

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212020Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 29, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212020
Product Name and Strength:	Tranexamic Acid in 0.7% Sodium Chloride Injection, 1,000 mg/100 mL (10 mg/mL) Intravenous Bag
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
FDA Received Date:	March 27, 2019
OSE RCM #:	018-1457-02
DMEPA Safety Evaluator:	asmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised carton and container labeling for Tranexamic Acid in 0.7% Sodium Chloride Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised carton and container labeling for Tranexamic Acid in 0.7% Sodium Chloride Injection is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Ogbonna, C. Label and Labeling Review for Tranexamic Acid in Sodium Chloride Injection (NDA 212020). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 21. RCM No.: 2018-1457-01

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/s/

CASMIR I OGBONNA
03/29/2019 02:44:13 PM

HINA S MEHTA
03/29/2019 03:35:54 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 21, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212020
Product Name and Strength:	Tranexamic Acid in 0.7% Sodium Chloride Injection, 1,000 mg/100 mL (10 mg/mL) Intravenous Bag
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
FDA Received Date:	March 7, 2019
OSE RCM #:	2018-1457-01
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Tranexamic Acid in 0.7 Sodium Chloride Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a We note Exela stated the outermost sealable carton of 10 units will include a label that contains the serialization requirements.

2 CONCLUSION

The revised container label and carton labeling for Tranexamic Acid in 0.7% Sodium Chloride Injection is unacceptable from a medication error perspective. The route of administration statement is missing the word “Infusion” in it, and the total quantity per volume and the concentration per mL both appears in the same prominence. Thus, we provide recommendations below to revise the product statement of route of administration, and the concentration per mL on the carton and container labeling.

^a Ogbonna C. Label and Labeling Review for Tranexamic Acid in Sodium Chloride Injection (NDA 212020). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 13. RCM No.: 2018-1457.

3 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC

We recommend the following be implemented prior to approval of this NDA 212020:

- A. Revise the statement “(b) (4)” in all the labels (Carton case, Container Intravenous Bag, and Overwrap) to “For Intravenous Infusion Only” for improved clarity and to avoid medication error.
- B. The total quantity per volume (1,000 mg per 100 mL) appears in the same prominence as the concentration per mL (10 mg per mL) in all the labels (Carton case, Container Intravenous Bag, and Overwrap). To improved clarity, revise the strength statement “10 mg per mL” of the concentration per mL to appear less prominent, i.e. decrease the font size of the 10 mg/mL statement.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CASMIR I OGBONNA
03/21/2019 01:22:56 PM

HINA S MEHTA
03/21/2019 06:28:26 PM

Medical Officer's Review of NDA 212020
Ophthalmology Consult

NDA 212020	Submission Date	
Consult Review	Consult Request Date:	February 26, 2019
	Review completed:	March 19, 2019
Product Name:	Tranexamic Acid	
Sponsor:	Exela Pharma Sciences	

Requested: Please review section 4 of the package insert and advise on the contraindication of defective color vision. DHP is reviewing an NDA 212020 of Tranexamic Acid (b) (4) Injection under 505(b)(2). The statement in the section 4, Contraindications of the proposed labeling is taken from the RLD (Cyklokapron, NDA19281): “In patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity [see Warnings (b) (4)].”

In addition, we noted that the oral formulation of tranexamic acid, Lysteda, NDA 22430, did not have this statement. Please advise whether this statement is appropriate based on the latest clinical evidence. The cited contraindication appears to have been in the Cyklokapron label since its initial approval in 1986. The Nov 6, 1985, Medical Officer’s Review (by ET Triantas) noted that eye changes were seen in cats and dogs as described in the excerpt below from the review. No changes were seen in monkeys. The results are also described in the Pharmacology/Toxicology Review (WC vanArsdel, 3rd, Apr 3, 1986).

“In cats I.V. administration of tranexamic acid at 250-500 mg/kg/day for 6 days induced proliferation of the pigmented epithelium at the tapetum lucidum (around the optic disc) and partial detachment of the retina resulting in folding of the outer nuclear layer and incipient atrophy. These changes were irreversible. Lower dosages induced mild pigmentation which was reversible after drug withdrawal. Oral administration of 500-1,500 mg/kg/day to cats and dogs for 16 days showed no evidence of eye damage but longer administration, up to a year at dosages 800 mg/kg/day in dogs induced changes in the reflectivity of the tapetum lucidum and sometimes along the major retinal vessels and also at the anterior eye (ora ciliaris retinae). These changes were similar to those observed after I.V. administration into cats.

I.V. administration of tranexamic acid in 3 dogs at 1 g/kg/day as a 5% solution for 3 days caused salivation, frequent vomiting and less frequently tremors. In addition, myocardial petechiae and necrosis were seen in 1 of these dogs who died in convulsions. Eye change were not observed. Such changes, (“focal accumulation of pigment-laden as well as non-pigmented laden mononuclear cells in the pigmented epithelium projecting into and somewhat compressing the underlying layers of the retina. Also in one eye, there was focal disruption and atrophy of the layer of the rods and cones and the inner nuclear layer”), however, were observed in dogs given 2 g/kg/day for 7 days.

Regarding ocular findings, the Medical Officer's Review concluded that "long-term administration of tranexamic acid (up to 9 years) did not seem to cause retinal damage. Retinal degeneration has been observed in dogs after oral administration of dosages 7 times larger than the maximum clinical dosage (~800 mg/kg/day) for up to a year; also in cats after IV administration of 250-500 mg/kg for 6 days." The proposed labeling for the new tranexamic acid injection product is attached. Please contact the clinical reviewer, Qin Ryan, at 301-796-1449 if there are any questions regarding this consult.

Reviewer's Comments:

Unlike cats and dogs, humans do not have a tapetum lucidum. The significance of tapetum lucidum findings are questionable. In addition to the non-clinical studies in cats and dogs, toxicology studies with evaluation of the retina have been performed in rabbits dosed 500 mg/day for 10 months. No abnormal findings were observed in the rabbit eyes.

Multiple clinical studies have been performed with tranexamic acid administered by a variety of different routes of administration in patients with a variety of conditions including traumatic hyphemas, hereditary angioneurotic oedema, and malignant choroidal melanoma. In some studies, patients were followed for an average of 6 years. No significant effects on the retina have been observed.

Current methodology for following retinal degeneration would involve the use of optical coherence tomography.

Summary: There is good human clinical information to conclude that the retinal findings in cats, dogs and rats are not consistent with findings in humans. There is no evidence of retinal degeneration in humans after years of treatment.

Recommendations:

1. The Contraindication “In patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity (see WARNINGS)” should be removed from the labeling.
2. The previous Warnings:

“Focal areas of retinal degeneration have developed in cats, dogs, and rats following oral or intravenous tranexamic acid at doses between 250 to 1600 mg/kg/day (6 to 40 times the recommended usual human dose) from 6 days to 1 year. The incidence of such lesions has varied from 25% to 100% of animals treated and was dose-related. At lower doses, some lesions have appeared to be reversible.

Limited data in cats and rabbits showed retinal changes in some animals with doses as low as 126 mg/kg/day (only about 3 times the recommended human dose) administered for several days to two weeks.

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.”

are recommended to be revised to read:

“Although not seen in humans, focal areas of retinal degeneration have been observed in cats, dogs and rats following oral or intravenous tranexamic acid at doses between 250 to 1600 mg/kg/day (6 to 40 times the recommended usual human dose) from 6 days to 1 year. No retinal changes have been observed in eye examinations of patients treated with tranexamic acid for up to 8 years. Patients expected to be treated for greater than 3 months may consider ophthalmic monitoring including visual acuity and optical coherence tomography at regular intervals.”

3. In the Precautions section of the labeling, the statement, “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.” is accurate and is recommended to be retained.

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
03/19/2019 09:08:01 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

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Division of Pediatric and Maternal Health Review

Date: February 27, 2019 **Date consulted:** August 24, 2018

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Hematology Products (DHP)

Drug: Tranexamic Acid in Sodium Chloride Injection

NDA: 212020

Applicant: Exela Pharma Sciences

Subject: Pregnancy and Lactation Labeling Formatting Recommendations

Proposed
Indication: in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.

**Materials
Reviewed:**

- July 6, 2018, submission for NDA 212020, a 505(b)(2) for Tranexamic Acid (b) (4) Injection
- August 24, 2018, the Division of Pediatric and Maternal Health (DPMH) consult from the Division of Hematology Products (DHP) for NDA 212020, DARRTS Reference ID 4311474

- November 21, 2017, Package insert for relied-upon listed drug, Cyklokapron (NDA 019281)

Consult Question: “Please review the PLLR conversion and two clinical information amendments related to PLLR (see section 1.11.3).”

INTRODUCTION AND BACKGROUND

On July 6, 2018, Exela Pharma Sciences submitted a 505(b)(2) application for Tranexamic Acid in Sodium Chloride Injection (NDA 212020) relying on FDA’s finding of safety and efficacy for the listed drug, CYKLOKAPRON (tranexamic acid) Injection (NDA 019281).

