CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212020Orig1s000

CLINICAL REVIEW(S)

M E M O R A N D U M

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

Date: April 3, 2019

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products, CDER

Subject: Medical Team Leader Secondary Review
NDA 212020 Tranexamic Acid (b) (4) Injection, 10 mg/mL, intravenous infusion; 505(b)(2) application for indication "in patients with hemophilia for short-term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction"

Sponsor: Excela Pharma Sciences, LLC

Received: July 6, 2018

To: NDA 212020

This submission is a new 505(b)(2) NDA seeking approval of a ready to use injectable formulation of tranexamic acid for intravenous infusion for the approved indication for the listed drug, Cyklokapron (NDA 19-281) for use in patients with hemophilia for short-term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during following tooth extraction. The application is seeking approval for the identical clinical indication as the approved product. The application does not include clinical data and relies upon the FDA finding of efficacy and safety for Cyklokapron.

Tranexamic acid is an antifibrinolytic agent approved as an injectable product (Cyklokapron Injection (NDA 19-281)) for use in patients with hemophilia for short-term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during following tooth extraction (approved December 30, 1986) and as an oral tablet for the treatment of cyclic heavy menstrual bleeding (Lysteda, NDA 22-430)(approved November 13, 2009).

In this submission the sponsor has included:

- A clinical information amendment to support Pregnancy and Lactation Labeling Rule conversion (PLLR)
- A clinical information amendment on safety of tranexamic acid
- Request for a full waiver of the requirement for pediatric studies under Pediatric Research Equity Act (PREA)

- Draft labeling in Physician's Labeling Rule (PLR) format
- Chemistry, manufacturing and controls (CMC) information for the drug substance and the drug product

Review:
The sponsor is seeking approval of Tranexamic Acid (b) (4) Injection, 10 mg/mL, intravenous infusion for the same indication as the approved product Cyklokapron. The sponsor refers to the Reference Listed Drug (RLD) CYKLOKAPRON (Tranexamic Acid), (NDA 019281) held by Pharmacia and Upjohn Co, for which FDA has made a finding of safety and effectiveness as the RLD for this application. The new product is a ready-to-use formulation that differs from the approved product only in that it contains sodium chloride while the RLD does not and the concentration and packaging are different. The CMC information for the application is being reviewed by Chemistry. The following sponsor's table is a side-by-side comparison of the two products.

Exela's Tranexamic Acid Injection, 10 mg/mL, 100 mL IV Bag		**RLD product CYKLOKAPRON[1] (Tranexamic Acid Injection), 100 mg/mL, 10 mL Ampules/vials**	
Ingredients	**Composition**	**Ingredients**	**Composition**
Tranexamic Acid, USP	1000 mg	Tranexamic Acid	1000 mg
Sodium Chloride, USP	700 mg	Sodium Chloride	Absent
Water for Injection, USP	q.s to 100.0 mL	Water for Injection	q.s to 10.0 mL
Container Closure	IV Bag	Container Closure	Vial/Ampule
Route of Administration	Intravenous Infusion	Route of Administration	Intravenous Injection

[1]Information regarding RLD, CYKLOKAPRON (Tranexamic Acid Injection) formulation was obtained from its approved labeling.

The sponsor requested full waiver of the requirement for pediatric studies under Pediatric Research Equity Act (PREA) stating that Excela's proposed product, Tranexamic Acid Injection, has the same active ingredient, indication, dosage form, dosing regimen, and route of administration as that of the reference drug, Cyklokapron.

Reviewer comment: The new product is not a new active ingredient and the sponsor does not propose a new indication, dosage form, dosing regimen or route of administration. Accordingly, the PREA requirement does not apply.

No clinical studies were conducted with the new product and no new clinical data are presented in support of the new product. Accordingly, the sponsor has indicated the Financial Certification is not applicable.

Reviewer comment: This is acceptable. Financial Disclosure is not applicable to this application as no new clinical data has been submitted with this application.

The Clinical Review of the application was completed by Qin Ryan (review final signature in DARRTS, 4/2/2019). The review focused on labeling aspects of the submission, including PLR conversion, clinical data for PLLR and updating labeling safety information. Major aspects of the review included updating the wording for the safety information in the labeling. Notably, Ophthalmology Consult Review (Wiley Chambers, 3/19/2019) provided recommendations for labeling with regard to ocular findings and adverse events, including that 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. Also, consideration was given to ensuring consistency, where appropriate, between labels for the new injectable tranexamic product and the oral tranexamic acid product (Lysteda, NDA 19281) which is approved for a different indication (i.e., "for the treatment of cyclic heavy menstrual bleeding"). See the Clinical Review for detailed discussion of clinical issues and labeling recommendations.

