CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-430

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 28, 2009
To:	Scott Monroe, MD Director Lisa Soule, MD Team Leader Division of Urology and Reproductive Products Office of New Drugs (OND), CDER
Thru:	Robert M. Boucher, MD, MPH, FACS Director Division of Pharmacovigilance II (DPV) Office of Surveillance and Epidemiology (OSE), CDER
From:	Melissa M. Truffa, R.Ph. Associate Director Division of Pharmacovigilance II Office of Surveillance and Epidemiology (OSE), CDER
Subject:	Proposed labeling for Lysteda regarding ocular and venous thromboembolic adverse effects (Contraindications and Warnings/Precautions)
Drug Name(s):	LYSTEDA (tranexamic acid) Tablets
NDA Number:	NDA 022430
Applicant/sponsor:	Xanodyne Pharmaceuticals, Inc.

A May 18, 2009 review of ophthalmologic and venous thromboembolic adverse events by the Division of Pharmacovigilance II (DPV II), Office of Surveillance and Epidemiology noted the following:

- The AERS database contains 7 cases of possible ophthalmologic adverse events associated with tranexamic acid.
- Serious ophthalmological events possibly associated with oral tranexamic acid use requiring interventions and leading to disabilities have been reported but are poorly characterized and lack formal ophthalmic testing.
- Previous labeling for oral and current labeling for intravenous tranexamic acid (Cyklokapron®) include a **Warning** for ophthalmological adverse events, and DPV II believes warnings of ophthalmological events should also be added to the Lysteda label.
- DPV II recommends including visual abnormalities and an ophthalmological examination advisory in the **Warnings and Precautions** section of the proposed label for Lysteda.

A September 22, 2009 meeting with representatives from the Division of Urology and Reproductive Products, DPV II, and Wiley Chambers, M.D., Director for the Division of Anti-Infective and Ophthalmological Products, was convened to discuss the safety data from the Lysteda NDA, the postmarketing ocular adverse events with tranexamic acid, and the proposed labeling to address these safety concerns. Consensus with regard to the proposed labeling for ocular adverse effects **(Contraindications and Warnings/Precautions)** was reached at this meeting between the meeting participants.

DPV II concurs with the proposed labeling for Lysteda (revised October 23, 2009) with regard to ocular adverse effects.

DPV II will continue to monitor postmarketing reports of ocular adverse effects with tranexamic acid.

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

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/s/

MELISSA M TRUFFA
10/28/2009

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10/28/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 8, 2009
To:	Scott Monroe, MD, Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	Robin Duer, RN, MBA Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling, Patient Package Insert
Drug Name(s):	LYSTEDA (tranexamic acid) Tablets
Application Type/Number:	NDA 22-430
Applicant/sponsor:	Xanodyne Pharmaceuticals, Inc.
OSE RCM #:	2009-430

1. INTRODUCTION

On January 30, 2009 the Applicant submitted a new drug application (NDA) for the Agency's review, NDA 22-430 for LYSTEDA (tranexamic acid) Tablets. This NDA included professional labeling in the form of a Package Insert (PI) and patient labeling in the form of a Patient Package Insert (PPI). On March 16, 2009, the Division of Reproductive and Urology Products (DRUP) requested that the Division of Risk Management (DRISK) provide DRUP with a review of the submitted patient labeling. This review is written in response to that request.

2. MATERIAL REVIEWED

- LYSTEDA Tablets Patient Package Insert (PPI) submitted January 30, 2009
- LYSTEDA Tablets Package Insert (PI) revised by DRUP as of June 26, 2009

3. DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

Content and formatting revisions are made to ensure that the information is legible, clear, and patient-friendly. Patient Information that is well designed and clearly worded can help to maximize patient use and understanding of important safety information that is presented.

The draft PPI submitted by the Applicant has a Flesch Kinkaid grade level of 53.2, and a Flesch Reading Ease score of 9.1%. To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8^{th} grade reading level). Our revised PPI has a Flesch Kinkaid grade level of 64.8, and a Flesch Reading Ease score of 7.1%.