CYKLOKAPRON was initially approved on December 22, 2008, and is indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.

DHP consulted DPMH on August 24, 2018, to assist with the Pregnancy and Lactation Labeling Rule (PLLR) subsections of labeling.

Tranexamic Acid in Sodium Chloride Injection is a competitive inhibitor of plasminogen activation and at high concentrations a noncompetitive inhibitor of plasmin. Tranexamic Acid in Sodium Chloride Injection has the following drug characteristics:¹

- Half-life of 2 hours after a 1g intravenous dose; antifibrinolytic concentration of tranexamic acid remains in different tissues for approximately 17 hours and in the serum for 7 or 8 hours.
- Molecular weight = 157.2 Daltons

REVIEW

PREGNANCY

Hemophilia and Pregnancy

Hemophilia is a type of bleeding disorder in which the blood does not clot correctly. Hemophilia is typically an inherited disorder; however, in very rare cases, hemophilia can develop in the elderly, in women in later stages of pregnancy or women who have recently given birth. In these rare cases the disorder often resolves itself after treatment. There are two types of hemophilia (hemophilia A and hemophilia B) both of which are caused by a gene mutation. Hemophilia A also known as classic hemophilia is caused by a lack of or low levels in clotting factor VIII. Hemophilia B is caused by a lack of or low levels in clotting factor IX. According to the Centers for Disease Control and Prevention (CDC),² hemophilia occurs in about 1 in every 5,000 male births and hemophilia A is about 4 times more common than hemophilia B. Hemophilia is an x linked recessive chromosome. Hemophilia in females is extremely rare as in this case both x

¹ July 6, 2018, submission for NDA 212020, a 505(b)(2) for Tranexamic Acid (b) (4) Injection.

² Hemophilia, Centers for Disease Control and Prevention, <https://www.cdc.gov/ncbddd/hemophilia/facts.html>, accessed 30 January 2019.

chromosomes would be affected, or one is affected and the other missing. Moreover, a female x chromosome carrier of hemophilia can have hemophilia symptoms.²

According to the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation, the primary treatment for hemophilia type A is concentrated FVIII (also called clotting factor). The primary treatment for hemophilia B is concentrated FIX (also called clotting factor). Also, the MASAC encourages the use of recombinant clotting factor products for both hemophilia type A and hemophilia type B as both are thought to be safer.³ According to MASAC guidelines for perinatal management of women with bleeding disorders and carriers of hemophilia A or B, pregnancy should be managed by a coagulation disorder specialist, an obstetrician and an anesthesiologist all familiar with treating patients with bleeding disorders. Additionally, the MASAC states that pregnant women are not generally at risk for miscarriage unless they have fibrinogen deficiency with a bleeding phenotype with fibrinogen levels below 100 mg/dL or severe factor XII deficiency. The MASAC recommends that these women receive replacement therapy monthly during pregnancy. The MASAC also recognizes that the majority of infants of hemophilia carriers can be safely delivered vaginally and stress the importance of being in the care of a multidisciplinary team of specialist knowledgeable about bleeding disorders.⁴

Nonclinical Experience

Reproduction studies performed in mice, rats, and rabbits have not revealed any evidence of impaired fertility or adverse effects on the fetus due to tranexamic acid.⁵ In a pre-IND correspondence with the Applicant on June 8, 2015, the Agency indicated the following regarding nonclinical studies: “We agree that additional nonclinical pharmacology and toxicology studies are not needed for Exela’s tranexamic acid (b) (4) injection.”⁶

Review of Literature

Applicant’s Review of Literature

The applicant conducted a review of published literature regarding the use of tranexamic acid in pregnant women. The reader is referred to the applicant’s submission for specific search parameters. A summary of the applicant’s search is below.

Kullander (1970),⁷ contains a small study of 12 healthy pregnant women in which tranexamic acid injection (10 mg/kg) was administered 5 to 10 minutes prior to cesarean delivery to determine the amount of drug in the umbilical cord immediately after birth. Maternal blood samples were drawn prior to delivery and 10 to 20 minutes after, and cord samples were also taken post-delivery. Maternal serum samples varied from 10 to 53 µg/mL after injection of 0.10 mg/kg and cord samples were between 4 to 31 µg/mL.

³ Hemophilia A, National Hemophilia Foundation, <https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A>, accessed 30 January 2019.

⁴ MASAC Guidelines for Perinatal Management of Women with Bleeding Disorders and Carriers of Hemophilia A or B, National Hemophilia Foundation, Document #251, 2017.

⁵ NDA 019281, Cyklokapron Package Insert, November 21, 2017.

⁶ June 8, 2017, Pre-IND 126243 Preliminary Meeting Comments, Type B meeting between FDA and Exela, DARRTS Reference ID 3776210.

⁷ Kullander S and I Nilsson, 1970, Human Placental Transfer of an Antifibrinolytic Agent (AMCA), Acta Obstet Gynec Scand, 49:241-242.

Svanberg et al., (1980),⁸ conducted a study of 73 women with placenta abruption, and tranexamic acid injection was administered just before cesarean delivery. Perinatal mortality was 8% and no maternal deaths were reported. The authors note that perinatal death rates of placental abruption at the time of this publication were 33% to 37%. Plasminogen levels were low and fibrin/fibrinogen degradation products were detected in most cases. The authors concluded that the administration of tranexamic acid may have prevented further activation of the fibrinolytic system therefore reducing the amount of fetal death.

In Walzman and Bonnar (1982),⁹ oral tranexamic acid (1g every 8 hours for 7 days) was administered to twelve pregnant women experiencing vaginal bleeding late in the third trimester. Healthy infants were delivered for all 12 subjects (8 vaginal deliveries, 4 cesarean deliveries and 1 infant was delivered at 30 weeks' gestation) and no maternal adverse events were reported. Treatment with tranexamic acid decreased fibrinolytic activity and plasma plasminogen most notably on day 7. In two subjects, reduced fibrinolytic activity was noted in cord samples. Cord blood in these two subjects demonstrated tranexamic acid levels of 9 mg/L and 12 mg/L.

In a systematic search of literature, Peisidis P and R Kadir (2011),¹⁰ reviewed all studies that looked at tranexamic acid exposure during pregnancy and the puerperium period. The analysis included a meta-analysis on three randomized controlled trials that evaluated the reduction in blood loss in women undergoing cesarean delivery exposed to tranexamic acid. The authors reviewed five randomized controlled trials, seven observational studies and 22 case reports. The estimate of combined effects of tranexamic acid compared to placebo from the meta-analysis demonstrated a difference of 32.5 ml reduction in blood loss (95% CI, -4.1 – 69.13, p=0.08). Additionally, tranexamic acid prevented and treated bleeding in the observational studies and case reports. The authors concluded that the administration of tranexamic acid during cesarean and vaginal deliveries reduces the amount of blood loss and the requirement for blood transfusion. See tables in Appendix A for characteristics from each of the publications reviewed by the authors.

In a case controlled clinical trial by Gai M et al., 2004,¹¹ 91 women received tranexamic acid injection 1g 10 minutes prior to cesarean delivery compared to 89 women in the control group. A complete blood count, urinalysis, liver and renal function, prothrombin time and activity were evaluated in both the treatment and the control groups. No complications or adverse events were reported in either group. Tranexamic acid administration reduced the quantity of blood from the cesarean delivery to 2 hours postpartum in the treatment group (42.75 ± 40.45 mL) group compared to (73.98 ± 77.09 mL) the control group. There was also a significant reduction in blood volume from placental delivery to 2 hours postpartum (341.57 ± 148.20 mL) in the

⁸ Svanberg L et al., 1980, Abruption Placentae – Treatment with the fibrinolytic inhibitor tranexamic acid, *Acta Obstet Gynecol Scand*, 59:127-13.

⁹ Walzman M and J Bonnar, 1982, Effects of Tranexamic Acid on the Coagulation and Fibrinolytic Systems in Pregnancy Complicated by Placental Bleeding, *Arch Toxicol*, 5:214-220.

¹⁰ Peisidis P and R Kadir, 2011, Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum, *Informa Healthcare, Expert Opin Pharmacother*, 12(4):503-516.

¹¹ Gai M et al., 2004, Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial, *European Journal Of Obstetrics & Gynecology and Reproductive Biology*, 112:154-157.

treatment group compared to (439.36 ± 191.48) the control group. In a similar follow-up study by Chandraka G and MC Venkateswarlu (2015),¹² 200 patients (100 in treatment group and 100 in control group) were evaluated using similar study parameters and similar results were demonstrated. Reduction in bleeding from delivery to 2 hours post-partum was shown to be 367.7 mL in the treatment group compared to 430.2 mL in the control group. Likewise, total blood loss was reduced by 76.8 mL as compared to the control group. The only side effects reported were nausea and vomiting.

