009

IND NO.

NDA NO.
22-430

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
January 30, 2009

NAME OF DRUG
Lysteda (Tranexamic Acid)

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
March 31, 2009

NAME OF FIRM: Xanodyne Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Environmental Assessment Review - electronic Submission in EDR
\\cdsesub1\evsprod\NDA022430\0000\m1\us\environ-anal.pdf. Xanodyne Pharmaceuticals, Inc. provided an environmental assessment (EA) in support of NDA 22-430. This NDA was submitted to seek approval for the development of modified release tablets containing 650 mg Tranexamic Acid. Please review and advise.

SIGNATURE OF REQUESTOR
{see attached signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

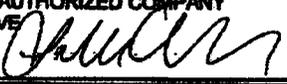
PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Moo-Jhong Rhee
2/17/2009 02:21:14 PM
Chief, Branch III

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See Instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/odufa/default.htm					
1. APPLICANT'S NAME AND ADDRESS OXANODYNE PHARMACEUTICALS INC Sabrina Girty ONE RIVERFRONT PLACE Newport KY 41071-4563 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-430			
2. TELEPHONE NUMBER 858-3422088		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:			
3. PRODUCT NAME Lysteda (Tranexamic Acid)		6. USER FEE I.D. NUMBER PD3008954			
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 738(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
<p>OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table border="0"> <tr> <td>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td> <td>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3048 Rockville, MD 20852</td> <td>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3048 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3048 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE <i>Associate Director, Regulatory Affairs</i> DATE <i>01/14/2009</i>			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$1,247,200.00					
Form FDA 3397 (03/07)					

Close Print Cover sheet



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,096

Xanodyne Pharmaceuticals, Inc.
ATTENTION: Sabrina R. Girty, Esq.
One Riverfront Place
Newport, KY 41071-4563

Dear Ms. Girty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tranexamic acid, 650 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 26, 2008. The purpose of the meeting was to discuss the Pharmacology/Toxicology and Chemistry, Manufacturing and Controls section of your proposed new drug application using a 505(b)(2) pathway.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Lisa M. Soule, M.D.
Clinical Team Leader
Division of Reproductive and Urologic
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 26, 2008
TIME: 2:00 P.M. – 3:30 P.M.
APPLICATION: IND 68,096
DRUG NAME: tranexamic acid, 650 mg tablets
INDICATION: Treatment of menorrhagia
TYPE OF MEETING: Type B, Pre-NDA—Chemistry and Pharmacology/Toxicology
MEETING CHAIR: Lisa M. Soule, M.D.
MEETING RECORDER: Nenita Crisostomo, R.N.

FDA ATTENDEES:

Lisa Soule, M.D. – Clinical Team Leader, Division of Reproductive and Urologic Products (DRUP)
Lesley-Anne Furlong, M.D. – Medical Officer, DRUP
Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, Branch III, Division of Pre-Marketing Assessment II, Office of New Drug Quality Assessment
Doanh Tran, Ph.D. – Clinical Pharmacology Reviewer, Office of Clinical Pharmacology @ DRUP
Nam Kim, J.D. – Regulatory Counsel, Division of Regulatory Policy 1, Office of Regulatory Policy
Lynnda Reid, Ph.D. – Supervisor, Pharmacology/Toxicology, DRUP
Kimberly Hatfield, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP
Zei-Pao Huang – Regulatory Information Specialist, Office of Business Support
Jennifer Mercier – Chief, Project Management Staff, DRUP
Nenita Crisostomo, R.N. – Regulatory Health Project Manager, DRUP

XANODYNE PHARMACEUTICALS, INC.