Pregnancy and Lactation Labeling Rule (PLLR) conversion: The sponsor conducted an internet search of the available literature regarding the use of tranexamic acid in pregnant and lactating women and effects of tranexamic acid on male and female fertility. The submission and labeling were reviewed by the Division of Pediatric and Maternal Health (Carrie Ceresa, final signature in DARRTS 2/28/2019) and the review provided recommendations for the PLLR labeling. (See the DPMH review).

Conclusions and Recommendations:
The sponsor has submitted a 505(b)(2) NDA seeking approval of a ready to use injectable formulation of tranexamic acid for intravenous infusion for the approved indication for the listed drug, Cyklokapron (NDA 19-281) for use in patients with hemophilia for short-term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during following tooth extraction. The application does not include new clinical data and relies upon the FDA finding of efficacy and safety for Cyklokapron. The label is updated into PLR format and PLLR conversion has been made. The final wording of the labeling has been developed in discussion with the entire review team.

From a clinical perspective the application may be approved with labeling in PLR format and with PLLR labeling as developed in labeling discussions and negotiation with the sponsor. Wording of the indication is revised to: "is indicated in patients with hemophilia for short-term use (two to eight days) to reduce the risk of hemorrhage during following tooth extraction" to update consistent with current clinical practice.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHY M ROBIE SUH
04/03/2019 05:54:29 PM

CLINICAL REVIEW

Application Type	NDA 505(2)(b)
Submission Number	212020
Submission Code	000
Letter Date	July 6, 2018
Stamp Date	July 6, 2018
PDUFA Goal Date	May 6, 2019
Reviewer Name	Qin Ryan, MD, PhD
Clinical Team Leader	Kathy Robie Suh, MD, PhD
Review Completion Date	March 28, 2019
Established Name	Tranexamic Acid
Trade Name	Tranexamic Acid (b) (4) Injection
Reference NDA	19281, Cyklokapron
Therapeutic Class	Antifibrinolytic agent
Applicant	Exela Pharma Sciences, LLC
Priority Designation	S
Formulation	(b) (4) Injection 10mg/ml
Indication	Reduce hemorrhage during and following tooth extraction
Intended Population	Patients with hemophilia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for Tranexamic Acid (b) (4) Injection was submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to request approval based on therapeutic equivalence of the proposed product to Tranexamic Acid, as defined in the FDA Orange Book for the proposed indication use 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. The reference product is Cyklokapron [Pharmacia and Upjohn], which was initially approved Dec 20, 1986 under NDA 19281. NDA 19281 exclusivity for the indication has been expired.

Cyklokapron (tranexamic acid) NDA 19281 has been previously reviewed and assessed for efficacy and safety. Most recent Cyklokapron labeling update was approved on Nov. 21, 2017. Tranexamic acid also is approved as an orally administered drug (Lysteda, NDA22430) for treatment of cyclic heavy menstrual bleeding. NDA 212020 included safety information based on the label of Lysteda (tranexamic acid, NDA 22430, original approval Nov 13, 2009, last labeling revision Oct 3, 2013), regarding a single case of myocardial infarction after concomitant use of Lysteda and hormonal contraception. Clinical review of the literature found additional myocardial infarction cases that were associated with tranexamic acid use and recommends including the relevant information in the label. In addition, modifications to update and improve the label are recommended based on literature and clinical practice guidelines. Furthermore, because the reference drug labeling (RDL) is not in PLR format, the new product label is updated to comply with PLR formatting. Finally, information regarding tranexamic acid effect in late pregnancy and outcomes were provided in NDA 212020 to support the updating of the tranexamic acid labeling to comply with requirements of PLLR. Along with clinical review, the DPMH team has reviewed these data and advised DHP for labeling review.

Based on the totality of clinical data, this medical reviewer recommends approval of Tranexamic Acid (b) (4) Injection, if pharmacological equivalence is supported adequately, for the indication in patients with hemophilia for short term use (two to eight days) to reduce the risk of hemorrhage during and following tooth extraction.

1.2 Risk Benefit Assessment

Please refer to NDA 19281 approval, Dec 30, 1986.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Tranexamic acid

Proprietary Name: Tranexamic Acid (b) (4) Injection

Applicant: Exela Pharma Science
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC. 28645

Drug Class: Antifibrinolytic agent

2.2 Availability of Proposed Active Ingredient in the United States

Tranexamic acid is marketed in the US as injection (Cyklokapron) for short-term use to reduce the risk of hemorrhage during and following tooth extraction in patients with hemophilia for short term use and as tablets (Lysteda) for the treatment of cyclic heavy menstrual bleeding.

