CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212020Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 212020
Review #1

Drug Name/Dosage Form	Tranexamic Acid Injection 10 mg/mL, 100 mL
Strength	10 mg/mL
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Exela Pharma Sciences, LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	06-Jul-18	All
Amendment	17-Jan-19	Process, Biopharm, micro
Amendment	09-Sept-18	Micro
Amendment	14-Dec-18	Micro
Amendment	08-Feb-19	Process, micro
Amendment	06-Mar-19	Process, micro
Amendment	28-Mar-19	Micro
Amendment	13-Mar-19	Micro

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sharron Kelly	Suong Tran
Drug Product	Danuta Gromek-Woods	Anamitro Banerjee
Process	Aditi Thakur	Christina Daniel-Capacci
Microbiology	Renee Rogers-Marcsisin	Neal Sweeney
Facility	Aditi	Christina Daniel-Capacci
Biopharmaceutics	Akm Thakur	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Danuta Gromek-Woods	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	n/a		Reviewed in conjunction with NDA
	Type II			n/a		Reviewed in conjunction with NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, LD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	126242	Exela Pharma Science
NDA	19281	Listed Drug- CYKLOKAPRON (tranexamic acid) Injection

2. CONSULTS

N/A

Executive Summary

1. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 212020 for Tranexamic Acid in Sodium Chloride Injection, 10 mg/mL. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance when stored at (b) (4) and a 24-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]". There are no outstanding issues or post-marketing commitments to be conveyed to the applicant.

2. Summary of Quality Assessments

1. Product Overview

NDA 212020 was submitted for Tranexamic Acid (b) (4) Injection, 10 mg/mL, (name originally proposed by the applicant) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Exela Pharma Sciences, LLC. Tranexamic Acid is a small chiral molecule with 2 asymmetric centers that was originally approved by the FDA for the treatment of patients with hemophilia for short-term (2-8 days) to reduce hemorrhage and reduce the need for replacement therapy during and following tooth extraction. Cyklokapron (Tranexamic Acid) Injection manufactured by Pharmacia and Upjohn Company was approved under NDA 19281 in 1986 and is the Listed Drug (LD) for this application.

Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. Tranexamic acid reduces postoperative blood losses and transfusion requirements in several types of surgery, with potential cost and tolerability advantages over aprotinin, and appears to reduce rates of mortality and urgent surgery in patients with upper gastrointestinal haemorrhage. Tranexamic drug substance is manufactured by (b) (4) (DMF (b) (4) and (b) (4) (DMF (b) (4)

The drug product, Tranexamic Acid Injection, 10 mg/mL, is presented as a 100 mL fill in single-dose, 100 mL IV bag. It is a sterile, non-pyrogenic, clear, colorless solution intended for intravenous infusion. The product is formulated as a (b) (4) solution. Each IV bag contains 1000 mg Tranexamic Acid, USP, 700 mg of Sodium Chloride, USP and Water for Injection, USP. The Exela formulation and the LD differ with respect to strength, container closure and excipients. The Exela product is presented as a 10 mg/mL solution in a 100 mL IV bag and the innovator product is presented as a 100 mg/mL solution in 10 mL ampules/vials and is designed for immediate use.

The recommended dosing regimen for 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.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 212020 and grants a (b) (4) month re-test period for the drug substance and a **24**-month expiration period for the drug product when stored at 20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].

Proposed Indication(s) including Intended Patient Population	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.
Duration of Treatment	2-8 days
Maximum Daily Dose	40 mg per kg
Alternative Methods of Administration	None

2. Quality Assessment Overview

Drug Substance

Tranexamic Acid, USP drug substance is a small molecule with 2 asymmetric centers. It is a white, odorless crystalline powder that is freely soluble in water and acetic acid and practically insoluble in alcohol and ether. Tranexamic Acid drug substance will be manufactured by (b) (4) (DMF (b) (4) or (b) (4) (DMF (b) (4) Because the drug product is formulated as clear solution (b) (4) .

A retest date of (b) (4) months has been established by (b) (4) for Tranexamic Acid and a retest date of (b) (4) months has been established by (b) (4) for Tranexamic Acid drug substance. Exela has indicated that they will follow a (b) (4) month retest period for the drug substance and they will not be performed beyond the drug substance expiry date established by the DMF holder

The applicant crossed referenced DMF (b) (4) and DMF (b) (4) for all aspects pertaining to the manufacture and control of the drug substance. Accordingly, limited information was included in the application. DMF (b) (4) and DMF (b) (4) were reviewed in conjunction with this NDA and were considered adequate to support the approval of this NDA.

NDA 212020 is recommended for approval from the API perspective.

Drug Product and Drug Process

The drug product, Tranexamic Acid Injection, 10 mg/mL, is presented as a 100 mL fill in 100 mL IV bag. It is a sterile, (b) (4) non-pyrogenic, clear, colorless solution intended for intravenous infusion. Each single-dose IV bag contains 1000 mg Tranexamic Acid, USP, 700 mg of Sodium Chloride, USP and Water for Injection, USP. The Exela formulation differs from the Listed Drug formulation with respect to strength, container closure and excipients. The Exela product is a is ready to use and does not require dilution. It is presented as a 10 mg/mL, (b) (4) solution in a 100 mL IV bag while the innovator product is presented as a 100 mg/mL solution in 10 mL ampules/vials which requires dilution.