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible,
- ensured that the PPI is consistent with the PI,
- removed unnecessary or redundant information

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI and Patient Instructions for Use. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4. CONCLUSIONS AND RECOMMENDATIONS

- We added the standard recommended introductory paragraph in patient information.
- We deleted [redacted]. The purpose of Patient Information is to enhance appropriate use and to provide important information to patients about medications. Preferably information [redacted] should be addressed with the patient separately from the product specific information. b(4)
- In the section heading "What is LYSTEDA [redacted]" we deleted the words [redacted] as that is not the standard section heading used in patient labeling [redacted] was deleted as this information is not appropriate for patient information. b(4)
- We added the section "Who should not take LYSTEDA?" as it is included in patient labeling and explains the Contraindications listed in the PI. The RD should determine if the last three bulleted statements we added should be included in this section. They were mentioned in the CI section of the RD's draft PI but not fully explained.
- In the "What should I tell my healthcare provider before taking LYSTEDA?" section
    - We removed the italics, and have instead used bolding to highlight important text.
    - We revised the pregnancy and breast-feeding statements to be consistent with other patient labeling.
- In the "How should I take LYSTEDA?" section we
    - [redacted]

b(4)

    -

The PPI must be consistent with the PI.

- In the "What are the possible side effects of LYSTEDA?" section
    - we added serious adverse events as listed in the Warnings and Precautions section of the PI.
    - Table 2 in the PI states that additional adverse events occurred in > 3 % of patients taking LYSTEDA and occurred more often than patients taking placebo. The RD should decide if those AEs are important enough to include in this section of the PPI.
- The Applicant's contact information is already included in the "General Information" section at the end of the PPI. To reduce redundancy, we encourage the Applicant to list their contact information in the "General Information" section only; however if the Applicant wants to include their phone number for reporting side effects in the "What are the possible side effects..." section too, they may do so. The additional language must be separated from the verbatim side-effects statement. We propose: "You may also report side effects to Xanodyne Pharmaceuticals, Inc. at 1-877-773-7793

Please let us know if you have any questions.

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/s/

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Jodi Duckhorn
7/8/2009 04:07:30 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 10, 2009
To:	Scott Monroe, MD, Director Division of Reproductive and Urology Products
Thru:	Melina Griffis, R.Ph, Acting Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, R.Ph, Director Division of Medication Error Prevention and Analysis
From:	Anne Crandall, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Lysteda (Tranexamic acid) Modified-release Tablets, 650 mg
Application Type/Number:	NDA # 22-430
Applicant/Applicant:	Xanodyne Pharmaceuticals Inc.
OSE RCM #:	2009-137

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis reviewed the Lysteda labels and labeling and noted that improvements could be made to the blister label and carton labeling to mimimize confusion and to increase readability of information presented on the labels and labeling. The risks we have identified should be addressed prior to drug approval. We provide recommendations in Section 5. Additionally, we noted the Applicant uses the term "modified-release" as part of the established name. The term 'modified-release' is not an official USP dosage form. We recommend CMC remove this designation but defer to them for the proper naming of this particular formulation.

1 BACKGROUND

1.1 INTRODUCTION

The Applicant, Xanodyne Pharmaceuticals Inc., submitted container labels, carton and insert labeling for NDA 22-430 when the request for the proprietary name was reviewed. DMEPA is currently reviewing the proposed name, Lysteda, under a different cover (OSE review # 2009-429). This review reflects DMEPA's evaluation of the labels and labeling.

1.2 REGULATORY HISTORY

The NDA, along with the label and labeling, were submitted January 30, 2009 to the Agency. The proprietary name review request was submitted on March 6, 2009. This NDA was submitted as a 505(b)(2) by Xanodyne Pharmaceuticals with the reference listed drug, Cyklokapron. Cyklokapron was available as a 500 mg tablet (discontinued in 2003) and is now marketed in an injectable formulation indicated for the treatment of patients with hemophilia for short-term use to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. Pharmacia and Upjohn hold the NDA for Cyklokapron.

1.3 PRODUCT INFORMATION

Lysteda is an antifibrinolytic drug indicated 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 recommended dose of Lysteda is two 650 mg taken three times daily (3.9 g/day) for up to 5 days during menstruation. Lysteda will be available as a 650 mg modified release tablet in bottles of 30, 100 and 500. Lysteda will also be available in a 30 tablet carton containing 5 blister cards, each containing 6 tablets.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA conducting a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name,

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

DMEPA reviewed the following labels and labeling submitted by the Applicant on January 30, 2009. See Appendices A through C for pictures of the labels and labeling.