Dorothy A. Frank, M.S., R.A.C. – Senior Vice President, Regulatory Affairs
Sabrina Girty, J.D. – Associate Director, Regulatory Affairs
Jim Young, Ph.D. – Vice President, Product Development
Ralph Heasley, Ph.D. – Executive Director, Product Development

b(4)

BACKGROUND:

This investigational new drug (IND) application was submitted in December 2003 by Xanodyne Pharmaceuticals, Inc. to study tranexamic acid for the treatment of menorrhagia. The application was granted a Fast Track designation in October 2004 under Section 506(a), because of the potential to address unmet medical needs. Tranexamic acid is a lysine analog that reversibly

blocks lysine binding sites on plasminogen and thereby prevents the degradation of fibrin by plasmin. An intravenous (IV) formulation (Cyklokapron[®]) of tranexamic acid is currently marketed in the US. Cyklokapron[®] was approved in 1986 as an orphan drug for hemophilia patients to reduce/prevent bleeding during and following tooth extraction. Xanodyne plans to submit a new drug application (NDA) via the 505(b)(2) pathway, relying on literature data and the Agency's findings of safety for Cyklokapron[®]. Xanodyne plans to reference the pharmacology/toxicology characterization of the drug but does not have a right of reference from Pfizer, Inc. The Sponsor plans to conduct a literature search to identify relevant studies to provide non-clinical information.

MEETING OBJECTIVES:

The objective of this meeting is to gain concurrence on the Chemistry and Non-Clinical sections for the proposed 505(b)(2) application.

SPONSOR'S QUESTIONS AND THE DIVISION'S COMMENTS

General

QUESTION 1: *In accordance with fast track designation, would the Agency be willing to accept submission of Modules 3 and 4 as a rolling submission in advance of the full electronic submission? (See Section 12.1.1. Rolling Submission)*

FDA RESPONSE:

No, the Division will have to determine, based on data submitted in your Pre-NDA meeting package (Clinical), whether the clinical studies still meet the criteria for fast track designation. After a preliminary evaluation of the data from the clinical trials, the Division may consider accepting portions of an application if 1) the clinical trials that will form the basis for the determination of the safety and effectiveness of the product and that would support drug labeling are nearing completion or have been completed, 2) the Division agrees that the preliminary evaluation of the clinical data supports a determination that the product may be effective, and 3) the Division agrees that the product continues to meet the criteria for fast track designation. Once a final determination has been made on the acceptability of fast track designation, the sponsor may submit complete modules for review. The application can only be filed after submission of an acceptable timeline for submission of all components of the application and after applicable user fees are paid. We recommend that the User Fee Office be consulted.

Additional Discussion at the Meeting:

The Sponsor asked whether reports of the results from the Statistical Analysis Plan-specified analyses, presented in tables and graphs, would be adequate for the Fast Track evaluation. The Division responded that a summary of the primary efficacy results and an overview of the safety results should suffice. The Sponsor anticipates that a Target Patient Profile (TPP) will be included in the meeting package for the Pre-NDA meeting. The Phase 3 studies should complete by late spring, and the Sponsor expects to be ready for a clinical Pre-NDA meeting following preliminary analysis of the data. The Sponsor has spoken to the User Fee Office and hopes to be able to make the submission in Fiscal Year 2008.

Comment by Information Technology:

All eCTD submissions must have a Module 1, which would include, at a minimum, a Form 356h and a cover letter explaining what is being submitted. Any other questions pertaining to electronic submission format may be emailed to ESUB@fda.hhs.gov.

QUESTION 2: *Does the Agency require any additional information related to the three Phase I studies prior to NDA submission? (See Section 12.1.2. Phase I Study Vendor)*

FDA RESPONSE:

Clinical Pharmacology:

The role of _____ site in _____ in the conduct of the three Xanodyne Phase 1 pharmacokinetic studies is not clear. If the bioanalytical method validation and bioanalytical analysis of all pharmacokinetic samples were performed by _____, the Division will not require, prior to NDA submission, additional information on these studies with respect to _____ as the studies' vendor. b(4)

Clinical:

The Division requests that the Sponsor submits full study reports, including all appendices, with the NDA submission.

Additional Discussion at the Meeting:

The Sponsor stated that only blood draws were done at the _____ facility; method development, validation and bioanalysis were all conducted at _____. b(4)

The Division noted that other Clinical Pharmacology issues will be discussed at the future Clinical Pre-NDA meeting.

The Sponsor has submitted full study reports (FSRs) to the IND; however, the Division noted that necessary appendices were missing. The Sponsor will resubmit the FSRs, with all appendices, to the NDA.