In a randomized case-control study by Mayur et al., (2007),¹³ 100 women undergoing cesarean delivery were randomized to receive tranexamic acid immediately before delivery (n=50) compared to no treatment (n=50). A significant reduction of blood loss was observed in the study group from end of delivery to 2 hours postpartum 75.71 mL compared to control group 133.03 mL. Also, a reduction in the quantity of blood loss from the placenta delivery to 2 hours post-partum was also observed at 372.71 mL in the treatment group compared to 469.70 mL in the control group.

The efficacy and safety of tranexamic acid in reducing blood loss during cesarean delivery was evaluated by Sekhvat L et al., (2008),¹⁴ in a randomized controlled study of 90 pregnant women (45 in treatment group and 45 in control group). In the treatment group, 1 g/mL intravenous was administered 10 minutes prior to delivery. Blood loss was reduced in the tranexamic acid group 28.02 ± 5.53 mL compared to the control group 37.12 ± 8.97 mL. No complications or side effects were reported in either group.

In a case report by Astedt B and I M Nilsson (1977),¹⁵ a pregnant woman with a history of a previous placenta abruption and previous delivery of a stillbirth following massive blood loss was treated during a third pregnancy for fibrinolysis with 1g IV of tranexamic acid every 4 hours for 3 days followed by 1g oral 4 times daily for 7 weeks during the third pregnancy (26-33 weeks gestation) after reported bleeding. Delivery of a healthy newborn occurred in the 34th week gestation.

In an abstract by Lindoff et al., (1993),¹⁶ a retrospective analysis of case records of 2,102 patients with various bleeding disorders during pregnancy were evaluated for the risk of thrombo-embolic complications. Out of the patients evaluated, 256 were treated with tranexamic acid for a mean duration of treatment of 46 days. Two patients in the tranexamic acid group experienced a pulmonary embolism and in the tranexamic acid untreated group three experienced deep vein thrombosis and one pulmonary embolism. No further information was provided.

¹² Chandrakala G and MC Venkateswarlu, 2015, Role of Tranexamic Acid in Control of Blood Loss during and after Caesarean Section, Journal of Dental and Medical Sciences, 14 (5):8-11.

¹³ Mayur G et al., 2007, Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section: A randomized case controlled prospective study, J Obstet Gynecol India, 57(3):227-230.

¹⁴ Sekhvat L et al., 2008, Efficacy of tranexamic acid in reducing blood loss after cesarean section, The Journal of Maternal-Fetal and Neonatal Medicine, 22(1):72-75.

¹⁵ Astedt B and I M Nilsson, 1978, Recurrent abruptio placentae treated with the fibrinolytic inhibitor tranexamic acid, British Medical Journal: 756-757.

¹⁶ Lindoff C et al., 1993, Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications, Thromb Haemost, 70(2):38-40. Abstract.

DPMH's Review of Literature

DPMH conducted a search of published literature using PubMed and Embase regarding tranexamic acid injection exposure during pregnancy using the following search terms, “tranexamic acid injection and fetal malformations,” “tranexamic acid injection and spontaneous abortion and miscarriage,” “tranexamic acid injection embryo-fetotoxicity. In addition to the applicant’s review of literature, no additional relevant data were found for review.

According to *Drugs in Pregnancy and Lactation* by Briggs and Freeman,¹⁷ “No adverse effects attributable to use of tranexamic acid during pregnancy, in either animals or humans, have been reported in the fetus or newborn. The drug crosses the placenta to the fetus, but its reported lack of effect on plasminogen activator activity in the vascular wall (vs. its known effect in the peripheral circulation) may protect the fetus and newborn from potential thromboembolic complications.”

According to Micromedex,¹⁸ “tranexamic acid does cross the placenta. After a tranexamic acid 10-mg/kg IV injection; the concentration in cord blood is about 30 mg/L which is about equal to the maternal concentration.”

Reviewer comment:

The applicant provided a sufficient review of published literature. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH’s opinion of the data submission and recommendations.

LACTATION

Nonclinical Experience

There are no available animal data with regard to tranexamic acid injection and lactation.

Review of Literature

Applicant’s Review of Literature

The applicant provided a review of published literature as well as a summary from LactMed¹⁹ and *Drugs in Pregnancy and Lactation* by Briggs and Freeman.¹⁷

Gilad et al. (2014),²⁰ evaluated the outcomes of infants exposed to tranexamic acid during lactation through follow-up phone interviews from women who contacted the Beilinson Teratology Information Services (BELTIS) with questions about tranexamic acid. The phone interview collected information on lactation, neonatal symptoms and outcomes for ages 1-3

¹⁷ Briggs, GG and Freeman, R., *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Online version: <http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi>.

¹⁸ Tranexamic acid.

<https://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch?navitem=topHome&isToolPage=true#>, accessed 30 January 2019.

¹⁹ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²⁰ Gilad O et al., Outcome Following Tranexamic Acid Exposure During Breastfeeding, *Breastfeeding Medicine*, 9(8):407-410.

years. Outcomes were compared to a matched group of breastfeeding mothers who were using amoxicillin during breastfeeding. The authors rationale for the matching of tranexamic acid breastfeeding mothers to those using amoxicillin was because they consider amoxicillin to be safe during breastfeeding. Twenty-one women who called BELTIS seeking advice about tranexamic acid during breastfeeding were included in the study group. Dose of tranexamic acid ranged from 1500 mg and 4000 mg daily. There was one report of decreased amount of breastmilk and one report of restlessness. No long-term adverse effects were reported.

According to LactMed,¹⁹ “Amounts of tranexamic acid in breastmilk appear to be low. Although an international consensus panel recommended against using tranexamic acid during breastfeeding, a subsequent controlled study found no adverse outcomes among breastfed infants whose mothers took tranexamic acid in dosages up to 4 grams daily during breastfeeding. One center in Canada reports routine use of tranexamic acid 3 grams daily in nursing mothers with bleeding disorders until bleeding stops. If tranexamic acid is required by a mother, it is not a reason to discontinue breastfeeding; however, until more data become available, medical supervision and follow-up of the breastfed infant is recommended. Unpublished data from the manufacturer indicates that the concentration of tranexamic acid in breastmilk is 1% of the peak serum concentration 1 hour after the last dose of a 2-day treatment course. Further details of the study have not been published.”

Drugs in Pregnancy and Lactation by Briggs and Freeman,¹⁷ “Tranexamic acid is excreted into human milk. One hour after the last dose following a 2-day treatment course in lactating women, the milk concentration of the agent was 1% of the peak serum concentrations.”

DPMH’s Review of Literature

DPMH conducted a review of *Medications in Mother’s Milk*²¹ and published literature using PubMed and Embase with the search terms “tranexamic acid injection” and the following terms, “lactation,” or “breast-feeding.” In addition to the applicant’s review of literature, no additional relevant data were found.

Reviewer comment:

The applicant provided a sufficient review of published literature. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH’s opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Reproduction studies performed in mice, rats, and rabbits have not revealed any evidence of impaired fertility or adverse effects on the fetus due to tranexamic acid.⁵ In a pre-IND correspondence with the Applicant on June 8, 2015, the Agency noted, “We agree that additional nonclinical pharmacology and toxicology studies are not needed for Exela’s tranexamic acid (b) (4) injection.”⁶

²¹ Hale, Thomas (2017). *Medications and Mother’s Milk*. Amarillo, Texas. Springer Publishing Company LLC.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature regarding the effects of tranexamic acid and fertility, and no data were found. Additionally, the applicant is proposing to add language to the package insert under WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, PATIENT INFORMATION AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL on the concomitant use of tranexamic acid with oral contraceptives given that oral contraceptives increase the risk of thromboembolic events and tranexamic acid's pharmacological class as an antifibrinolytic. The following is a summary of the submitted published literature to support the inclusion of this language.

A case report by Iacobellis and Iacobellis (2004),²² describes a possible association between acute myocardial infarction and the combined treatment of tranexamic acid and oral contraceptives in a healthy female. A 42-year-old female presented to the emergency room for rapid onset of precordial pain. She was diagnosed with an acute myocardial infarction due to elevated cardiac enzymes and an abnormal electrocardiogram. The patient reported no history of smoking, cardiovascular or metabolic disease and active thrombotic, embolic or hemostatic disorders. However, she was taking tranexamic acid administered intramuscularly at 3 grams daily in divided doses and combined oral contraceptives (ethinylestrodial 20 mcg and gestodene 75 mcg) in order to reduce heavy menorrhagia associated with uterine leiomyoma. The authors believe that the combined pro-thrombotic effect of tranexamic acid and the oral contraceptive may explain the development of the coronary plaque.

Sirker et al. (2008),²³ reports on a 21-year-old female with a history of bleeding diathesis who developed acute inferior wall myocardial infarction after tranexamic acid use. After a successful cesarean section and dental procedure using DDAVP (desmopressin) the patient underwent elective shoulder arthroscopy and decompression from an old tendon injury. One hour prior to surgery she received a single dose of DDAVP and after surgery was given 1g of oral tranexamic acid taken four times daily for one week. Ten days after surgery the patient returned with chest pain and an electrocardiogram revealed an acute inferior ST segment elevation MI. The patient was discharged three days later.