- Container Label: 6 tablets, 30 tablets, 100 tablets, 500 tablets
- Blister Label
- Carton Labeling: 5 blister cards of 6 tablets
- Package Insert (no image)

3 RESULTS AND DISCUSSION

The proposed labels and labeling use the term "modified-release" to describe the dosage form. The term "modified-release" is not a recognized dosage form by USP and the Center for Drug Evaluation and Research Data Standards Manual (CDER DSM). We recommend this be removed from the labels and labeling and defer the final decision to LNC for the appropriate dosage form designation for this product.

3.1 PRESENTATION OF STRENGTH AND ESTABLISHED NAME

Our evaluation also noted that the 650 mg strength is presented in small font on both the carton label and blister label. Both the location and size make the strength less prominent. Additionally, the strength is located in close proximity to the net quantity statement on the carton label. The strength should be revised so that it is displayed more prominently on the principle display panel and should be relocated away from the net quantity so that it appears immediately following the proposed proprietary and established name.

In addition, although the established name is ½ the height of the proprietary name, the established name does not have a prominence commensurate with the proprietary name. Revising the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2) will improve the prominence of the established name.

3.2 WARNING STATEMENT

Finally, the warning on the container label and carton labeling indicates that no more then 3 doses should be taken in a 24 hour period. However as written, the statement is prone to medication errors, as the term dose could be misinterpreted for 1 tablet. This statement should be described in

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[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

number of tablets rather then doses as 6 tablets more clearly states the upper limit allowed for a 24 hour period.

4 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container label, carton labeling and package insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEPA notes problems with the prominence and presentation that is vital to the safe use of the product. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 4.2 that aim at reducing the risk of medication errors. Additionally, the use of the term 'modified-release' is not acceptable and should be removed from all labels and labeling.

4.1 COMMENTS TO THE DIVISION

The use of the term "modified-release" is not acceptable because it is not a recognized dosage form by the United States Pharmacopeia (USP) nor is it in the Center for Drug Evaluation and Research Data Standards Manual (CDER DSM). We defer to the CMC reviewer and if necessary LNC is consulted for further guidance on the appropriate dosage form designation for this product.

We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Darrell Jenkins, OSE project manager, at 301-796-0558.

4.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, 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 ½ 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) which 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 which is currently located to the upper right of the name.
2. Revise the prominence of the established name to ensure that it is ½ 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) which 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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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 18, 2009
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic (DRUP)
Through:	Melissa M. Truffa, RPh, Team Leader Division of Pharmacovigilance II (DPV II)
	Robert M. Boucher, MD, MPH, FACS Acting Deputy Director Division of Pharmacovigilance II Office of Surveillance and Epidemiology (OSE), CDER
From:	Mark Miller, PharmD, Safety Evaluator Division of Pharmacovigilance II (DPV II)
Subject:	VTE and ophthalmologic adverse events
Drug Name(s):	Cyklokapron® and Lysteda™ (tranexamic acid)
Application Type/Number:	NDA 22-430, NDA 19280, NDA 19281
Applicant/sponsor:	Xanodyne Pharmaceuticals, Inc.
OSE RCM #:	2009-496

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EXECUTIVE SUMMARY

This review summarizes cases of venous thromboembolism (VTE) events and ophthalmologic adverse events in the Adverse Event Reporting System (AERS) with tranexamic acid (Cyklokapron®).

In the United States, tranexamic acid (Cyklokapron®) was approved in 1986 for short term use (two to eight days) by intravenous administration in patients with hemophilia, to reduce or prevent hemorrhage and to reduce the need for replacement therapy during and after toothextraction. Xanodyne Pharmaceuticals, Inc. is developing Lysteda™ (tranexamic acid) as a new modified-release (MR) oral dose formulation, new tablet strength (650mg), and new dosage regimen (2 tablets administered 3 times daily for up to 5 days) to treat heavy menstrual bleeding (HMB) as seen in menorrhagia. The NDA for Lysteda™ is currently under review in the Division of Reproductive and Urology Products (DRUP), and DRUP requested the Division of Pharmacovigilance II (DPV II) analyze AERS cases of VTE and ophthalmologic events with tranexamic acid to supplement the NDA review of Lysteda™.