Quality Topics

QUESTION 3: *Does the Agency agree with Xanodyne's specification for the API? (See Section 12.2.1. Active API Specification)*

FDA RESPONSE: The specifications appear to be adequate at this time, but the final determination will be made during review of the Drug Master Files (DMFs) during the NDA review cycle. For example, if the synthetic schemes used by the two suppliers are different, this may change the identity and amount of the residual solvents, which will only become apparent during the DMF review.

Additional Discussion at the Meeting:

The Sponsor stated that the two active pharmaceutical ingredient (API) suppliers use _____

_____. The other manufacturer uses _____

_____ The Sponsor asked if the _____ should be controlled with a

b(4)

different specification. The Division advised that a _____ should be sufficient and that the justification should be clearly explained in the NDA submission. For the Related Substances specifications, the Sponsor asked if a specification for "Total of all impurities" should also be included in addition to the specification for "Total content of other impurities." The Division agreed that the additional specification should be added. The Sponsor also provided copies of the European Pharmacopeia (EP) and Japanese Pharmacopeia (JP) compendial specifications for tranexamic acid.

b(4)

QUESTION 4: *Both API suppliers will meet Xanodyne's common API specification. Does the Agency agree that equivalence between the two API suppliers has been demonstrated? (See Section 12.2.2. API Supplier Equivalence Plans)*

FDA RESPONSE: The information provided is adequate at this time, but equivalence of the APIs will be determined at the time of the NDA review and will involve review of the DMFs.

QUESTION 5: *Does the Agency agree with the proposed particle size acceptance criteria for tranexamic acid? (See Section 12.2.3. API Particle Size Acceptance Criteria)*

FDA RESPONSE: The particle size acceptance criteria appear to be adequate at this time. Detailed information and justification should be provided in the NDA to support the particle size specification.

Additional Discussion at the Meeting:

The Sponsor stated that one API supplier tests for particle size, but the other supplier does not because tranexamic acid is soluble in water. The Sponsor states that the DMF holder has agreed to test particle size for the Sponsor, but is hesitant to include the test in the DMF because of the water solubility. The Sponsor also performs release testing of the API which includes particle size testing. If the Sponsor has determined that particle size is important for the dosage form, as long as the testing is performed by the Sponsor in order for the API to be released to manufacture the drug product, such testing would not need to be performed by the DMF holder or included in the DMF. This should be clearly stated in the NDA submission.

QUESTION 6: *Does the Agency agree with Xanodyne's specification for the modified release tablet? (See Section 12.2.4. Modified Release Tablet)*

FDA RESPONSE: The specifications appear to be adequate at this time, but the final determination will be made during the NDA review cycle.

QUESTION 7: *Does the Agency agree that the stability data set and comparative dissolution testing will support the acceptance of the commercial product presentation? (See Section 12.2.5. Commercial Product Stability)*

FDA RESPONSE: Comparative dissolution profiles should be repeated with non-debossed and debossed tablets held on stability to demonstrate that aging of the samples will not affect the tablet performance.

Additional Discussion at the Meeting:

The Sponsor stated that they will manufacture a pilot scale batch that is three times larger than their previous batches and compress half the batch with debossing and half without. They will then place this batch on stability and include a comparative dissolution as part of their stability testing. They also stated that at the time of NDA submission, they should have at least three months of accelerated stability data, with additional data being generated throughout the stability program. The Division stated that this should be sufficient to demonstrate that debossing will not affect the release characteristics of aged samples. The Sponsor also stated that they plan to scale up for the validation batches, which will also be debossed and will be placed on stability.

QUESTION 8: *Does the Agency agree that the stability data on the clinical trial materials is adequate to support the commercial blister package? (See Section 12.2.6. Stability Requirements for Blister Packaging 9.3.)*

FDA RESPONSE: A comparison of the blisters used in the stability studies and the to-be-marketed blisters should be provided in the NDA demonstrating that the commercial packaging will provide equal or better protection. In addition, please be aware that drug product packaged in blisters for commercial distribution needs to comply with 16 CFR 1700.14(a)(10) for child resistance. Refer to the US Consumer Product Safety Commission website (<http://www.cpsc.gov/businfo/dreg.html>) for more information.