Reviewer comment: DPMH notes that the Sirker et al. (2008) article described above includes the combination of tranexamic acid and desmopressin and not oral contraceptives.

DPMH's Review of Literature

DPMH conducted a review of published literature regarding tranexamic acid exposure and females and males of reproductive potential as well as any publications regarding tranexamic acid in combination with hormonal contraception and cardiovascular risk. No additional data were found.

²² Iacobellis G and G Iacobellis, 2004, Combined Treatment with Tranexamic Acid and Oral Contraceptive Pill Causes Coronary Ulcerated Plaque and Acute Myocardial Infarction, *Cardiovascular Drugs and Therapy*, 18:238-240.

²³ Sirker A et al., 2008, Acute myocardial infarction following tranexamic acid use in a low cardiovascular risk setting, *Br J Haematol*, 141(6):907-8.

Reviewer comment:

The applicant provided a sufficient review of published literature. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

As described earlier in the review, reproduction studies performed in mice, rats, and rabbits have not revealed any evidence of impaired fertility or adverse effects on the fetus due to tranexamic acid, and the applicant was not required to submit any new nonclinical studies as outlined in a pre-IND communication dated June 8, 2015.⁶ Prolonged experience with tranexamic acid exposure in pregnant women during the second and third trimesters, according to published clinical studies and case reports, have not identified a drug-associated risk of miscarriage or adverse maternal or fetal outcomes. However, it should be noted that the majority of published literature includes the administration of tranexamic acid immediately prior to delivery, and there are little data on exposure during pregnancy. In addition, there are no data on first trimester exposure; therefore, there are no data regarding the risk of major birth defects.

Lactation

Tranexamic acid appears to be present in human milk in low amounts. There are no relevant data on the effects on the breastfed infant or the effects on milk products. Because no risk have been identified that would preclude breastfeeding, DPMH recommends the addition of the following risk/benefit statement to the lactation subsection of labeling:

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tranexamic acid injection and any potential adverse effects on the breastfed infant from tranexamic acid injection or from the underlying maternal condition.

Females and Males of Reproductive Potential

Reproduction studies performed in mice, rats, and rabbits have not revealed any evidence of impaired fertility. There is one case report showing a possible association between hormonal contraception use and tranexamic use and an increased risk of acute myocardial infarction. The applicant is proposing to add Warning and Precaution language on the use of tranexamic acid with oral contraceptives given that oral contraceptives increase the risk of thromboembolic events and tranexamic acid's pharmacological class is an antifibrinolytic. Based on these findings, DPMH recommends that language is included under Warnings and Precautions, Drug Interactions and Females and Males of Reproductive Potential warning the prescriber to avoid concomitant use of the tranexamic acid injection with hormonal contraceptives due to the increased risk of thromboembolic events.

LABELING RECOMMENDATIONS

DPMH revised sections, 5.4, 7.1, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

- Risk of thrombosis with concomitant use of hormonal contraceptives: Avoid concomitant use (5.4, 7.1, 8.3)

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.4 Thromboembolic Risk

Concomitant Use of Hormonal Contraceptives

Because tranexamic acid is an antifibrinolytic, the risk of thromboembolic adverse reactions may increase further when hormonal contraceptives are administered with Tranexamic Acid in Sodium Chloride Injection. Avoid concomitant use of Tranexamic Acid in Sodium Chloride Injection with hormonal contraceptives. Venous and arterial thrombosis or thromboembolism has been reported in patients treated with tranexamic acid [*see Drug Interactions (7.1) and Use in Specific Populations (8.3)*].

7.1 Drug Interactions

Avoid concomitant use of Tranexamic Acid in Sodium Chloride Injection with hormonal contraceptives because concomitant use can further increase the risk of thromboembolic adverse reactions associated with tranexamic acid. [*see Warnings and Precautions (5.4) and Use in Specific Populations (8.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published studies, case series and case reports with tranexamic acid use in pregnant women in the second and third trimester and at the time of delivery have not identified a drug- associated risk of miscarriage or adverse maternal or fetal outcomes. There are no reports regarding the use of tranexamic acid during the first trimester of pregnancy; therefore, there are no data regarding the risk of major birth defects with use of tranexamic acid during pregnancy. However, tranexamic acid is known to pass the placenta and appears in cord blood at concentrations approximately equal to maternal concentration (*see Data*). Reproduction studies performed in mice, rats, and rabbits have not revealed any adverse effects on the fetus due to tranexamic acid.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Tranexamic acid passes through the placenta. The concentration in cord blood after an intravenous injection of 10 mg per kg to pregnant women is about 30 mg per liter, as high as in the maternal blood.

8.2 Lactation

Risk Summary

Published literature reports the presence of tranexamic acid in human milk. There are no data on the effects of tranexamic acid on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tranexamic Acid in Sodium Chloride Injection and any potential adverse effects on the breastfed infant from Tranexamic Acid in Sodium Chloride Injection or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Concomitant use of Tranexamic Acid in Sodium Chloride Injection, which is an antifibrinolytic, with hormonal contraceptives may increase the risk of thromboembolic adverse reactions. Advise patients to use an effective alternative (nonhormonal) contraceptive method [see *Warnings and Precautions (5.4) and Drug Interactions (7.1)*].

17 PATIENT COUNSELING INFORMATION

Advise patients using hormonal contraception that combined use with Tranexamic Acid in Sodium Chloride Injection may increase the risk for thromboembolic adverse reactions and to use effective alternative (nonhormonal) contraception with Tranexamic Acid in Sodium Chloride Injection [see *Warnings and Precautions (5.4) Drug Interactions (7.1) and Use in Specific Populations (8.3)*].

Appendix A.

Table 1. Characteristics of randomized trials including exposure to tranexamic acid during pregnancy and postpartum from Peitidis and Kadir 2011 (corresponds to Table 1, page 507 of publication)¹⁰

Study [ref.]	Country	Study design	Sample size	Study groups	Age (years)	Interventions	Dosage/route/ duration	Outcome measures	P value	Adverse effects	Schulz score
<i>Vaginal delivery</i>											
Yang <i>et al.</i> (2001) [7]	China	Multicenter, comparative, randomized	n = 400 primiparas	n = 94 (study) n = 92 (study) n = 92 (study) n = 87 (placebo)	27.6 ± 2.9 27 ± 2.6 28 ± 2.4 28 ± 2.6	Infusion of TA after delivery of fetal shoulders in the first 2 groups and infusion of AMBA in the 3rd group. Measurement of PP blood loss in ml	1 g i.v. 0.5 g i.v. 0.5 gr i.v.	2 h > PP/243.3 ml vs 242.9 ml vs 308.1 ml vs 314.8 ml	< 0.01	Nausea n = 2	B
Bouthors <i>et al.</i> , 2010 [13]	France	Prospective, randomized, case controlled	n = 144	n = 72 (study) n = 72 (placebo)	NS	Infusion of TA in women PP	4 g in 1 h i.v. 1 g/h over 6 h i.v.	2 h PP/46% reduction of blood loss and bleeding time 31 vs 65 min	0.0026	Transient	C
<i>Cesarean section</i>											
Gai <i>et al.</i> (2004) [8]	China	Multicenter, prospective, randomized, case controlled	n = 180 primiparas	n = 91 (study) n = 89 (placebo)	29.71 ± 4.18 29.75 ± 4.01	Infusion of TA 10 min before CS and measurement of PP blood loss in ml	1 g i.v. > 5 min	2 h > CS/42.75 ± 40.45 ml vs 73.98 ± 77.09 ml	0.001	Transient NS	B
Gohel <i>et al.</i> (2007) [10]	India	Prospective, randomized, case controlled	n = 100 primiparas/ multiparas	n = 50 (study) n = 50 (placebo)	24.30 ± 3.65 24.89 ± 3.99	Infusion of TA 20 min before CS and measurement of PP blood loss in ml.	1 g i.v. > 5 min	2 h > CS/75.71 ± 20.02 ml vs 133.03 ± 14.68 ml	0.001	NS	C
Sekhavat <i>et al.</i> (2009) [11]	Iran	Prospective, randomized, case controlled	n = 90 primiparas	n = 45 (study) n = 45 (placebo)	26.2 ± 4.7 27.1 ± 4.1	Infusion of TA 10 min before CS and measurement of PP blood loss in ml	1 gr i.v. > 5 min	2 h > CS/28.0 ± 5.5 ml vs 37.1 ± 19.0 ml	0.000	NS	B
<i>Recurrent miscarriages</i>											
Tetruashvili <i>et al.</i> (2007) [12]	Russia	Prospective, randomized, case controlled	n = 80	n = 40 (study) n = 40 (placebo)	32.1 ± 2.6 31.2 ± 2.5	Administration of TA in women with history of miscarriages and calculation of frequency of bleeding by days	750 mg p.o. 7 days	2.1 ± 0.2 vs 5.6 ± 0.3 days	< 0.01	NS	C

CS: Cesarean section; AMBA: Aminobenzoic acid; PP: Post-partum; NS: Not stated; TA: Tranexamic acid; i.v.: Intravenous; p.o.: per os.