The AERS database contains 40 cases of possible VTE events associated with tranexamic acid (Cyklokapron®). Serious thromboembolic-related events possibly associated with intravenous and oral tranexamic acid leading to one possible death and hospitalizations (N=18) have been reported. Based on the serious outcomes reportedwith the spontaneous postmarketing data, DPV II believes the sponsor's proposal for labeling thromboembolic-related events should be strengthened. DPV II recommends adding thromboembolic-related adverse events to both the Contraindications and the Warnings and Precautions sections of the proposed label for Lysteda™.

The AERS database contains 7 cases of possible ophthalmologic adverse events associated with tranexamic acid (Cyklokapron®). Serious ophthalmological events possibly associated with oral tranexamic acid use requiring interventions and leading to disabilities have been reported but are poorly characterized and lack formal ophthalmic testing. However, the previous labeling for oral and current labeling for intravenous tranexamic acid (Cyklokapron®) includes a Warning for ophthalmological adverse events, and DPV II believes warnings of ophthalmological events should also be added to the Lysteda™ label. DPV II recommends the sponsor include visual abnormalities and an ophthalmological examination advisory in the Warnings and Precautions section of the proposed label for Lysteda™.

1 INTRODUCTION

1.1 BACKGROUND

This review summarizes cases of venous thromboembolism (VTE) events and ophthalmologic adverse events in the Adverse Event Reporting System (AERS) with Cyklokapron® (tranexamic acid). The Division of Reproductive and Urology Products (DRUP) requested the Division of Pharmacovigilance II (DPV II) analyze AERS cases of VTE and ophthalmologic events with Cyklokapron® (tranexamic acid) due to the development and NDA review of Lysteda™ (tranexamic acid). Xanodyne Pharmaceuticals, Inc. is developing Lysteda™ (tranexamic acid) as a new modified-release (MR) oral dose formulation, new tablet strength (650mg), and new dosage regimen (2 tablets administered 3 times daily for up to 5 days) to treat heavy menstrual bleeding (HMB) as seen in Menorrhagia.[1] The NDA for Lysteda™ is currently under review in DRUP.

Tranexamic acid is an antifibrinolytic drug which inhibits breakdown of fibrin. [1]

1.2 REGULATORY HISTORY

In the United States, tranexamic acid (Cyklokapron®) was approved in 1986 for short term use (two to eight days) by intravenous administration in patients with hemophilia, to reduce or prevent hemorrhage and to reduce the need for replacement therapy during and after tooth extraction. Orally administered Cyklokapron® received approval in 1986 for short term (two to eight days, at doses up to 6g/day) for the same hemophilia indication. However, the oral formulation's NDA was withdrawn from the sponsor unrelated to safety concerns. [1]

1.3 PRODUCT LABELING

In regards to VTE events, the proposed labeling for Lysteda™ includes information in the Contraindications section.[2]

- [redacted]

b(4)

VTE events are labeled for the intravenous Cyklokapron® formulation and oral formulation when marketed in 1986, in the Contraindication and Precaution sections[3]:

- **Contraindications:** CYKLOKAPRON tablets and injections are contraindicated in patients with active intravascular clotting.
- **Precautions:** Venous and arterial thrombosis or thromboembolism has been reported in patients treated with CYKLOKAPRON. In addition, cases of central retinal artery and central retinal vein obstruction have been reported. Patients with a history of thromboembolic disease may be at increased risk for venous or arterial thrombosis.

In regards to ophthalmologic adverse events, the proposed Lysteda™ label includes information in the **Animal Toxicology and/or Pharmacology** section under Ocular effects. The section states that no clinically significant retinal changes have been reported in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials. [2]

Ophthalmologic adverse events are labeled for the intravenous Cyklokapron® formulation and oral formulation when marketed in 1986, in the Contraindications and Warnings sections[3]:

- **Contraindications:** CykloKapron® Tablets and Injection are contraindicated in patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity
- **Warnings:** No retinal changes have been reported or noted in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials. However, visual abnormalities, often poorly characterized, represent the most frequently reported postmarketing adverse reaction in Sweden. For patients who are to be treated continually for longer than several days, an ophthalmological examination, including visual acuity, color vision, eye-ground and visual fields, is advised, before commencing and at regular intervals during the course of treatment. Tranexamic acid should be discontinued if changes in examination results are found.