Additional Discussion at the Meeting:

The Sponsor stated that the clinical supplies have not been packaged in child-resistant blisters, but stated that they want to comply with the requirement for child-resistance and they would change the packaging. The Sponsor provided information on both the _____ material used for the clinical supplies and the _____ lidding to be used for the commercial supplies. _____

b(4)

_____ The drug contact layer for the lidding material of both blisters is identical. There is no change to the _____ layer of the blister. The Sponsor also stated that future batches (see Additional Discussion for Question 8) would be packaged using the _____ material. The Division stated that _____

b(4)

_____ and that the stability data to be submitted in the NDA should provide assurance of this. The Sponsor was advised to include this reasoning in the NDA submission.

b(4)

The Sponsor also asked for clarification on the comparison of the blisters to demonstrate equal or better protection and was advised that, because the packaging site would be changed, some assurance should be provided that the packaging process was comparable, for example, by performing a leak test on blister packs (or a similar functional test).

Safety Topics

QUESTION 9: *Does the Agency agree with the proposed cross referencing and plans for the Safety module of the eCTD? (See Section 12.3.1. Safety References)*

FDA RESPONSE: This question suggests that the Sponsor may be proposing to reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries

for support of safety and/or efficacy. A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on that finding only as it is reflected in the approved labeling for the listed drug.

The Division cannot cross-reference the nonclinical data for NDA 19-281 without specific right of reference from the NDA holder. However, reliance on the current prescribing information for Cyklokapron[®], previous findings of safety for Cyklokapron[®], published nonclinical literature data, and use of data from the three Sponsor-conducted nonclinical studies (Study # TUS0001, TUS0002 and TUS0003) will all support the Safety module of the eCTD. As previously discussed, the Sponsor is encouraged to submit relevant literature articles published since 1986 to support additional nonclinical findings of safety. A complete summary of these literature reports including how they support the nonclinical findings of safety should be included, as well as complete copies of the cited literature.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision [see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)].

If the Sponsor intends to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, it must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). The Sponsor should establish a "bridge" (e.g., via comparative bioavailability data) between the proposed drug product and each listed drug upon which the Sponsor proposes to rely to demonstrate that such reliance is scientifically justified. If the Sponsor intends to rely on literature or other studies for which it has no right of reference but that are necessary for approval, the Sponsor also must establish that reliance on the studies described in the literature is scientifically appropriate.

If the Sponsor intends to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), it should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Additional Discussion at the Meeting:

The Sponsor noted that guidance provided by the Division in 2003 had recommended that they submit the Summary Basis of Approval (SBA) and approved label for the approved tranexamic acid NDA 19-281. The Division clarified that current policy for 505(b)(2) applications specifies that the data from the original NDA and the SBA for that NDA cannot be relied upon in evaluating the current application without a right of reference from the original NDA holder. FDA's prior finding of safety and/or effectiveness, as reflected in the approved labeling, may support the current application. There is no need to submit the SBA for NDA 19-281, as the Division will not review it.

The Sponsor will revise its pharmacology/toxicology tables to represent only their nine-month dog study and their Segment 2 and 3 studies, omitting studies noted in the SBA. The Division requested that the Sponsor's submission of literature supporting

nonclinical safety include a comprehensive summary as well as full copies of all articles referenced. Relevant literature should be submitted regardless of the route of administration.

HANDOUTS:

1. _____ (packaging information)
2. _____ Material (packaging information) **b(4)**
3. European Pharmacopeia Compendial Specifications
4. Japanese Pharmacopeia Compendial Specifications

ACTION: Meeting minutes will be conveyed to the Sponsor within 30 days.

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

6 Page(s) of
Copyright Material
have been Withheld from this
Portion of the Review.

Linked Applications

Sponsor Name

Drug Name

IND 68096

XANODYNE
PHARMACEUTICS INC

TRANEXAMIC ACID 650MG TABLETS

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

/s/

LISA M SOULE
03/18/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,096

Xanodyne Pharmaceuticals, Inc.
Attn: James Young, Ph.D.
Vice President, Product Development and Professional Services
7300 Turfway Road, Suite 300
Florence, KY 41042