Table 2. Characteristics of observational studies and case series including exposure to tranexamic acid during pregnancy and postpartum from Peitidis and Kadir 2011 (corresponds to Table 2, page 510 of publication)¹⁰

Study [ref.]	Country	Study design	Sample size	Mean age	Indications for treatment with TA	Weeks	Dosage/route	Duration of treatment	Response	Adverse effects, level of evidence*
Svanberg <i>et al.</i> (1980) [14]	Sweden	Prospective, nonrandomized	73 women	NS	Antepartum hemorrhage (placental abruption)	26 –40	1 g i.v. in all patients at 'acute phase' of the hemorrhage. 6 patients received 4 g p.o. for 1 – 12 wks until delivery	1 – 12 wks	No patient had bleeding diathesis	No, 2+
Walzman <i>et al.</i> (1982) [15]	Ireland	Prospective, nonrandomized	12 women	NS	Antepartum hemorrhage	24 – 36	3 g p.o.	7 days	No patient had bleeding diathesis	No, 2+
Bekassy <i>et al.</i> (1990) [16]	Sweden	Prospective, nonrandomized	45 women	NS	Hemostasis after laser cervical conisation	NS	1 g i.v. before surgery + 1 g in surgery + 1 g after surgery	14 days	NS	No, 2-
Lindoff <i>et al.</i> (1993) [17]	Sweden	Prospective, nonrandomized	256 women TA group, 1846 women control	NS	Antepartum hemorrhage, 186 for placental abruption, 68 for placenta previa	NS	3 g daily	152 women > 3 days 104 women > 7 days	No patient had bleeding diathesis	2 patients developed pulmonary embolism after 61 days and 15 days of treatment respectively 4 patients developed embolism in the control group (no TA) OR = 3.6, 95% CL, p > 0.16 (not significant statistically) No, 3
Singh <i>et al.</i> (2003) [20]	UK	Case series	3 women	1st 25 2nd 28 3rd 30	Primary PPH Antepartum hemorrhage Antepartum hemorrhage	Postpartum 30 34	1 g i.v.	1 day	Stopped	No, 3
Chi <i>et al.</i> (2009) [18]	UK	Prospective, nonrandomized	8 women	NS	Prophylaxis of (F)XI deficiency	During labor	3 g i.v. daily	3 – 5 days	NS	No, 2+
Chi <i>et al.</i> (2009) [19]	UK	Prospective, nonrandomized	12 women	NS	Prophylaxis of (F)XI deficiency	Antepartum	NS	NS	NS\$	No, 2-

PPH and 2 secondary (late) PPH occurred despite prophylaxis.

*Scottish Intercollegiate Guidelines Network (SIGN).

^ZIn 11 of these the mother had a positive bleeding history, and in one case tranexamic acid was given in view of a cesarean delivery.

However, 1 primary (early). CL: Confidence level; i.v.: Intravenous; NS: Not stated; OR: Odds ratio; p.o.: per os; PPH: Postpartum hemorrhage; TA: Tranexamic acid.

Table 3. Characteristics case reports including exposure to tranexamic acid during pregnancy and postpartum from Peitidis and Kadir 2011 (corresponds to Table 3, page 511 of publication)¹⁰

Author (year)	Country	Age (years)	Indication (symptomatology)	Concomitant disease	PLT count	Blood loss (ml)	Weeks (period)	Dosage of TA	Duration	Additional treatment	Adverse effects	Response	Pregnancy outcome, level of evidence
Storm <i>et al.</i> (1976) [25]	Denmark	NS	Vaginal bleeding	No	NS	NS	21	4 g p.o.	64 days	No	No	Gradually stopped	Good, 3
Astedt <i>et al.</i> (1978) [38]	Sweden	NS	Placental abruption	No	Normal	NS	26	6 g i.v. + 4 g p.o.	3 days	No	No	Gradually stopped	Good, 3
Sundqvist <i>et al.</i> (1981) [44]	Sweden	35	Coagulopathy	Glanzmann's thrombasthenia	110 × 10 ⁹ L	NS	35	4 g p.o.	1 day	PLT + uterotonics	No	Gradually stopped	Good, 3
Heslop <i>et al.</i> (1986) [29]	Sweden	23	Secondary PPH	Bernard Soulier s.	57 × 10 ⁹ L	NS	PP	3 g p.o.	10 days	PLT + blood + DDAVP-	No	Gradually stopped	Good, 3
Fagher <i>et al.</i> (1990) [39]	Sweden	21	Vaginal bleeding	No	Normal	NS	26	4 g i.v. + 4 g p.o.	1 day 10 days	Terbutaline + CC	Pulmonary embolism	Gradually stopped	Good, 3
Greer <i>et al.</i> (1991) [30]	UK	NS	Secondary PPH	Hemophilia	NS	NS	PP	NS	NS	Cryoprecipitates + PLT	No	Stopped	Good, 3
Hahn (1995) [45]	Sweden	35	Coagulopathy due to amphetamine	No	93 × 10 ⁹ L	NS	23	4 g i.v.	1 day	FFP + fibrinogen	No	Stopped	Good, 3
Alok <i>et al.</i> (1996) [27]	UK	39	Primary PPH due to placenta accreta	No	NS	> 1300	PP	3 g i.v.	1 day	Blood + FFP + colloids + uterotonics	No	Gradually stopped	Good, 3
Dauleh <i>et al.</i> (1997) [46]	Qatar	36	Hematuria due to placenta percreta invasion of bladder	No	NS	4500	36	2 g i.v.	1 day	STH + cystectomy + FFP + colloids	No	Not stopped	Complicated, 3
Selcuk <i>et al.</i> (2001) [31]	Turkey	26	Secondary PPH	Evans syndrome	49 × 10 ⁹ L	NS	PP > 20 days	NS	1 day	Methylergonovin + blood	No	Stopped	Good, 3
Carradice <i>et al.</i> (2002) [28]	New Zealand	16	Multiple hemorrhagic features	Leukemia	23x10 ⁹ L	NS	25	NS	NS	DDAVP + CC + antibiotics	No	Gradually stopped	Complicated*, 3
Poutamo <i>et al.</i> (2003) [40]	Finland	21	Vaginal bleeding after termination	No	NS	NS	16	NS	1 day	Misoprostol + intrauterine alcohol tamponade	No	Gradually stopped	Complicated†, 3

*Preterm delivery of a growth retarded neonate.

‡Massive infection-sepsis the patient was subjected to multiple operations.

§Patient expired.

AFE: Amniotic fluid embolism; CC: Corticosteroids; DDAVP: Desmopresin; FFP: Fresh frozen plasma; i.v.: Intravenous; NS: Not stated; PLT: Platelets; p.o.: per os; PP: Post-partum; PPH: Post-partum hemorrhage;

RF: Villa-recombinant factor VIIa; STH: Subtotal abdominal hysterectomy; TA: Tranexamic acid; TAH: Total abdominal hysterectomy.

Table 3. (cont.)

Author (year)	Country	Age (years)	Indication (symptomatology)	Concomitant disease	PLT count	Blood loss (ml)	Weeks (period)	Dosage of TA	Duration	Additional treatment	Adverse effects	Response	Pregnancy outcome, level of evidence
Bouwmeester <i>et al.</i> (2003) [32]	Netherlands	30	Primary PPH + coagulopathy	No	135×10^9 L	NS	PP	NS	NS	TAH + ligation of iliac arteries + RF-Vlla + FFP	No	Not stopped	Complicated, 3
Gupta <i>et al.</i> (2003) [41]	India	27	Vaginal bleeding due to uterine rupture	No	NS	2000	36	1 g i.v.	1 day	Uterine artery ligation Uterotonics + FFP + blood	No	Gradually stopped	Complicated, 3
Nagar <i>et al.</i> , 2005 [42]	UK	38	Primary PPH and coagulopathy	AFE	48×10^9 L	2000	PP	1 g i.v.	3 days	FFP + blood + PLT + uterotonics	No	Gradually stopped	Complicated
Porteous <i>et al.</i> (2005) [33]	UK	32	Primary PPH	Hemophilia	NS	2600	PP	1 g i.v.	19 days	RF-Vlla + DDAVP + FFP + CC pudendal embolisation	No	Not stopped	Good, 3
Kopec <i>et al.</i> (2005) [34]	Poland	24	Secondary PPH	Bernard Soulier s. PP	50×10^9 /L	NS	PP	NS	NS	DDAVP + uterotonics	No	Stopped	Good, 3
Kriplani <i>et al.</i> (2005) [35]	India	31	Secondary PPH	Bernard Soulier s.	47×10^9 /L	> 1500	PP	500 mg i.v. 500 mg p.o.	1 day 13 days	Blood + FFP	No	Stopped	Good, 3
Prabu <i>et al.</i> (2006) [36]	UK	1st 23	Secondary PPH	Bernard Soulier s.	37×10^9 L	1000	PP	1 g i.v. + 1 g p.o.	1 day	Blood + FFP + colloids + PLT	No	Gradually stopped	Good, 3
		2nd 37	Secondary PPH	Bernard Soulier s.	14×10^9 L	1500	PP	1 g p.o.	1 day	Blood + FFP + colloids + PLT	No	Gradually stopped	Good, 3
Rahman <i>et al.</i> (2008) [37]	UK	37	Primary PPH due to placenta diffusa	Platelet storage pool disease	Normal	8000	PP	1 g i.v. before delivery	1 day	Hysterectomy + blood + PLT + FFP + oxytocin	No	Not stopped	Complicated, 3
Nohira <i>et al.</i> (2008) [43]	Japan	33	Vaginal bleeding due to placenta accreta	No	46×10^9 L	19000	35	4 g i.v.	3 days	Hysterectomy + blood + RF-Vlla + FFP + PLT	No	Not Stopped	Complicated, 3
Anneck <i>et al.</i> (2010) [26]	Germany	36	Primary PPH and coagulopathy	AFE	75×10^9 L	NS	PP	1 g i.v.	1 day	Hysterectomy + blood + FFP + fibrinogen	No	Gradually stopped	Complicated [§] , 3

*Preterm delivery of a growth retarded neonate.