2.3 Summary of Pre-submission Regulatory Activity Related to Submission

May 29, 2018: FDA sent written response to meeting questions. The FDA response stated that an 505(b)(2) application appears to be an acceptable approach, based on the information provided. Also, the critical information regarding 505(b)(2) regulatory pathway was included.

2.4 Pediatric Waiver

A full pediatric waiver request was submitted with NDA 212020 submission. The waiver is granted because the NDA is submitted under 505(b)(2), proposed drug product, Tranexamic Acid Injection, has the same active ingredient, indication, dosage form, dosing regimen, and route of administration as that of the reference drug, Cyklokapron (tranexamic Acid), (NDA 019281) held by Pharmacia and Upjohn Co. Therefore, Pediatric Research Equity Act (PREA) requirements do not apply.

2.5 Other Relevant Background Information

Refer to NDA 19281 and NDA 22430.

3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 19281 and the labeling. PMHS was consulted and provided input for pediatric and PLLR information in the label.

4 Sources of Clinical Data

Refer to NDA 19281.

5 Review of Efficacy

Refer to NDA 19281.

6 Review of Safety

Refer to NDA 19281. In addition, information regarding cardiac toxicity and pregnancy safety submitted in NDA 212020 is reviewed and summarized below. Furthermore, additional information regarding cardiac toxicity, disseminated intravascular coagulation, intracranial hemorrhage, and acquired visual defects, including the ophthalmology consult recommendation is reviewed.

6.1 Myocardial infarction

Three cases were found in Literature.[1-3] Two of the three are likely associated with tranexamic acid use. These two cases are summarized as follows.

A case reported in 2004,[1] a 42-year old Italian female who was receiving concomitant intramuscular Lysteda (tranexamic acid) and oral contraceptive pill as treatment for menorrhagia suffered acute myocardial infarction. The otherwise healthy woman presented in the emergency room with precordial pain. The woman had no history of smoking, cardiovascular or metabolic disease, or thrombotic disorders. An ECG suggested acute myocardial infarction by showing early appearance of deep negative T waves and Q wave present in leads V1 to V4. The woman had been taking tranexamic acid and combined oral contraceptive pills to reduce heavy menorrhagia associated with leiomyoma for 2 months. She was taking 3 grams of tranexamic acid by intramuscular injection daily and the combination of 20 mcg ethinylestradiol and 75 mcg gestodene daily as a contraceptive. A coronary angiogram revealed ulcerative plaque build-up of the left anterior descending artery. This case suggested that the combined hypercoagulability effect of tranexamic acid and contraceptive pill could be responsible for the formation of coronary plaque in a woman with no previous health concerns.

Another case reported in 2002,[3] a 77-year-old woman who received one-week tranexamic acid treatment for intermittent hemoptysis presented with acute chest pain and diagnosed with MI by ECG and troponin, with a cardiac ejection fraction of 45%. Her past medical history was significant for tuberculosis and hypertension. She took tranexamic acid 500 mg bid x 5 days followed by 1 g bid x 2 days. She also takes angiotensin-converting enzyme inhibitors chronically for mild hypertension. A diagnostic angiogram revealed a single vessel disease with a 30% focal stenosis of the middle portion of the left anterior descending artery. Although a causal relationship cannot be firmly established, these clinical case reports suggests the possibility of tranexamic acid administration associated with an increased risk of acute coronary syndrome. The magnitude of the risk deserves further evaluation.

6.2 Conflicts on concomitant use of factor replacement and tranexamic acid

The Warning on Thromboembolic Risk states "Tranexamic acid should not be administered concomitantly with Factor IX Complex concentrates or Anti-Inhibitor Coagulant concentrates, as the risk of thrombosis may be increased." However, the Dosage and administration section states" Before Extraction: Administer 10 mg/kg body weight of Tranexamic Acid in Sodium Chloride injection intravenously with replacement therapy (b) (4) (b) (4)." Also, the indication statement mentions "reduce the need for replacement therapy". These statements appear in conflict and may be confusing to the health professionals.