Dear Dr. Young:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tranexamic Acid 650 mg Tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 20, 2004 to discuss End of Phase 2 and clinical development.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Medical Team Leader
Division of Reproductive and Urologic
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Date: September 20, 2004
Time: 10:30 AM – 12:00 Noon
Location: PKLN; Conference Room "C"
IND 68,096
Drug: Tranexamic Acid 650 mg Tablet
Indication: Menorrhagia
Sponsor: Xanodyne Pharmaceuticals, Inc.
Meeting Type: Guidance
Meeting Chair: Scott Monroe, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Meeting Recorder: Karen Kirchberg, N.P. - Project Manager, DRUDP (HFD-580)

FDA Attendees:

Donna Griebel, M.D. – Deputy Director, DRUDP (HFD-580)
Scott Monroe, M.D. – Medical Team Leader, DRUDP (HFD-580)
Jennifer Mercier – Chief, Project Management Staff
Lesley Furlong, M.D. – Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Julie Bullock, Pharm.D. – Pharmacokinetics Reviewer, OCPB, DRUDP (HFD-580)
Myong-Jin Kim, Pharm.D. – Pharmacokinetics Reviewer, OCPB, DRUDP (HFD-580)
Wafa Harrouk, Ph.D. – Pharmacology Reviewer, DRUDP (HFD-580)
Sarah Pope, Ph.D. – Chemistry Reviewer, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Karen Kirchberg, N.P. – Project Manager, DRUDP (HFD-580)

External Participants:

James Young Ph.D. – Vice President, Product Development and Professional Services
Keith Moore, Pharm.D. – Senior Director, Clinical Development and Scientific Affairs
Ralph Heasley, Ph.D. – Executive Director, Product Development
Heather Sweeney, Pharm. D. – Medical Affairs Manager

b(4)

Meeting Objective:

To discuss the clinical development program.

Background:

Tranexamic Acid is currently marketed in the U.S. as an injectable for short-term use to treat hemorrhage in a restricted population. Xanodyne is developing a tablet formulation for intermittent, long-term use to treat menorrhagia. The Sponsor plans to file a 505(b)(2) application referencing Pfizer's NDA 19-280 and NDA 19-281.

Discussion:**Clinical Questions and Division's Responses**

1. *Is the pharmacokinetic and safety data obtained during the Phase 1 clinical trials sufficient for Xanodyne to continue into Phase 3 (please see "PK Report Section")?*

Division Response: Yes, the Division notes that the Sponsor is doing dose ranging in Phase 3.

2. *Does the Agency agree with the proposed protocol design for the proposed Phase 3 studies? Specifically: Are the primary and secondary endpoints, sample size, study population, exposure period, and statistical design appropriate? (Please see "Phase 3 Protocols Section")*

Division Response: Based on a review of the draft protocols included in the meeting package, the Division has the following comments:

General Study Design Issues

- The Sponsor needs to clarify the definition of a clinically significant improvement/benefit in the final protocol. The Division notes that the Sponsor chose a sample size to detect a 30-ml difference in menstrual bleeding between treatment and placebo groups, but defines a clinically significant difference as a >50 ml reduction. Furthermore, the Sponsor states that they are asking for an expert opinion about the clinical significance of a 35% reduction in menstrual blood loss. When the Sponsor has settled on an endpoint, the protocol should be consistent throughout. (The Sponsor stated that a >50 ml reduction in menstrual bleeding was the current goal.)
- For Study 301, the Division would like to review the expert opinion(s) regarding the clinical significance of a 35% reduction in menstrual blood loss before commenting on the acceptability of this value. (See question #4.) The Division also recommends that the Sponsor assess what is clinically meaningful to patients. The Division will provide additional comments about the process of determining "what is clinically meaningful" to patients later in the meeting.
- The Division views the _____ as useful and supportive for providing information but does not consider them as adequate for labeling claims. b(4)
- The Division notes that Study 302 is open label and uncontrolled, and the Division acknowledges that such a design will provide only supportive efficacy information. The Division recognizes that there is substantial literature to support efficacy in the 3 to 4 gm dosage range. The Division is willing to consider a single robust efficacy trial for the 3.9 gm dose (i.e., Study 301) with support from the safety trial and the literature. The Division requests that the Sponsor power Study 301 for $P \leq 0.01$ or better if they are planning to support primarily by a single clinical trial. The Division's preference, however, is that the Sponsor conduct 2 adequate and the well-controlled efficacy trials.