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

For VTE events, AERS was searched on April 1, 2009 using the product name Cyklokapron® and active ingredient tranexamic acid and HLGT Embolism and Thrombosis.

For ophthalmological events, AERS was searched on April 4, 2009 using the product name Cyklokapron® and active ingredient tranexamic acid and System Organ Class (SOC) Eye Disorders, High Level Group Term (HLGT) Neurological Disorders of the Eye, and High Level Term (HLT) Ophthalmic function diagnostic procedures.

2.2 AERS SELECTION OF CASES

For VTE events, the AERS search retrieved 71 reports containing 6 duplicate reports. Using the World Health Organization-UPPSALA Monitoring Centre (WHO-UMC) causality categories (see Appendix 1), 23 cases were unassessable, 2 cases were unlikely, and 40 cases were possible.[4]

For ophthalmological events, the AERS search retrieved 28 reports. Using the WHO-UMC causality categories (see Appendix 1), 20 cases were unassessable, 1 case was unlikely, and 7 cases were possible.[4]

3 RESULTS

AERS contains 40 cases of VTE events possibly associated with tranexamic acid (Cyklokapron®). There were nine deaths and eighteen hospitalizations reported. Sixty percent (24/40) of cases were the oral tranexamic acid formulation. There were thirty-seven foreign reports and no domestic reports. The average total daily dose of tranexamic acid for oral and intravenous formulations were 2780 and 2930 milligrams, respectively. There were 2 cases with a history of thromboembolic disease and 6 cases without a history of thromboembolic disease.

See Appendix 2 for case characteristics and a brief case summary of possible VTE events associated with tranexamic acid (Cyklokapron®).

Six out of seven possible ophthalmological events were associated with oral Cyklokapron® use. Serious reported outcomes were hospitalization, required intervention, and disability. Adverse events were reported from the United States, United Kingdom, Sweden, and India.

See Appendix 3 for a summary of possible ophthalmological adverse events associated with intravenous and oral tranexamic acid (Cyklokapron®).

4 DISCUSSION

Serious thromboembolic-related events possibly associated with intravenous and oral tranexamic acid leading to one possible death and hospitalizations (N=18) have been reported. The nine death reports lack information and contain confounding factors such as surgery and multiple comorbidities which may have contributed towards a VTE event. However, in one death case (ISR#3486917), a 51-year-old female took oral tranexamic acid and subsequently experienced a fatal pulmonary embolism. AERS data contains similar cases in which women treated with oral tranexamic acid for menorrhagia were hospitalized due to a thromboembolic event. Serious thromboembolic-related events with tranexamic acid have been reported in patients with or without a history of thromboembolic disease. Thromboembolic-related events is mentioned in the proposed labeling for Lysteda™ in the Contraindications section.[2] DPV II believes the sponsor's proposal for labeling thromboembolic-related events should be strengthened.

Serious ophthalmological events possibly associated with oral tranexamic acid use requiring intervention and leading to disability have been reported as of April 2009. However, the cases are poorly characterized visual abnormalities lacking formal ophthalmic testing. The visual abnormalities include blindness, hazy and blurred vision, visible purple circles, and Holmes-Adie pupil which is typically characterized by a tonically dilated pupil.[6] The proposed Lysteda™ label includes information about visual abnormalities associated with oral tranexamic acid in the Animal Toxicology and/or Pharmacology section under Ocular effects.[2] The original Cyklokapron® labeling for oral tranexamic acid and current label for intravenous tranexamic acid includes information about visual abnormalities in the **Contraindications** and **Warnings** sections. Specifically, the Warnings section recommends an ophthalmological examination for patients who are treated continually for longer than several days. The labeling states "visual acuity, color vision, eye-ground and visual fields is advised before commencing and at regular intervals during the course of treatment. Tranexamic acid should be discontinued if changes in examination results are found.[3] DPV II believes it is reasonable to request the sponsor add recommendations for a baseline eye examination to the label since the proposed duration of therapy is 5 days with the possibility of multiple courses of therapy. The reviewer is aware that current postmarketing data for ophthalmological events associated with tranexamic acid lacks information to fully evaluate an association. However, labeling for Cyklokapron® indicates the product contains risks of ophthalmological events to the public health. DPV II believes warnings of ophthalmological events should also be added to the Lysteda™ label.