Both labeling descriptions were taken from RDL. This is most likely an inaccurate wording of RDL, since the statement in the dosage and administration referred to the statement in the Appears this way on original

For several decades, antifibrinolytic drugs, such as tranexamic acid, have been used prophylactically to reduce blood loss. More than a decade ago, several published randomized clinical trials showed that tranexamic acid significantly reduces blood loss and transfusion requirements in patients with a priori healthy coagulation system during elective orthopedic surgery[4-7], cardiac surgery[8-10], and liver surgery[11-12]. Also, a trial demonstrated that tranexamic acid reduced the frequency of re-bleeding and mortality when used during the pre-neurosurgical phase in patients with an aneurismal subarachnoid hemorrhage[13]. The European clinical practice in some hemophilia centers includes the use of factor replacement and adjunctive administration of tranexamic acid in hemarthroses events. A single institution trial evaluated the efficacy and safety of tranexamic acid combined with recombinant factor VIII in patients with severe hemophilia A and suggested simultaneous treatment with tranexamic acid and recombinant factor VIII significantly improved clot stability in the study patients. In this trial, tranexamic acid was given at least 10 minutes after recombinant factor VIII replacement. No clinical data support concomitant administration of Tranexamic acid and factor replacement.

Reviewing recent AABB (former American Association of Blood Banks) citations in patient blood management (2014)[14], which included 203 articles reporting tranexamic acid clinical uses. No reports regarding addition of tranexamic acid to factor replacement therapy were included among these 203 articles. With the advent of substitution therapy, such as emicizumab, and bioengineered novel FVIII and novel FIX products that achieved more effective and longer

bleeding prevention[15], the addition of tranexamic acid to factor replacement therapy is gradually fading out in the clinical practice.

6.3 Pregnancy and Lactation

The applicant submitted literature to support labeling addition regarding pregnancy[16-29] and lactation, as summarized in Table 1.[30, 31]

Table 1: Literature based pregnancy and lactation clinical study data.

Reference	Trial design	Subjects (n)	Result
Kullander 1970	Women about to undergo cesarean section were administered intravenous tranexamic acid, 10 mg/kg, for 5-10 minutes just prior to delivery.	12	Maternal and cord blood samples tested indicate that tranexamic acid crosses the human placenta to the fetus
Svanberg 1980	Women with deliveries complicated by abruptio placentae were given 1 g of tranexamic acid intravenously just before delivery by cesarean section	73	Immediate treatment with tranexamic acid may have prevented further activation of the fibrinolytic system therefore reducing the amount of fetal deaths in abruptio placentae cases
Walzman 1982	Women in second half of pregnancy with vaginal bleeding given tranexamic acid 1 g IV. q8 hrs. for 7 days	12	Tranexamic acid cross placenta
Peitsidis 2011	Literature based metanalysis on reduction of blood loss in women undergoing cesarean sections with the use of tranexamic acid.	3235	The result suggested that tranexamic acid reduces the amount of blood loss after delivery during cesarean sections and virginal deliveries and reduces the requirement for blood transfusion.
Eriksson 1987	n/a	n/a	tranexamic acid is excreted into breast milk in human
Gilad 2014	Prospective, controlled study regarding use of tranexamic acid while breastfeeding.	32:42	No increase in adverse long-term outcomes was found in infants exposed through breastfeeding to tranexamic acid, as previously estimated very low drug exposure support continuation of breastfeeding in women requiring treatment with tranexamic acid.

Source: References.

Pregnancy

Based on a study in 12 pregnant women administered tranexamic acid 10 mg/kg for 5-10 minutes prior to cesarean section delivery, tranexamic acid crosses the human placenta to the fetus[22]. In order to have enough clinical data, the Applicant identified additional literature reporting findings from single arm or randomized trials to meta-analysis study, in which pregnant women received tranexamic acid during pregnancy and post-partum[16-28]. The additional published clinical information did not provide additional safety information, but increased exposure sampled size of the safety data pool to support the Applicant proposed wording for pregnancy and lactation sections to meet PLLR requirements. The applicant's 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

Research has shown that tranexamic acid, orally administered to breastfeeding mothers, can be secreted into breast milk. [30] 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). [31] The tranexamic acid level was not measured in maternal plasma/milk nor neonatal plasma in this study. The applicant 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."

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

Reviewer comments:
The reviewer agrees with the applicant's conclusion. For further detail regarding pregnancy and lactation please see DPMH consult review.

6.4 Use for Trauma Induced Coagulopathy

The proposed labeling adopted following statement from reference drug labeling (RDL):

"Patients with disseminated intravascular coagulation (DIC), who require treatment with tranexamic acid, must be under strict supervision of a physician experienced in treating this disorder."