If the Sponsor does a second study for efficacy, it can be of shorter duration than the first.

- The Division further notes that the Sponsor has not defined the PBAC, nor is the Sponsor planning to validate the PBAC under study conditions before starting Study 302. If the Sponsor has problems with validation, the PBAC data from Study 302 may be uninterpretable.

Sample size: The sample size for Study 301 will need to be recalculated based (1) on our recommendations regarding power if the Sponsor elects to conduct one principal efficacy study and (2) upon final agreement as to the efficacy endpoint or endpoints. The Sponsor indicate that the overall sample size will allow for 10,000 treatment cycles and 200 women completing 1 year of treatment to assess safety. If the Sponsor achieves this, the Sponsor will meet our request for safety exposure, assuming that no safety issues are identified.

Study population: The study population should be as similar as possible to the target population in order to get a realistic assessment of safety and efficacy. For example:

- The Division sees no reason to exclude women based on size of fibroids unless labeling will reflect this exclusion. The Division recommends that fibroid size not be a basis for exclusion since women with fibroids of various sizes are likely to be candidates for this therapy.
- The Division recommends that the Sponsor remove weight restrictions because menorrhagia is a common complaint among overweight women.
- The Division agrees with the exclusion of women who are using oral contraceptives and notes that use of oral contraceptives will be a contraindication in the label.
- IUD users should be allowed into the study. Menorrhagia is a common complaint among women using copper IUDs. Subjects will need to agree to use the IUD at least until the primary efficacy endpoint is assessed.
- Provide a line listing of screening failures with the reason for screening failure when the NDA is filed.

Exposure period: Overall, the proposed exposure is in accord with our previous recommendations, and the Division agrees that the proposal for exposure is adequate unless there are unexpected safety findings. The Division reminds the Sponsor that we require safety data from at least 200 women through one year of treatment at doses as great as or greater than the to-be-marketed dose. Protocol 302 will give the Sponsor that amount of exposure if discontinuation rates are not high.

Statistical design: In addition to our previous comments about the primary efficacy endpoint, the Division has the following comment:

- Study 302 will enroll some women who were in Study 301 to gather additional safety information. From the study description, it appears that some of these women may increase dose levels (from placebo or low dose to high dose) when they enter Study 302. For the descriptive efficacy statistics, provide a breakdown by previous exposure (i.e., naïve, placebo in 301, low dose in 301, or high dose in 301). If Study 301 indicates that 1.95 gm per day is an effective dose, Study 302, as presently proposed, will not provide any supportive efficacy data.

Other Comments:

- The Division recommends that the Sponsor ask women to collect used sanitary products in such a way that blood loss can be assessed daily. (The Sponsor stated that there are technical barriers to doing this with the alkaline hematin method, but that it may be feasible with the PBAC method).

Dosing issues:

- The Division notes that the Sponsor plans to tell women to start tablets up to 8 hours before anticipated start of heavy menstrual bleeding and to take tablets for five days. In addition, women who are less than 80% compliant may be dropped from the study. In contrast, European labeling states that dosing is 3 gm daily for up to 4 days and that treatment should not be started until menstrual bleeding has started. The Division requests that the _____ so that treatment is not started until menstrual bleeding has started and change the wording from, _____ to "for up to five days".
- Women who usually experience one or two days of problem flow should not be dropped from the study if they stop treatment on their light bleeding days.
- The Division plans to consult with a FDA ophthalmologist about the adequacy of the planned ophthalmologic assessment.
- The Division recommends that the protocol include stopping criteria for thrombotic events.
- The Division recommends that subjects who have iron-deficiency anemia receive iron and that the Sponsor propose an exclusion criterion for severe anemia.
- To better detect thrombotic events, the final follow-up should be scheduled for at least one month following the last drug intake instead of the proposed 15 days.

b(4)

3. *Does the Reviewing Division agree with the approach to the use the PBAC as the inclusion criteria for XP12B-MR-302 (please see "Phase 3 Protocols Section)?"*

Division Response:

- As previously discussed, the PBAC method of quantifying blood loss is acceptable as long as the Sponsor validates it by the alkaline hematin method under the conditions of the Sponsor's study (same population, same sanitary pads, tampons, diary card, and so on). The Division will not consider in vitro validation alone as adequate.
- The Sponsor appears to be planning to correlate PBAC with alkaline hematin method within Study 301. If the correlation is poor, then the Sponsor may not get useful efficacy data from Study 302. However, efficacy should be adequately addressed with a strongly powered single efficacy study, or two efficacy studies as recommended earlier.