[†]Massive infection-sepsis the patient was subjected to multiple operations.

[§]Patient expired.

AFE: Amniotic fluid embolism; CC: Corticosteroids; DDAVP: Desmopresin; FFP: Fresh frozen plasma; i.v.: Intravenous; NS: Not stated; PLT: Platelets; p.o.: per os; PP: Post-partum; PPH: Post-partum hemorrhage; RF: Vlla-recombinant factor Vlla; STH: Subtotal abdominal hysterectomy; TA: Tranexamic acid; TAH: Total abdominal hysterectomy.

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/s/

CARRIE M CERESA
02/27/2019 09:29:06 AM

MIRIAM C DINATALE
02/28/2019 11:02:59 AM

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02/28/2019 11:10:35 AM

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	NDA 212020
Applicant	Exela Pharma Sciences LLC
Nonproprietary name	Tranexamic Acid in Sodium Chloride Injection Note: No proprietary name was requested
Receipt Date	07/06/18
PDUFA Goal Date	05/06/19
Review Classification	Standard
Proposed Indication (or current indication if unchanged)	In patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.
Dosing Regimen	10 mg/kg body weight intravenously with replacement therapy before tooth extraction and then 3-4 times daily for 2-8 days after extraction
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

Exela Pharma Sciences LLC has submitted NDA 212020 per the 505(b)(2) pathway for Tranexamic Acid in Sodium Chloride Injection. The referenced listed drug is Cyklokapron (tranexamic acid) Injection (NDA 019281; Pharmacia and Upjohn Co).

NDA History for Tranexamic Acid Products:

NDA 19280 Cyklokapron (tranexamic acid injection) [Pharmacia and Upjohn] is active and the RLD for this 505(b)(2).

NDA 19280 Cyklokapron (tranexamic acid tablets) [Pharmacia and Upjohn] is discontinued.

NDA 22430 Lysteda (tranexamic acid tablets) [Ferring Pharms Inc] is active.

There are 15 generic tranexamic acid injection products and 3 generic tranexamic acid tablet products.

Summary: The RLD is the only active NDA for injection tranexamic acid.

Documents Reviewed:

Received 07/06/18

Module 1:

Regional: Form FDA 356h, Cover Letter, Patent and Exclusivity, References, Request for Waiver of Pediatric Studies, Clinical Information Amendment for PLLR, Clinical Information Amendment for Safety, other correspondence, and Labeling

Review Process:

The proposed labeling was reviewed as submitted in PLR format. The RLD USPI is not in PLR format so I referred somewhat to the Lysteda USPI (oral tranexamic acid). There is no USPI for tranexamic acid in PLLR format, so this will be the first. The Applicant conducted a review of the available literature regarding the use of tranexamic acid in pregnant and lactating women and its effects on male and female fertility. I conducted a review of the literature, including tertiary literature sources (e.g., Micromedex) to ensure that the labeling conveys updated information regarding the safe and effective use of tranexamic acid.

Summary of Known PLLR Information***Human Data******Pregnancy***

Based on a study in 12 pregnant women administered tranexamic acid (TA) 10 mg/kg for 5-10 minutes prior to cesarean section delivery, TA crosses the human placenta to the fetus [Acta Obstet Gynec Scand 49; 241-242; 1970]. The Applicant identified 6 published articles reporting findings from 388 women enrolled to randomized controlled trials in which pregnant women received TA during pregnancy and post-partum. Their conclusions are that "tranexamic acid is an effective treatment for antepartum and postpartum hemorrhage with no significant adverse effects to the mother or fetus. The safety profile is good, especially since there are no teratogenic effects in the fetus."

Lactation

A prospective, controlled observational study reported the safety of tranexamic acid use during Lactation in 21 breastfeeding mothers and 42 in a control group (taking amoxicillin, known to be safe for lactating women) [Source: Beilinson Teratology Information Service (BELTIS)]. There was no collection maternal plasma/milk of neonatal plasma drug levels in this study. The authors concluded that "no increase in adverse long-term outcomes was found in infants exposed through breastfeeding to tranexamic acid. Our data in conjunction with previous estimates of very low drug exposure support continuation of breastfeeding in women requiring treatment with tranexamic acid." [Gilad, et al; 9; 407-410; 2014]

Animal Data: The Applicant stated that no relevant animal data was found concerning pregnancy, lactation, or teratogenic effects in the literature search.

Reviewer Comment: We have consulted DPMH to assist with review of the PLLR data submitted in this application.

Patent and Exclusivity Information

The Applicant submitted a Patent Certification stating that there are no relevant patents that claim the reference listed drug, per search of the Orange Book. The Applicant also submitted an Exclusivity Statement that the “Approved Drug Product with Therapeutic Equivalence Evaluation” as of 07/06/18, lists no unexpired exclusivities associated with NDA 019281.

General Labeling Recommendations

In this review, I summarize the DHP labeling recommendations and edits in the Tranexamic Acid in Sodium Chloride Injection labeling. These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Tranexamic Acid in Sodium Chloride Injection.

The following pages contain a summary of the labeling recommendations for the Tranexamic Acid in Sodium Chloride Injection labeling. Given that the scientific review of the labeling is ongoing, the labeling recommendations in this review should be considered preliminary and may not represent DHP’s final recommendations for the Tranexamic Acid in Sodium Chloride Injection labeling.

Summary of Labeling Recommendations (not mentioned in USPI):

Labeling Section	Applicant Proposed Text	Recommended Text	Rationale
Indication Statement (Highlights) and Product Title	(b) (4)	Tranexamic Acid (b) (4) in Sodium Chloride Injection is <u>an antifibrinolytic</u> indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. <u>(1)</u>	-Though the current Indications and Usage guidance recommends that for new indications, we should include age groups in the indication statement to provide clear and consistent communication about the indicated populations for which FDA grants approval, it is not recommended to specify the ages in the indications statement for this 505b2 product labeling as it is not a “new” indication and adding mention of ages here may provide a disadvantage to the innovator or to this product. The indication should remain the same between this and innovator product, other than the revision of NP name, the addition of the EPC and cross-reference to Section 1.

Throughout USPI	(b) (4)	Revised to Tranexamic Acid in Sodium Chloride Injection	Per Debbie Beitzell, Lead for Product Title Guidance and consistent with previously approved 505b2 applications [e.g., Gemcitabine NDA 209604; NP name Gemcitabine Injection].
Highlights, Warnings and Precautions		Recommendation for clinical team.	I advise the clinical team to reconsider the order of the Warnings and Precautions. Of note, the risk of thrombosis warning is 5.5 in this labeling but 5.1 in the Lysteda labeling.
Highlights, Adverse Reactions		Revised to provide a list (b) (4) "Most common adverse reactions are"	Per 21CFR201.57(a)(11), this section must contain "a list of the most frequently occurring adverse reactions." Details are not recommended for this section, as it is intended to be brief. We have revised to reflect the preferred format. (b) (4)
Highlights, Drug Interactions		I recommend adding this subsection.	I advise the clinical team to consider that Lysteda (oral tranexamic acid) has Drug Interactions listed for hormonal contraceptives (incr risk of thrombosis), TPA (decreased efficacy of both products), Factor IX Complex Concentrates, or Anti-Inhibitor Coagulant Concentrates, (incr risk of thrombosis), ATRA (exacerbation of procoagulant effect of ATRA). Please consider whether any are relevant to this product. DO NOTE that this IV indication is in combination with replacement therapy.
Full Prescribing Information, Indications and Usage		Tranexamic Acid in Sodium Chloride Injection is indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.	<i>Corrected the nonproprietary name.</i> (b) (4), (b) (5) consider removing, "prevent" and changing it to, "reduce the risk of hemorrhage. If the indication for a drug is to reduce the risk of the occurrence of a particular clinical outcome, phrases such as "reduce the risk of" or "reduce the incidence of" should be considered rather than using "prevent" in the indication. The use of a term such as prevent may imply a guarantee of success that is not supported by the data. However, for certain indications, the use of terms such as prevent (e.g., for preventive vaccines) or prophylaxis (e.g., drugs for post-exposure prophylaxis) in the indication may be appropriate because, in a given context, these terms are well established and understood by the clinical community. (b) (4), (b) (5)