No indication or dosing recommendations for DIC are in the RDL or proposed product labeling. According to World Health Organization (WHO) world top 10 cause of death analysis, 1.3 million individuals die from severe trauma in year 2016.[32] The Center of Disease Control (CDC) analysis indicated that over 161 thousand individuals die from accidents, which made unintentional injury to be the third leading cause of death in the United States.[33] Therefore, trauma management is critical for life saving. It is known that 25% of patients with trauma has hemostatic abnormality. As an option in trauma management for hemostasis, tranexamic acid long history of use in DIC, or specifically in trauma induced coagulopathy (TIC).[34] The risk versus benefit of this clinical practice has been a long debate and determined in case by case base.[35]

Recently, tranexamic acid has attracted attention for clinical use in the trauma field. In 2010, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial, a large randomized placebo controlled trial that evaluated the efficacy of tranexamic acid in patients with trauma included 20,211 patients from 274 hospitals in 40 countries from Europe and Asia, demonstrated that intravenous administration of TRANEXAMIC ACID improved mortality significantly in trauma patients with significant bleeding.[36,37] After the launch of its sensational results, the main stream treatment protocol in trauma changed worldwide to include TRANEXAMIC ACID administration,[38-48] as shown in Table 2.

These changes were supported by the Cochrane review titled "Antifibrinolytic drug for acute traumatic injury" in 2015 update.[49] However, CRASH-2 trial accounted 99% of the study population in the Cochrane review update, although the update included three trials, two assessed the effect of TRANEXAMIC ACID and the other assessed that of aprotinin. Therefore, the result from pooled analysis of Cochrane update was predominately based on CRASH-2 trial data.

Table 2: Recommendations in the related guidelines worldwide.

Guidelines	Year	Committee	Recommendation
Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines.	2013	The Scientific Standardization Committee on DIC of the International Society on Thrombosis Haemostasis	Trauma patients who present with severe bleeding, characterized by a marked hyperfibrinolytic state could be treated with antifibrinolytic agents (moderate quality).
A practical guideline for the hematological management of major haemorrhage.	2015	British Committee for Standards in Haematology	Adult trauma patients with, or at risk of, major hemorrhage, should be given TXA as soon as possible after injury (grade 1A).
The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition.	2016	The pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma	TXA administration was recommended as early as possible to a trauma patient who is bleeding or at risk of significant hemorrhaging (grade 1A) Consider administration of the first dose of TXA en route to the hospital (grade 2C)
Major trauma: assessment and initial management.	2016	National Clinical Guideline Centre	Use intravenous TXA as soon as possible in patients with major trauma and active or suspected active bleeding. Do not use intravenous TXA more than 3 h after injury in patients with major trauma unless there is evidence of hyperfibrinolysis.

DIC disseminated intravascular coagulation, *TXA* tranexamic acid

On the contrary, tranexamic acid administration following trauma has not been proven to improve survival in US. A recent report of a small randomized trial reported by Moore et al.[50] indicated there was no clear benefit of receiving TRANEXAMIC ACID. Based on the result of their single institutional study, patients who presented to the hospital with physiologic levels of fibrinolysis, who received TRANEXAMIC ACID, had the highest mortality. Moore et al. concluded the role of TRANEXAMIC ACID in mature trauma systems remains unclear, and emerging data supports it may have adverse effects. However, the latest meta-analysis by Nishida et al.[51] (Table 3), in which 70% of pool data was from CRASH-2 trial, resulted the opposite conclusion. The result indicated that TRANEXAMIC ACID may have a survival benefit in trauma patients with significant hemorrhaging. Data and reports from CRASH-2 and the other studies have not been submitted to the agency for review.

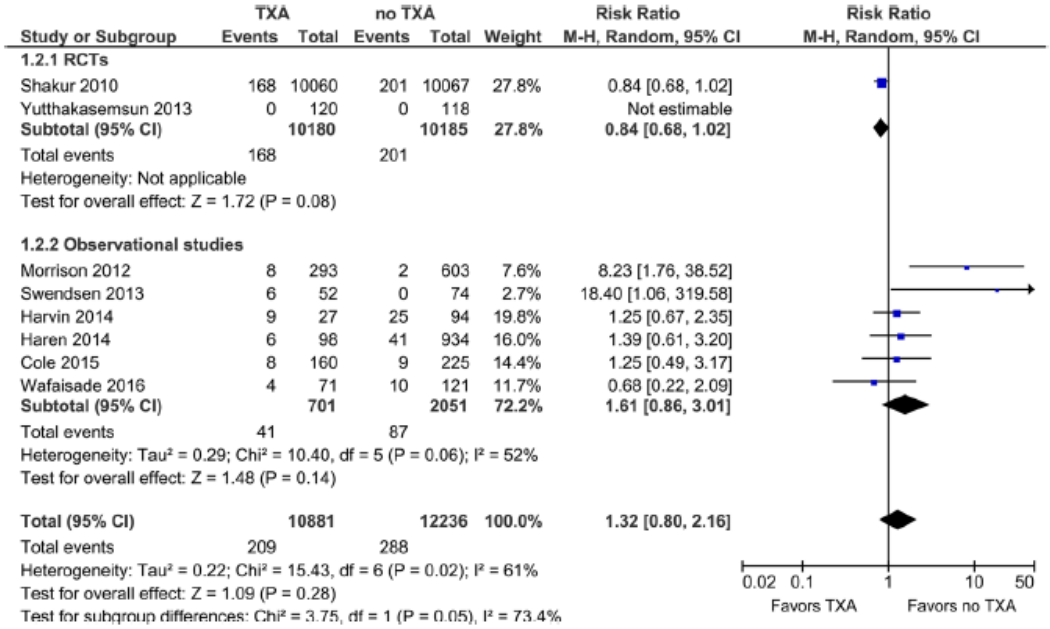
Table 3: Nishida Meta-analysis data pool