4. *Xanodyne is gathering expert medical opinion to justify an average reduction in menstrual blood loss of 35% as being clinically significant. Is this approach of using expert medical opinion to set the criteria for a minimally effective dose acceptable to the agency?*

Division Response:

The Division is not able to concur with this approach since it appears that women will be eligible for treatment based primarily on quality of life (QOL) issues and not medical issues. As mentioned earlier, we will need to review the expert opinions and the rationale supporting them. The Division also requests that the Sponsor determines what women with menorrhagia view as a clinically significant change or improvement and incorporate this change, as well as that suggested by the medical experts into the endpoint(s). You should seek guidance from experts in quality of life instrument design and validation as to how to obtain such data.

5. *Xanodyne has proposed to use the Ruta Quality of Life (QOL) instrument in Phase III clinical studies to collect QOL information from patients with heavy menstrual bleeding. Is the use of the Ruta QOL questionnaire acceptable as a validated QOL instrument?*

Division Response:

- If the Sponsor wishes to use a QOL questionnaire for labeling claims, the Division must agree that it is fully validated and the data generated from the instrument must be part of the statistical analysis plan, that is, a pre-specified endpoint. If the Sponsor wishes to use the Ruta questionnaire in this manner, please send us support for its validation, and the Division will request an internal consult. The Division suggests that inclusion of the response to a fully validated QOL instrument be a co-primary endpoint.
 - If the Sponsor plans to use the QOL questionnaire for exploratory analyses, validation is unnecessary.
6. *The agency has expressed concern about the incidence of thromboembolic events with tranexamic acid. The frequency of these thromboembolic events will be monitored and reported in the safety database. Does the agency concur that Xanodyne can use the historical spontaneous incidence rate of thromboembolic events in women from the literature to compare the incidence of these events found in the safety database?*

Division Response: The expected number of thrombotic events for the proposed sample size in the clinical trials is 0 for reproductive aged women who are neither pregnant nor using birth control pills. The occurrence of any serious thrombotic adverse events (e.g., pulmonary embolus) will be a concern.

7. *Does the Agency agree with the proposed strategy to evaluate the potential effect of tranexamic acid on the QT interval (please see "General Investigational Plan Section" and "Electrocardiographic Data Section")?*

Division Response: The Division has not done a detailed QT review of the three Phase 1 PK studies that the Sponsor submitted in the meeting package. The Division cautions the Sponsor that the science of drug effects on QT is rapidly evolving, and the Division does not know what the FDA's position on QT assessments will be when the Sponsor is ready to submit the NDA. However, it is likely that by the time the NDA is submitted, the Agency will have a definite position on assessing all new drugs (new molecules or new indications) thoroughly for their

QT/QTc effects. The Sponsor should consider these concerns during the development of tranexamic acid for this indication.

8. *Does the Agency agree that the proposed Phase 3 clinical trials and the completed Phase 1 studies will be adequate to support approval of the product for the reduction of heavy menstrual bleeding (please see "PK Report Section" and "Phase 3 Protocols Section")?*

Division Response:

- Approval is a review issue. The Division can better address whether the proposed studies will be adequate for submission of a NDA after the Division has reviewed the revised protocols. As noted above, the Division requests that the Sponsor respond to the issues related to the Phase 3 protocols that were brought up in the meeting.
- The Division requests that the Sponsor submit the final study protocols for review prior to initiating the Phase 3 studies. The Sponsor can request a Special Protocol Assessments to ensure a timely review. To facilitate review, please include copies of patient diaries, all QOL instruments, and the case report forms with the finalized protocols.

Administrative Questions

9. *Xanodyne expects to complete the tranexamic clinical program in 2006 or early 2007 and submit the NDA in 2007. Will the Reviewing Division require the NDA to be an electronic submission?*

Division Response: Electronic NDA submissions are not required at this time but the Agency is moving in that direction and it may be required by 2007. The Division recommends an electronic CTD submission.