			(b) (4) I suggest qualifying the term “replacement therapy” as W&P ^(b)₍₄₎ states that TA “should not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor coagulant concentrates, as the risk of thrombosis may be increased”. This conflicts with the indication statement if these are considered replacement therapy.
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Attachment: DRAFT Tranexamic Acid in Sodium Chloride Injection Labeling

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 13, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212020
Product Name and Strength:	Tranexamic Acid in Sodium Chloride Injection, 10 mg/mL (1,000 mg/100 mL) Intravenous Bag
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
FDA Received Date:	July 6, 2018
OSE RCM #:	2018-1457
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Hematology Products (DHP) to review the Prescribing Information (PI), carton labeling, and container labels for Tranexamic Acid in Sodium Chloride Injection, for areas of vulnerability that may lead to medication errors. On July 6, 2018, Exela Pharma Sciences, LLC submitted a 505(b)(2) NDA 212020 for Tranexamic Acid in Sodium Chloride Injection, and relies on Agency's finding of safety and effectiveness for the reference listed drug CYKLOKAPRON (Tranexamic Acid), NDA 019281 held by Pharmacia and Upjohn Co.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the proposed Prescribing Information (PI), carton and container labeling for areas of vulnerability in regards to medication error.

Our review of the proposed PI identified the use of inappropriate symbols that may cause confusion in Section 2 *Dosage and Administration*. We note the use of the word “(b) (4)” as part of the naming of tranexamic acid injection throughout the PI, carton and container. In addition, we identified areas in the PI, carton labeling and container labels that can be modified to improve the clarity of the information presented.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We recommend the removal of “(b) (4)” as part of the naming of Tranexamic Acid in Sodium Chloride Injection throughout the PI, carton and container. We provide recommendations in Section 4.1 for the PI and 4.2 for the carton and container labels to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights and Full Prescribing Information

1. Dosage and Administration

- a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the symbols “>” and “μ” with their intended meaning to prevent misinterpretation and confusion.
- b. Consider stating numbers greater than or equal to 1,000 in tables with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000” (e.g. 1,000 mg instead of 1000 mg), per Draft Guidance: Container and Carton April 2013 (lines 475-476), and ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations.

B. Highlights of Prescribing Information (HPI)

1. Dosage and Administration

- a. Replace the symbol “-” with its intended meaning to prevent misinterpretation and confusion (i.e. Revise “3-4 times” with “3 to 4 times”).
- b. Remove the “(b) (4)” statements as this information can be found in Section 2 of the full PI and is redundant.
- c. Remove “(b) (4)” statements as this information can be found in Section 2 of the PI and is redundant.
- d. We note the use of the terminology “(b) (4)” in addition to “(b) (4)” in different portions of the PI. We recommend consistency among the product packaging terminology to prevent confusion. Revise to “Single-dose bag only. Discard unused portion.”

C. Full Prescribing Information (PI)

1. Dosage and Administration

- a. We recommend maintaining consistency throughout labeling when describing dosing to prevent misinterpretation and confusion. Section 2 states dosing as “10 mg per kg body weight” while in other sections of the PI dosing is described as “10 mg/kg”.
- b. Add section for important administration instructions. This section can be 2.2 and place dosing information in section 2.1. In section 2.2 title it “Important Administration Instructions” add the following: “Inspect Tranexamic Acid in Sodium Chloride Injection visually before use. It should appear as a colorless solution. Do not use Tranexamic Acid in Sodium Chloride Injection if particulate matter or coloration is seen.”
- c. The dosage adjustment for renal function should be described in a separate section. This section should be Section 2.3 and titled “Dosage Adjustment for Renal Impairment”.

4.2 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC

We recommend the following be implemented prior to approval of this NDA212020:

A. Carton Labeling for 10 (b) (4) Bags:

1. The net quantity statement currently presented as “10 units” on the top right is redundant. Remove this statement as the net content is already present on the principle display panel (PDP).
2. Revise product title to current format recommendations. Revise to “Tranexamic Acid in Sodium Chloride Injection”.
3. Consider stating numbers greater than or equal to 1,000 in tables with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000” (e.g. 1,000 mg instead of 1000 mg), per Draft Guidance: Container and Carton April 2013 (lines 475-476), and ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. Revise the strength statement from “1000 mg per 100 mL (10 mg per mL)” to “1,000 mg per 100 mL (10 mg per mL)”.
4. The route of administration is not present on the PDP. We recommend placing the route of administration of the PDP per 21 CFR 201.100(b)(3).
5. Revised the statement “See package insert for complete information on dosing and administration” to “See prescribing information for complete information on dosing and administration” for increased clarity.
6. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

7. Consider revising the statement “Single-Dose Container” to read “Single-Dose Container – Discard Unused Portion” to minimize risk of the entire contents of the vial being given as a single dose.
8. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
9. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.^a The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling.

B. Container for Intravenous Bag Label:

1. See A.2., through A.5., A.7., and A.8.
2. Separate out the route of administration from the single-dose statement. In addition, consider revising the statement “Single-dose” to read “Single-Dose–Discard Unused Portion” to minimize risk of the entire contents of the vial being given as a single dose.

C. Overwrap Label:

1. (b) (4)
Remove this statement as the net quantity of 100 mL in the bag is already on the PDP.
2. See A.2., through A.8.

^a The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tranexamic Acid in Sodium Chloride Injection received on July 6, 2018 from Exela Pharma Sciences, LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Tranexamic Acid in Sodium Chloride Injection and the Listed Drug										
Product Name	Tranexamic acid injection	Cyklokapron (tranexamic acid) ^b								
Initial Approval Date	N/A	December 30, 1986								
Active Ingredient	tranexamic acid	tranexamic acid								
Indication	indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.	Indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.								
Route of Administration	Intravenous injection	Intravenous injection								
Dosage Form	Solution for injection	Solution for Injection								
Strength	1,000 mg/100 mL (10 mg/mL)	100 mg/mL								
Dose and Frequency	Before Extraction: Administer 10 mg/kg body weight of tranexamic acid intravenously with replacement therapy. After Extraction: Administer 10 mg/kg body weight 3-4 times daily for 2-8 days. <u>Patients with Moderate to Severe Renal Impairment:</u> <table><tr><td><u>Serum Creatinine (μmol/L)</u></td><td><u>Tranexamic Acid Intravenous Dosage</u></td></tr><tr><td>120 to 250 (1.36 to 2.83 mg/dL)</td><td>10 mg/kg twice daily</td></tr></table>	<u>Serum Creatinine (μmol/L)</u>	<u>Tranexamic Acid Intravenous Dosage</u>	120 to 250 (1.36 to 2.83 mg/dL)	10 mg/kg twice daily	Immediately before tooth extraction in patients with hemophilia, administer 10 mg per kg body weight of CYKLOKAPRON intravenously together with replacement therapy. Following tooth extraction, intravenous therapy, at a dose of 10 mg per kg body weight three to four times daily. <u>Patients with Moderate to Severe Renal Impairment:</u> <table><tr><td><u>Serum Creatinine (μmol/L)</u></td><td><u>Tranexamic Acid Intravenous Dosage</u></td></tr><tr><td>120 to 250 (1.36 to 2.83 mg/dL)</td><td>10 mg/kg twice daily</td></tr></table>	<u>Serum Creatinine (μmol/L)</u>	<u>Tranexamic Acid Intravenous Dosage</u>	120 to 250 (1.36 to 2.83 mg/dL)	10 mg/kg twice daily
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120 to 250 (1.36 to 2.83 mg/dL)	10 mg/kg twice daily									

	250 to 500 (2.83 to 5.66 mg/dL)	10 mg/kg daily	120 to 250 (1.36 to 2.83 mg/dL)	10 mg/kg twice daily
	>500 (>5.66 mg/dL)	10 mg/kg every 48 hours or 5 mg/kg every 24 hours	250 to 500 (2.83 to 5.66 mg/dL)	10 mg/kg daily
			>500 (>5.66 mg/dL)	10 mg/kg every 48 hours or 5 mg/kg every 24 hours
How Supplied	As a sterile, unpreserved, colorless solution in a single-dose polymeric bag containing 1000 mg tranexamic acid in 100 mL of solution (10 mg/mL) sealed with a Twist Off port and oversealed in an aluminum pouch (NDC 51754-0108-1).		NDC 0013-1114-10 10 × 10 mL single-dose ampules NDC 0013-1114-15 1 × 10 mL single-dose ampule NDC 0013-1114-21 10 × 10 mL single-dose vials	
Storage	Store at 25°C (77°F); excursions permitted to 15°to 30°C (59°to 86°F) [see USP Controlled Room Temperature].		Store at 25°C (77°F); excursions permitted to 15°to 30°C (59°to 86°F) [see USP Controlled Room Temperature].	
Container Closure	Sterile, unpreserved, colorless solution in a single-dose polymeric bag		15 mL (b) (4) glass vial with a rubber stopper and flip-off cap	

^b Cyklokapron [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 DEC 13. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019281>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 13, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, tranexamic acid. Our search identified three previous reviews^{c,d,e}, and we confirmed that our previous recommendations were implemented.