Authors	Year	Entry criteria of trauma patients	No. of patients			Mean ISS			Rate of VTE		
			Total	TXA	No TXA	TXA	No TXA	*p* value	TXA (%)	No TXA (%)	*p* value
RCTs											
Shakur et al. [14]	2010	Adult trauma patients with, or at risk of, significant bleeding	20,127	10,060	10,067	N.A.	N.A.	N.A.	1.7[a]	2.0[a]	0.084
Yutthakasemsun et al. [42]	2013	Adult trauma patients with moderate to severe traumatic brain injury (post-resuscitation Glasgow Coma Scale 4 to 12)	238	120	118	N.A.	N.A.	N.A.	0	0	–
Observational studies											
Morrison et al. [38]	2012	Patients who received at least 1 unit of PRBCs within 24 h of admission following combat-related injury	896	293	603	25.2	22.5	<0.001	2.7	0.3	0.001
Swendsen et al. [41]	2013	Adult trauma patients who met triage criteria for serious injury and at least one of the following: hypotension, massive transfusion guideline activation, or transport directly to the operating room or interventional radiology suite	126	52	74	27.1	20.5	0.02	11.5	0	0.004
Haren et al. [43]	2014	Adult trauma patients with hypercoagulable state defined as Greenfield's risk assessment profile (RAP) ≥10	121	27	94	31	26	0.117	33	27	0.492
Harvin et al. [44]	2014	Adult trauma patients with hyperfibrinolysis determined by rapid thrombelastography	1032	98	934	29	14	<0.001	6.3	4.4	0.389
Cole et al. [19]	2015	Adult trauma patients with severe injury defined as injury severity score (ISS) >15	385	160	225	33	29	<0.05	5	4	ns
Wafaisade et al. [45]	2016	Trauma patients with/without prehospital TXA administration	516	258	258	24	24	0.46	5.6	8.3	0.58

ISS injury severity score, *VTE* venous thromboembolism, *RCTs* randomized controlled trials, *TXA* tranexaminc acid, *N.A.* not available, *ns* not significant
[a]These data indicate the rate of pulmonary embolisms

It is still controversial as to whether the administration of TRANEXAMIC ACID is associated with the thrombotic complications. The pooled relative risk of meta-analysis for venous thromboembolisms (VTEs) were 0.84 (95% CI, 0.68-1.02) in the RTCs and 1.61 (95% CI 0.86-3.01) in the observational studies, as shown in Figure 1. The pooled result for RTCs was derived from only CRASH-2 trial, since the other RTC did not report any VTEs. As for observational trials, a significant heterogeneity was observed (I^2 = 52%) in the variability of each study's point estimate: two with significant increased risks (8.2 and 18.4) and three with non-significant increase risk of VTEs, as detailed in Figure 1.[51]

Figure 1: Forest plot of the relative risk of VTE in trauma patients: tranexamic acid TRANEXAMIC ACID versus no TRANEXAMIC ACID



Source: Nishida et al. 2017.
VTEs=venous thromboembolisms, RCTs=randomized controlled trials, M-H=Mantel–Haenszel, CI confidence interval

In conclusion, the available clinical evidence suggested that TRANEXAMIC ACID must be used cautiously and selectively from the perspective of the basic mechanism that TRANEXAMIC ACID potentially possesses the risk of VTEs. Further investigation is needed to delineate the optimal targeted trauma patients to earn the maximum survival benefit with the minimum risk of thrombotic complications. Therefore, this reviewer recommends that the labeling under review should include the statement from the RDL: "Patients with disseminated intravascular coagulation (DIC), who require treatment with tranexamic acid, must be under strict supervision of a physician experienced in treating this disorder."