10. *Will the Reviewing Division allow the different sections of the NDA to be submitted as completed by Xanodyne and will the Reviewing Division implement a "rolling" review process?*

Division Response: A rolling review is offered for selected "fast track" applications. The Division is currently reviewing the request for a "fast track" designation. If "Fast Track" is designated, a Sponsor may submit complete portions as they become available. However, the Division is under no obligation to review the submissions until the complete NDA is submitted. If "Fast Track" is not designated, "pre-submission" sections can be submitted. However, there is no designated review time frame for pre-submissions.

11. *If a rolling review process is acceptable, will the Reviewing Division issue "section complete" or "section incomplete" letters following the review of each section? This would enable Xanodyne to address any questions or deficiencies in a timely manner.*

Division Response: The Division defers answering Questions 11 and 12 at this time. If the request for a Fast Track review is granted (submitted August 17, 2004), the Division will address Questions 11 and 12 at that time.

12. *If individual section letters are issued, would Xanodyne, after all sections have been submitted and reviewed and complete letters are issued by section need to re-submit an administrative NDA, which will contain all complete letters before a final approval letter can be issued?*

Division Response: The Division defers answering this question (see response to Question 11).

13. *Xanodyne has submitted a document to the FDA requesting clarification on the need for drug-drug interaction studies for this product (May 7, 2004, IND 68,096, Correspondence 006). When does the Reviewing Division expect to have an answer regarding this submission?*

Division Response: Based on information that you have provided, the Division concurs that no drug-drug interaction studies are required between tranexamic acid and other drugs that are primarily renally eliminated.

14. *Xanodyne has submitted a request for expedited review (August 17, 2004, IND 68,096, Correspondence 009). When does the Reviewing Division expect to have an answer regarding this submission?*

Division Response: A written response will be sent by October 15, 2004.

Pediatric Studies

15. *Does the Agency agree with Xanodyne's approach to pediatric labeling as addressed in the Pediatric Research Equity Act (please see "Pediatric Deferral Section")?*

Division Response: The pediatric population is likely to have a higher proportion of subjects with clotting disorders and the distribution of other underlying causes also may differ from that in an adult population. The Division therefore request that efficacy in pediatric patients be supported with a clinical trial enrolling adolescents. This can be done as a Phase 4 commitment.

16. *Xanodyne will obtain concordance with the Agency on the pharmacokinetic study's design and will inform the Agency of study initiation as evidence that the study is proceeding. The projected date until which the submission of the study will be deferred is approximately one year after drug approval. Can this study be conducted in the post-approval period and does the Agency agree with the proposed submission date (please see "Pediatric Deferral Section")?*

Division Response: The pediatric study can be conducted in the post-approval period.

Chemistry Manufacturing Controls Questions

17. *Xanodyne does not have any questions.*

Other Comments

Clinical Pharmacology and Biopharmaceutics Comments:

1. The addition of sparse PK sampling is recommended in Phase 3 trials. This is to provide the agency with PK data for the TID dosing regimen. This can be accomplished in two ways, either by (1) including sparse sampling in a Phase 3 protocol where patients can

come in during their 5 day treatment period for a single blood sample or (2) by having an in-patient stay for 10-20 patients with intense PK sampling.

2. For modified release formulations, more than one time point for release (dissolution) specifications is needed. The sponsor should select appropriate dissolution time points, based on the full dissolution profile of the drug product. The selected dissolution time points should sufficiently assure the quality and equivalence of the clinical and stability batches.
3. Information should be provided on effect of renal impairment on tranexamic acid exposure. The Sponsor should refer to the guidance "Pharmacokinetics in patients with impaired renal function – Study design, Data Analysis, and Impact on Dosing and Labeling" to address this issue.
4. In the absolute BA study (XP12B-101) provide the appropriate documentation of the Canadian IV formulation and U.S. IV formulation if the Canadian formulation was used. This can be submitted with the NDA.

Action Items:

- Sponsor to summarize for Division the clinical data that have been obtained or that will be obtained regarding the effects of treatment with tranexamic acid on laboratory parameters of coagulation.
- Meeting minutes to Sponsor by October 20, 2004.

o/c

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/s/

Scott Monroe

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