5 CONCLUSION

Serious thromboembolic-related events possibly associated with oral tranexamic acid have been reported. Based on the spontaneous postmarketing data, DPV II believes the sponsor's proposal for labeling thromboembolic-related events should be strengthened.

Serious ophthalmological events possibly associated with oral tranexamic acid use requiring interventions and leading to disabilities have been reported but are poorly characterized and lack formal ophthalmic testing. However, the previous labeling for oral and current labeling for intravenous tranexamic acid (Cyklokapron®) includes a Warning for ophthalmological adverse events and DPV II believes warnings of ophthalmological events should also be added to the Lysteda™ label.

6 RECOMMENDATIONS

DPV II recommends adding thromboembolic-related adverse events to both the Contraindications and the Warnings and Precautions sections of the proposed label for Lysteda™.

Specific recommendations include the following:

- Revised Contraindications section: Patients with active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism and cerebral thrombosis) should not be given tranexamic acid.
- Add Warnings and Precautions sections: Patients with a previous history of thromboembolic disease may be at an increased risk for venous and arterial thrombosis. Although clinical evidence with tranexamic acid documented in published literature shows no significant increase in thrombosis, possible risk of thrombotic complications cannot be ruled out. Venous and arterial thrombosis or thromboembolism as well as cases of central retinal artery and central retinal vein obstruction have been reported with tranexamic acid.

DPV II recommends the sponsor include visual abnormalities and an ophthalmological examination advisory in the Warnings and Precautions section of the proposed label for Lysteda™.

7 REFERENCES

1. Electronic Document Room (EDR), Summary of Clinical Pharmacology Studies. NDA 22-430. Section 2.7.2. Xanodyne Pharmaceuticals, Inc.

2. Lysteda™ (tranexamic acid modified-release tablets) label. NDA 22-430. Label not approved, proposed label revised 01/2009.

3. Cyklokapron® label. NDA 19-280 (oral formulation). NDA 19-281, intravenous formulation label approved September 1999.

4. The use of the WHO-UMC system for standardized case causality assessment. The UPPSALA Monitoring Centre.

5. OPDRA Post Marketing Safety Review. Tranexamic acid (Cyklokapron®) and Neurological events associated with tablets. Martin Pollock, PharmD, Safety Evaluator. November 11, 2000.

6. Adams and Victor's Principles of Neurology-8th Edition. Disorders of Ocular Movement and Pupillary Function, Alterations of the Pupils. Chapter 14, 2005.

APPENDIX 1

World Health Organization-UPPSALA Monitoring Centre (WHO-UMC) Causality Categories

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

APPENDIX 2

Case characteristics for possible VTE events associated with tranexamic acid (Cyklokapron®). AERS was searched on April 1, 2009	
Number of Reports	**N=40**
Age (N=38)	Average: 49 Range: 20-77
Gender (N=40)	Male: 6 cases Female: 34 cases
Most Common Reported Indication	Menorrhagia: 12 reports
Country of Origin	Foreign: 37 cases Unknown: 3 cases
Reported Formulation	Oral: 24 reports Intravenous: 9 reports Unknown: 7 reports
History of thromboembolic disease?	Yes: 2 cases No: 6 cases Not Reported: 32 cases
Reported Total Daily Dosing Oral (N=24) Intravenous (N=9)	Oral, average: 2780 milligrams Intravenous, average: 2930 milligrams
Reported Outcome	Deaths: 9 reports Life Threatening: 7 reports Hospitalization: 18 reports Disabling: 2 reports Other: 4 reports

Brief Summary of possible VTE events associated with tranexamic acid (Cyklokapron®)