6.5 Precaution for Acquired Color Synesthesia

The Cyklokapron label has contraindication for patients with acquired defective color vision and the Warning section of the label discusses that visual abnormalities are among the more common adverse reaction reported postmarketing. Acquired forms of synesthesia commonly arise from drug ingestion or neurological disorders, including thalamic lesions and sensory deprivation (e.g., blindness). Cerebral exploration using structural and functional imaging has demonstrated distinct patterns in cortical activation and brain connectivity for controls and synesthetes. Acquired color vision deficits can be part of the presentation of acquired synesthesia.

The proposed labeling included [redacted] (b) (4). In addition, the labeling also proposed "In patients with acquired defective color vision, since this prohibits

measuring one endpoint that should be followed as a measure of toxicity" in contraindication. These wordings are consistent with the Cyklokapron RDL. However, the labeling of Lysteda, an oral formulation of tranexamic acid for a different indication, (NDA19281) does not contain this language.

In DARRTS under Lysteda NDA 19281, The clinical review by Dr. D. Davis (DARRTS dated 11/6/2009) and CDTL review by Dr. LM Soule (DARRTS dated 11/6/2009) for Lysteda, NDA 19281, described that the labeling sections regarding the visual toxicity were based on the data from two randomized clinical trials of Lysteda and the recommendation of ophthalmology consult.

Reviewer comments: The labeling difference for Lysteda regarding ocular safety is based on clinical evidence form randomized placebo-controlled trials, which also supported by the preclinical animal testing. This is unique for the oral tranexamic acid formulation and does not apply to the proposed labeling under this NDA review, because Tranexamic Acid (b) (4) *Injection is an IV formulation like Cyklokapron, an ophthalmology consult has been requested.*

The ophthalmology consult review by Dr. Wiley Chambers for this submission, NDA212020, (DARRTS dated 3/19/2019), summarized the pertinent results in his review:

> "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."

Dr. Chambers then summarized "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."

Dr. Chambers recommended to include the following language for the labeling:

> "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."

Additionally, Dr. Chambers recommended for 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.

Reviewer comment: Agree with the recommendation by ophthalmology consult.

7 Appendices

7.1 Literature Review/References

In addition to NDA 19281, the following reference has been reviewed for this NDA.

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7.2 Labeling Recommendations

The pertinent information from the major components of proposed labeling and reviewer comments are summarized as following.

Proposed Indications:

Tranexamic Acid (b) (4) 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.

Proposed Dosage and Administration

Immediately before tooth extraction in patients with hemophilia, administer 10 mg per kg body weight of tranexamic acid intravenously together with replacement therapy (b) (4)]. Following tooth extraction, intravenous therapy, at a dose of 10 mg per kg body weight three to four times daily, may be used for 2 to 8 days.

Reviewer Comments: The term "replacement therapy", taken from the Cyklokapron RDL, should not be included in either the indication statement or the dosage and administration. See safety review section 6.2 for clinical reasoning and discussion.

For patients with moderate to severe impaired renal function, the following dosages are recommended:

Serum Creatinine (µmol/L)	Tranexamic Acid Intravenous Dosage
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
>500 (>5.66 mg/dL)	10 mg/kg every 48 hours or 5 mg/kg every 24 hours

TRANEXAMIC ACID (b) (4) INJECTION should NOT be mixed with blood. The drug is a synthetic amino acid and should NOT be mixed with solutions containing penicillin.

Dosage forms and strengths:
Injection: 1000 mg of tranexamic acid in 100 mL (10 mg per mL) (b) (4), colorless solution in a single-dose bag for intravenous use.

The premix flexible plastic container bag contains no preservative; therefore, any unused portion should be discarded after each use.

Contraindications
TRANEXAMIC ACID (b) (4) INJECTION is contraindicated:

1. In patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity [see Warnings and Precautions].
2. In patients with subarachnoid hemorrhage. Anecdotal experience indicates that cerebral edema and cerebral infarction may be caused by tranexamic acid in such patients.
3. In patients with active intravascular clotting [see Warnings and Precautions].
4. In patients with hypersensitivity to tranexamic acid or any of the ingredients.

Reviewer comments: The labeling team suggested to remove contraindication #1 regarding defective color vision because the Lysteda labeling does not have this statement. Ophthalmology was consulted and made recommendations for the proposed labeling, see discussion under safety review section 6.5.

