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APPLICATION NUMBER:

212020Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	212020
Supporting document/s:	1
Applicant's letter date:	July 6, 2018
CDER stamp date:	July 6, 2018
Product:	Tranexamic Acid in Sodium Chloride Injection
Indication:	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.
Applicant:	Exela Pharma Sciences, LLC PO Box 818 1245 Blowing Rock Blvd Lenoir, NC 28645
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Matthew D Thompson, PhD, MPH
Supervisor/Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD, DABT Ann Farrell, MD (DHP)
Project Manager:	Kris Kolibab, PhD

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1 Executive Summary

1.1 Introduction

Tranexamic acid is a synthetic lysine amino acid derivative, which diminishes the dissolution of hemostatic fibrin by plasmin. In the presence of tranexamic acid, the lysine receptor binding sites of plasmin for fibrin are occupied, preventing binding to fibrin monomers, thus preserving and stabilizing fibrin's matrix structure.

The Applicant, Exela Pharma Sciences, LLC, has submitted this 505(b)(2) NDA to support the use of Tranexamic Acid in Sodium Chloride Injection (10 mg per mL) 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. This 505(b)(2) application is relying on FDA's finding of safety and effectiveness for the listed drug CYKLOKAPRON (NDA # 019281, Pharmacia and Upjohn Co.). Cyklokapron was initially approved in 1986.

The Applicant's formulation differs from the Cyklokapron formulation in the strength (concentration), (b) (4) and the unit dose volume. Therefore, the Applicant is not pursuing a 505(j) ANDA pathway.

Exela Pharma Sciences submitted a statement that as of July 06, 2018, there are no unexpired exclusivities associated with NDA # 019281 and no relevant patent claims.

1.2 Brief Discussion of Nonclinical Findings

The Applicant is relying on the FDA's previous findings of safety and effectiveness for Cyklokapron. There is no nonclinical section in the submission.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, TRANEXAMIC ACID IN SODIUM CHLORIDE Injection may be approved for the proposed indication.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

At the time of this review, the labeling negotiations with the Applicant are ongoing. The nonclinical sections of the label will be based on the label of Cyklokapron, the listed drug. The label will be updated based on the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR). Under section 12.1 of the label, the general mechanism of action for tranexamic acid is described; text used in the Cyklokapron label comparing tranexamic acid to other products has been removed based on 21 CFR 201.56(a)(2) whereby suggestions of therapeutic advantages based upon mechanism of action may be false or misleading, and therefore, must be avoided

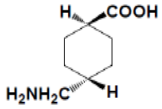
(see *Guidance for Industry - Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*).

2 Drug Information

2.1 Drug

CAS Registry Number
1197-18-8
Generic Name
Tranexamic acid
Chemical Name
trans-4-aminomethylcyclohexanecarboxylic acid
Molecular Formula/Molecular Weight
$C_8H_{15}NO_2$, 157.21 g/mol

Structure



(*Excerpted from Applicant's submission*)

Pharmacologic Class
Antifibrinolytic

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND # 126242 (Exela Pharma Sciences)
NDA # 019841 (Pharmacia and Upjohn Co.)
DMF # (b) (4)
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

2.3 Drug Formulation

Tranexamic Acid in Sodium Chloride Injection is a clear to colorless sterile, nonpyrogenic injectable solution for intravenous administration. Each IV bag contains 1000 mg tranexamic acid, USP, 700 mg of sodium chloride, USP, and Water for Injection, USP. The aqueous solution has a pH of 6.5 to 8.0.

Table 1: Formulation of Tranexamic Acid in Sodium Chloride Injection

Component	Quality Standard	Function	Amount		
			% w/v	mg/mL	Per Unit
Tranexamic Acid	USP	Drug Substance	1.0%	10 mg/mL	1000 mg/100mL
Sodium Chloride	USP	(b) (4)	0.7%	7.0 mg/mL	700 mg/mL
Water For Injection	USP		q.s to 100%	q.s. to 1mL	q.s. to 100 mL

(*Excerpted from Applicant's submission*)

Table 2: Comparison of Ingredients in Exela's Tranexamic Acid in Sodium Chloride Injection with Cyklokapron

Exela's Tranexamic Acid (b) (4) Injection, 10 mg/mL, 100 mL IV Bag		RLD product CYKLOKAPRON[1] (Tranexamic Acid (b) (4) 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/Infusion

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

(*Excerpted from Applicant's submission*)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

The recommended dose of Tranexamic Acid in Sodium Chloride Injection is 10 mg per kg body weight intravenously administered as a single dose, immediately before tooth extractions. Following tooth extraction, Tranexamic Acid in Sodium Chloride Injection may be administered for 2 to 8 days at a dose of 10 mg per kg body weight three to four times daily, intravenously. This dosing is consistent with the listed drug Cyklokapron.

2.7 Regulatory Background

In correspondence with the Applicant on June 8, 2015 under IND # 126242, regarding the need for nonclinical studies, the Agency stated: "With regard to nonclinical studies: We agree that additional nonclinical pharmacology and toxicology studies are not needed for Exela's tranexamic acid (b) (4) injection."

In Type C WRO correspondence under IND # 126242, the Agency indicated a 505(b)(2) application appeared to be an acceptable approach based on the information provided.

3 Studies Submitted

None

4 Pharmacology

No new pharmacology studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

Not submitted

6 General Toxicology

Not submitted

7 Genetic Toxicology

Not submitted

8 Carcinogenicity

Not submitted

9 Reproductive and Developmental Toxicology

Not submitted

10 Special Toxicology Studies

Not submitted

11 Integrated Summary and Safety Evaluation

See Executive Summary

12 Appendix/Attachments

None

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/s/

MATTHEW D THOMPSON
03/26/2019 03:55:47 PM

CHRISTOPHER M SHETH
03/26/2019 03:59:50 PM
I concur.