ISR Number	Case Number	Reported Outcome	FDA Received Date	Reported total daily Tranexamic dose	Reported formulation	Narrative Comments
3157176	3163799	DE	13-Nov-98	1500	oral	A 77-year-old treated with oral tranexamic acid for hereditary angioedema experienced a fatal pulmonary embolism.
3168510	3178530	DE	8-Dec-98	3000	oral	A 48-year-old female patient developed a pulmonary embolism and died following surgery that was preceded by treatment with Cyklokapron for menorrhagia.
3446352	3425704	DE	19-Jan-00	1500	oral	A 49-year-old female underwent hysterectomy and died from a pulmonary embolism. The patient took tranexamic acid for menorrhagia for three weeks pre-operatively.
3486917	3458947	DE	11-Apr-00	4000	oral	A 51-year-old female took tranexamic acid for menorrhagia and subsequently experienced a fatal pulmonary embolism.
3726241	3119402	DE	18-May-01	6000	U	49-year-old female patient died from a thromboembolism after the use of tretinoin and tranexamic acid for acute promyelocytic leukemia.
4643171	5741856	DE	21-Apr-05	U	U	A 64-year-old female experienced a deep vein thrombosis following Cyklokapron therapy. Patient died due to cardiac arrest.
4695058	5807870	DE	17-Jun-05	1100	Intravenous	A 67-year-old male treated with tranexamic acid pre and post hip replacement surgery died from a pulmonary embolism.
4697330	5808842	DE	20-Jun-05	1360	Intravenous	A 63-year-old male treated with tranexamic acid pre and post hip replacement surgery died from pulmonary embolism.
5809090	6506501	DE	14-Jul-08	2000	Intravenous	Thromboembolic complications most likely due to heparin-induced thrombocytopenia rather than Minirin and Cyklokapron.
1370627	5037343	HO	27-Sep-93	U	oral	Patient taking Cyklokapron was hospitalized due to a cerebral thrombosis.
1854437	5500495	HO	2-Jan-97	2000	oral	A woman developed a deep vein thrombosis after two days of Cyklokapron therapy.
1867023	5512620	HO	8-Jan-97	4000	oral	A 20-year-old female experienced a retinal vein thrombosis on the eighth day of Cyklokapron therapy.
1870169	5515665	HO	14-Nov-96	500	oral	A female experienced deep thrombophlebitis on the fourth day of treatment with Cyklokapron.

3058838	3027737	HO	31-Mar-98	3000	oral	A woman treated with Cyklokapron for 5 days developed a pulmonary embolism.
3068501	3033932	HO	24-Apr-98	4000	oral	51-year-old treated with Cyklokapron for menorrhagia developed a deep vein thrombosis.
3133329	3147202	HO	21-Sep-98	3000	oral	49-year-old female taking Cyklokapron developed a deep vein thrombosis.
3399089	3372785	HO	16-Nov-99	6000	oral	A female patient of unknown age took Cyklokapron for the treatment of menorrhagia experienced a thromboembolic stroke.
3512234	3484742	HO	12-Jun-00	3000	oral	A 38-year-old treated with Cyklokapron for menorrhagia was hospitalized due to a pulmonary embolism.
3579650	3543260	HO	25-Sep-00	1500	oral	A 48-year-old female was treated with Cyklokapron for menorrhagia developed a cerebral thrombosis.
4177637	3996677	HO	25-Aug-03	U	U	A 41-year-old treated with Cyklokapron for epistaxis developed a thrombosis of the superior mesenteric vein.
4241759	4039981	HO	24-Nov-03	U	U	A 44-year-old female treated with tranexamic acid was hospitalized due to an unspecified thrombus.
4377673	4159595	HO	15-Jun-04	U	U	24-year-old female developed renal artery thrombosis during the use of tretinoin and tranexamic acid for acute promyelocytic leukemia.
5028283	6072296	HO	13-Jun-06	3000	oral	A 64-year-old female experienced a deep vein thrombosis following 12 days of oral Cyklokapron therapy.
5215948	6220867	HO	23-Jan-07	100	Intravenous	40-year-old female treated with NovoSeven, Pro-thromplex, and Cyklokapron during surgery due to retention placenta. One week later, she experienced a right sided pelvis thrombosis.
5245788	6244538	HO	23-Feb-07	U	Intravenous	A male adult patient given Cyklokapron to prevent post operative bleeding developed a thrombus.
5863664	6734605	HO	28-Aug-08	U	Intravenous	Patient treated with multiple medications including NovoSeven and tranexamic acid due to uncontrollable postoperative blood loss. Patient subsequently developed middle cerebral artery thrombosis.
5965797	6821301	HO	25-Nov-08	1500	oral	Extensive venous thrombosis following administration of high-dose glucocorticosteroids and tranexamic acid in relapsed Evans syndrome. Article published.
1637575	5289863	LT	24-Aug-95	5600	Intravenous	Patient treated with Cyklokapron experienced a thromboembolism following coronary artery bypass surgery.