Warnings and Precautions

Reviewer general comments: The order of clinical toxicities listed in Warnings and Precautions will be reorganized, as suggested by the deputy director for labeling.

Ocular Effects

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.

Reviewer Comments: This section has been revised as recommended by the ophthalmology consultant. See section 6.5 for details.

Convulsions

Convulsions have been reported in association with tranexamic acid treatment, particularly in patients receiving tranexamic acid during cardiovascular surgery and in patients inadvertently given tranexamic acid into the neuraxial system.

Anaphylactic Reaction

Cases of allergic reaction with use of intravenous tranexamic acid, including anaphylaxis or anaphylactoid reaction have been reported that are suggestive of a causal relationship.

Hepatic Impairment

The dose of TRANEXAMIC ACID (b) (4) INJECTION should be reduced in patients with renal insufficiency because of the risk of accumulation.

Reviewer Comments: 'Hepatic' impairment is a mistake in the subsection title. It should be renal. However, please see clinical pharmacology review for recommendation on renal impairment.

Thromboembolic Risk

Ureteral obstruction due to clot formation in patients with upper urinary tract bleeding has been reported in patients treated with tranexamic acid. Venous and arterial thrombosis or

thromboembolism has been reported in patients treated with tranexamic acid. In addition, cases of central retinal artery and central retinal vein obstruction have been reported. Patients with a previous history of thromboembolic disease may be at increased risk for venous or arterial thrombosis. Tranexamic acid should not be administered concomitantly with Factor IX Complex concentrates or Anti-Inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.

Patients with disseminated intravascular coagulation (DIC), who require treatment with tranexamic acid, must be under strict supervision of a physician experienced in treating this disorder.

Combination hormonal contraceptives are known to increase the risk of venous thromboembolism, as well as arterial thrombosis such as stroke and myocardial infarction. Because tranexamic acid is an antifibrinolytic, concomitant use of hormonal contraception and tranexamic acid may further exacerbate this increased thrombotic risk. Women using hormonal contraception should use tranexamic acid only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event.

Reviewer comments: The language in the above paragraph and the proposed labeling section 7.1 are taken from Lysteda label, based on a single case of myocardial infarction in a 42-year-old female who received concomitant i.m. Lysteda (tranexamic acid) and oral contraceptive, see this review section 6.1 for clinical reasoning and discussion. Furthermore, the statement regarding combination hormonal contraceptives should be revised to simplify and make more general in relevant sections.

In addition, there is a statement in Dose and Administration section that in conflict with one of the thrombosis risk statements above "Tranexamic acid should not be administered concomitantly with Factor IX Complex concentrates or Anti-Inhibitor Coagulant concentrates, as the risk of thrombosis may be increased." The conflicting statement in Dosage and Administrations section that stated "Before Extraction: Administer 10 mg/kg body weight of Tranexamic Acid in Sodium Chloride injection intravenously with replacement therapy (b) (4) *" is misleading. Both statements were from RDL, it appears that the wording Dosage and Administrations was an error, since it was referred to the statement in the Precautions section of the RDL. See clinical safety section 6.2 above for clinical reasoning and discussion.*

Furthermore, the labeling team proposed removal the wording of "Patients with disseminated intravascular coagulation (DIC), who require treatment with tranexamic acid, must be under strict supervision of a physician experienced in treating this disorder" is not acceptable based on the international emerging data in trauma induced coagulopathy. Please see safety section 6.4 for clinical reasoning and discussion.

Risks of Driving and Operating Machinery

Tranexamic may cause dizziness and therefore may influence the ability to drive or use machines.

Adverse Reactions

- Gastrointestinal (b) (4): nausea, vomiting, diarrhea occur but disappear when dose is reduced.
- (b) (4) Allergic dermatitis has been reported (b) (4) Convulsion has also been reported.
- (b) (4): Hypotension may occur when intravenous injection is too rapid.
- (b) (4) Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery, vein obstruction and cases associated with concomitant use of combination hormonal contraceptives) have been rarely reported in patients receiving tranexamic acid for indications other than hemorrhage prevention in patients with hemophilia.
- (b) (4) vision impairment (chromatopsia).
- (b) (4) Anaphylaxis and anaphylactoid reactions.

Clinical reviewer additional comments:

- *See clinical pharmacology input for general dosing and renal impairment dosing modification recommendation.*
- *See DPMH consult review for recommendation on labeling regarding pregnancy, lactation and pediatric setting.*
- *See labeling team recommendation for overall labeling wordings.*
- *See ophthalmology consult recommendation for ocular toxicity wording for labeling.*

7.3 Advisory Committee Meeting

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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