^c Vora N. Label and Labeling Review Memorandum for Cyklokapron (NDA 19281). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 DEC 9. 5 p. OSE RCM No.: 2014-1791-2.

^d Vora N. Label and Labeling Review Addendum for Cyklokapron (NDA 19281). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 NOV 24. 13 p. OSE RCM No.: 2014-1791-1.

^e Vora N. Label and Labeling Review for Cyklokapron (NDA 19281/S-033). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 OCT 28. 13 p. OSE RCM No.: 2014-1791

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Tranexamic Acid in Sodium Chloride Injection labels and labeling submitted by Exela Pharma Sciences, LLC.

- Container label received on July 6, 2018
- Carton labeling received on July 6, 2018
- Prescribing Information (Image not shown) received on July 6, 2018
<\\cdsesub1\evsprod\nda212020\0001\m1\us\114-labeling\draft-labeling\draft-label-text\pi\draft-package-insert.doc>

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	NDA 212020
Applicant	Exela Pharma Sciences LLC
Nonproprietary name	Tranexamic Acid in Sodium Chloride Injection Note: No proprietary name was requested
Receipt Date	07/06/18
PDUFA Goal Date	05/06/19
Review Classification	Standard
Proposed Indication (or current indication if unchanged)	In patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.
Dosing Regimen	10 mg/kg body weight intravenously with replacement therapy before tooth extraction and then 3-4 times daily for 2-8 days after extraction
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

Exela Pharma Sciences LLC has submitted NDA 212020 per the 505(b)(2) pathway for Tranexamic Acid in Sodium Chloride Injection. The referenced listed drug is Cyklokapron (tranexamic acid) Injection (NDA 019281; Pharmacia and Upjohn Co).

NDA History for Tranexamic Acid Products:

NDA 19280 Cyklokapron (tranexamic acid injection) [Pharmacia and Upjohn] is active and the RLD for this 505(b)(2).

NDA 19280 Cyklokapron (tranexamic acid tablets) [Pharmacia and Upjohn] is discontinued.

NDA 22430 Lysteda (tranexamic acid tablets) [Ferring Pharms Inc] is active.

There are 15 generic tranexamic acid injection products and 3 generic tranexamic acid tablet products.

Summary: The RLD is the only active NDA for injection tranexamic acid.

Documents Reviewed:

Received 07/06/18

Module 1:

Regional: Form FDA 356h, Cover Letter, Patent and Exclusivity, References, Request for Waiver of Pediatric Studies, Clinical Information Amendment for PLLR, Clinical Information Amendment for Safety, other correspondence, and Labeling

Review Process:

The proposed labeling was reviewed as submitted in PLR format. The RLD USPI is not in PLR format so I referred somewhat to the Lysteda USPI (oral tranexamic acid). There is no USPI for tranexamic acid in PLLR format, so this will be the first. The Applicant conducted a review of the available literature regarding the use of tranexamic acid in pregnant and lactating women and its effects on male and female fertility. I conducted a review of the literature, including tertiary literature sources (e.g., Micromedex) to ensure that the labeling conveys updated information regarding the safe and effective use of tranexamic acid.

Summary of Known PLLR Information***Human Data******Pregnancy***

Based on a study in 12 pregnant women administered tranexamic acid (TA) 10 mg/kg for 5-10 minutes prior to cesarean section delivery, TA crosses the human placenta to the fetus [Acta Obstet Gynec Scand 49; 241-242; 1970]. The Applicant identified 6 published articles reporting findings from 388 women enrolled to randomized controlled trials in which pregnant women received TA during pregnancy and post-partum. Their conclusions are that "tranexamic acid is an effective treatment for antepartum and postpartum hemorrhage with no significant adverse effects to the mother or fetus. The safety profile is good, especially since there are no teratogenic effects in the fetus."

Lactation

A prospective, controlled observational study reported the safety of tranexamic acid use during Lactation in 21 breastfeeding mothers and 42 in a control group (taking amoxicillin, known to be safe for lactating women) [Source: Beilinson Teratology Information Service (BELTIS)]. There was no collection maternal plasma/milk of neonatal plasma drug levels in this study. The authors concluded that "no increase in adverse long-term outcomes was found in infants exposed through breastfeeding to tranexamic acid. Our data in conjunction with previous estimates of very low drug exposure support continuation of breastfeeding in women requiring treatment with tranexamic acid." [Gilad, et al; 9; 407-410; 2014]

Animal Data: The Applicant stated that no relevant animal data was found concerning pregnancy, lactation, or teratogenic effects in the literature search.

We have consulted DPMH to assist with review of the PLLR data submitted in this application.

Patent and Exclusivity Information

The Applicant submitted a Patent Certification stating that there are no relevant patents that claim the reference listed drug, per search of the Orange Book. The Applicant also submitted an Exclusivity Statement that the “Approved Drug Product with Therapeutic Equivalence Evaluation” as of 07/06/18, lists no unexpired exclusivities associated with NDA 019281.

General Labeling Recommendations

In this review, I summarize the DHP labeling recommendations and edits in the Tranexamic Acid in Sodium Chloride Injection labeling. These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Tranexamic Acid in Sodium Chloride Injection.

The following pages contain a summary of the labeling recommendations for the Tranexamic Acid in Sodium Chloride Injection labeling. Given that the scientific review of the labeling is ongoing, the labeling recommendations in this review should be considered preliminary and may not represent DHP’s final recommendations for the Tranexamic Acid in Sodium Chloride Injection labeling.

Summary of Labeling Recommendations (not mentioned in USPI):

Labeling Section	Applicant Proposed Text	Recommended Text	Rationale
Indication Statement (Highlights) and Product Title	(b) (4)	Tranexamic Acid (b) (4) in Sodium Chloride Injection is an antifibrinolytic indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. (1)	-Though the current Indications and Usage guidance recommends that for new indications, we should include age groups in the indication statement to provide clear and consistent communication about the indicated populations for which FDA grants approval, it is not recommended to specify the ages in the indications statement for this 505b2 product labeling as it is not a “new” indication and adding mention of ages here may provide a disadvantage to the innovator or to this product. The indication should remain the same between this and innovator product, other than the revision of NP name, the addition of the EPC and cross-reference to Section 1.
Throughout USPI		Revised to Tranexamic Acid in Sodium Chloride Injection	Per Debbie Beitzell, Lead for Product Title Guidance and consistent with previously approved 505b2 applications [e.g., Gemcitabine NDA 209604; NP name

			Gemcitabine Injection].
Highlights, Warnings and Precautions	(b) (4)	Recommendation for clinical team.	I advise the clinical team to reconsider the order of the Warnings and Precautions. Of note, the risk of thrombosis warning is 5.5 in this labeling but 5.1 in the Lysteda labeling.
Highlights, Adverse Reactions		Revised to provide a list (b) (4) "Most common adverse reactions are"	Per 21CFR201.57(a)(11), this section must contain "a list of the most frequently occurring adverse reactions." Details are not recommended for this section, as it is intended to be brief. We have revised to reflect the preferred format. (b) (4)
Highlights, Drug Interactions		I recommend adding this subsection.	I advise the clinical team to consider that Lysteda (oral tranexamic acid) has Drug Interactions listed for hormonal contraceptives (incr risk of thrombosis), TPA (decreased efficacy of both products), Factor IX Complex Concentrates, or Anti-Inhibitor Coagulant Concentrates, (incr risk of thrombosis), ATRA (exacerbation of procoagulant effect of ATRA). Please consider whether any are relevant to this product. DO NOTE that this IV indication is in combination with replacement therapy.
Full Prescribing Information, Indications and Usage		Tranexamic Acid in Sodium Chloride Injection is indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.	<i>Corrected the nonproprietary name.</i> (b) (4) consider removing, "prevent" and changing it to, "reduce the risk of hemorrhage. If the indication for a drug is to reduce the risk of the occurrence of a particular clinical outcome, phrases such as "reduce the risk of" or "reduce the incidence of" should be considered rather than using "prevent" in the indication. The use of a term such as prevent may imply a guarantee of success that is not supported by the data. However, for certain indications, the use of terms such as prevent (e.g., for preventive vaccines) or prophylaxis (e.g., drugs for post-exposure prophylaxis) in the indication may be appropriate because, in a given context, these terms are well established and understood by the clinical community. (b) (4) I suggest qualifying the term "replacement therapy" as W&P (b) (4) states that TA "should

			not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor coagulant concentrates, as the risk of thrombosis may be increased". This conflicts with the indication statement if these are considered replacement therapy.
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