1687376	5338127	LT	13-Dec-95	U	oral	A 45-year-old female treated with Cyklokapron following surgery for 2 weeks experienced a pulmonary embolism.
1825943	5472699	LT	8-Nov-96	6000	oral	A women experienced a pulmonary embolism on the third treatment day of tranexamic acid for menorrhagia.
3186043	3197574	LT	26-Jan-99	6000	oral	52-year-old female developed a pulmonary embolism associated with the use of tranexamic acid.
3807526	3692668	LT	10-Oct-01	4000	oral	A 52-year-old experienced a pulmonary embolism in association with tranexamic acid, captopril, and nonmegestrol.
4052663	3860947	LT	30-Jan-03	4000	U	Published article: Venous thrombosis following use of intermediate purity FVIII concentrate to treat patients with Von Willebrand's disease. Patient also administered tranexamic acid four times daily.
4359655	4144188	LT	13-May-04	U	U	The reporting physician concludes that tranexamic acid was the most likely cause of a pulmonary embolism in a patient treated for menorrhagia.
1821725	5468632	DS	15-Oct-96	U	oral	A female developed retinal vein thrombosis associated with the use of Cyklokapron for excessive menstruation.
3194436	3031669	DS	9-Feb-99	1500	oral	48-year-old female treated with Cyklokapron tablets for 5 days. Two months later, the patient developed thrombus in a brain artery.
3394224	3385734	OT	10-Nov-99	U	oral	A 46-year-old treated with tranexamic acid for menorrhagia experienced a retinal artery thrombosis.
4116305	3954415	OT	21-May-03	U	Intravenous	Patient given tranexamic acid during the first 48 postoperative hours developed a deep vein thrombosis.
4286907	4088074	OT	4-Feb-04	1000	oral	A 61-year-old male with a history of ischemic heart disease treated with Cyklokapron developed an acute thrombosis.
5802005	6692207	OT	7-Jul-08	500	Intravenous	Cyklokapron given once preoperatively. Clot formation at the site of operation was noticed.

Outcome: DE=Death, HO=Hospitalization, LT=Life Threatening, DS=Disabling, OT=Other

APPENDIX 3

Brief Summary of possible Ophthalmological events associated with tranexamic acid (Cyklokapron®)

ISR number	FDA Received date	Tranexamic acid dose	Oral or IV formulation	Country	Reported Outcome	Narrative
5995744	12/2008	1 gram injection	Intravenous	India	OT	60-year-old male with past medical history of hypertension was administered tranexamic acid intravenously prior to spinal surgery. The patient experienced complete loss of vision in the left eye. Product discontinued.
4627368	03/2005	Unknown	Oral	United Kingdom	OT	46-year-old female was treated with oral tranexamic acid for menorrhagia for 5 days. The patient experienced Holmes Adie pupil in her left eye. Product was discontinued with no recovery.
4200477	09/2003	1-1.5 grams three times daily	Oral	United Kingdom	HO	48-year-old female took tranexamic acid 1-1.5 grams tid for menorrhagia. After taking the product, she had visual disturbances. Admitted to the hospital due to low hemoglobin.
3730708	05/2001	40 mg daily	Oral	United Kingdom	OT	55-year-old female with past medical history of malignant breast neoplasm and esophageal reflux was treated with tranexamic acid for menorrhagia. The patient developed purple circle visible in the right eye only. Vision worsened. Patient gradually recovered.
1924409	05/1997	Unknown	Oral	United Kingdom	OT	32-year-old male was treated with tranexamic acid for hereditary angioneurotic edema for over 3 years. Patient developed hazy/blurred vision in his right eye. Product discontinued and patient recovered completely.
1554573	02/1995	3-4 grams daily	Oral	Sweden	DS	20-year-old female was treated with tranexamic acid for excessive menstruation. Patient experienced severe visual field defect. Six months later, diagnosed with infarct of retina.
1396346	12/1993	3 grams daily	Oral	United States	RI	60-year-old female with past medical history of chronic renal failure and hypertension was treated with tranexamic acid for dysfibrinogenemia for 2 years. The patient experienced blindness. Product discontinuation led to improvement of vision.

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