The drug product contains no antimicrobial preservatives (b) (4). The drug product is manufactured, packaged and release tested by Exela Pharma Sciences of Lenoir, NC, at a commercial batch size of (b) (4) L which corresponds to (b) (4) units.

The manufacturing process of this drug product includes (b) (4)
(b) (4)

The description of the manufacturing process includes well defined CQAs and CPPs. The proposed process parameters and in-process controls are described in sufficient detail and are justified. The applicant has demonstrated the suitability of the manufacturing process for the drug product. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

The drug product specifications included description, identification, pH, osmolality, assay, related substances, fill volume, loss of weight, container integrity, particulate matter, elemental impurities, (b) (4) sterility and bacterial endotoxins. The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications are adequate to establish the drug product identity, potency and purity and provide adequate controls to ensure the quality of the drug product throughout the proposed product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 24-month expiry, 24 months of long-term (25°C/60% RH) and 6 months accelerated (40°C/75% RH) primary stability data were provided for three registration batches (batches XLNE1451, XLNE1452 AND XLNE1453) of the

drug product. In addition to the long term and accelerated data, the applicant includes photostability and (b) (4) data.

The registration batches were manufactured using a batch size of (b) (4) which corresponds to (b) (4) units respectively. The registration batches were manufactured via the commercial process and were stored in the commercial container closure system (100 mL polypropylene bags supplied by (b) (4) sealed with Twist offs supplied by (b) (4)).

The applicant requested a 24-month expiry for the drug product when stored under controlled room temperature. The available stability data shows consistency over time and supports the proposed expiry. Based on the 24 months of stability data included in this application for Tranexamic Acid in Sodium Chloride Injection, 10 mg/mL, Exela proposed and the FDA accepts the expiration dating period of **24 months** for the drug products when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

NDA 212020 is recommended for approval from a drug product and drug process perspective with an assigned drug product expiry of 24-months. The drug product reviewer included the following Lifecycle Management considerations:

(b) (4)

Biopharmaceutics

The Exela product is intended for intravenous infusion. The Exela product is available as 10 mg/mL solution in 100 mL IV bag whereas, RLD drug product is supplied as 100 mg/mL solution in 10 mL ampules/vials. The Exela drug product contains Sodium Chloride, USP (b) (4) whereas, the RLD drug product does not contain any (b) (4)

The biopharm review of this application focused on:

1. the biowaiver request
2. bridging of clinical product to the to the to-be-marketed product.

It was concluded that the request for a biowaiver based on 21 CFR §320.22(b) could not be granted due to differences in strength (10 mg/mL vs. 100 mg/mL) and the presence of sodium chloride in the Exela formulation.

The applicant demonstrated that there were no significant differences in the physiochemical properties of the Exela product and the LD. While there is

a difference in the strengths the proposed drug product will be administered in the same manner as the LD (i.e. 10 mg/kg). Accordingly, a bridge was established between the Excela product and Listed Drug based on 21 CFR §320.24(b)(6).

Based on the information provided, this application is recommended for approval from a biopharmaceutics perspective.

Quality Microbiology

The drug product manufacturing process includes (b) (4) The validation information supporting the (b) (4) manufacturing demonstrates that the (b) (4) processes are controlled and are suitable for (b) (4) processing at the drug product manufacturing facilities. Accordingly, this application is recommended for approval from a quality microbiology perspective.

Facilities

NDA 212020 included 4 sites and all sites were listed as ready for inspection:

- **Exela Pharma Sciences, LLC. (FEI 3008563008)**– Drug Product Manufacturing Site, Release Testing of Drug Substance, Release Testing of the Drug Product, Release Testing for Excipients, Drug Product Stability Testing, Drug Product Packaging and Labeling
- (b) (4) - Drug Substance Manufacturing Site, Release Testing of Drug Substance, Drug Substance Stability Testing, Drug Substance Packaging and Labeling
- (b) (4))– Drug Substance Manufacturing Site, Release Testing of Drug Substance, Drug Substance Stability Testing, Drug Substance Packaging and Labeling
- (b) (4) Alternative lab for Release Testing of Drug Substance, Release Testing of the Drug Product, Release Testing for Excipients, Drug Product Stability Testing

All facilities listed in NDA 212020 were deemed acceptable for the responsibilities listed in the application. NDA 212020 is recommended for approval from a compliance perspective.

Environmental Assessment

The drug product reviewer confirmed that the applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(a). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

3. Special Product Quality Labeling Recommendations (NDA only)

n/a

4. **Final Risk Assessment (see Attachment)**

Attached.

BIOPHARMACEUTICS

Application No: NDA: 212020

Drug Product Name/Strength: CYKLOKAPRON (Tranexamic Acid) Injection, 10 mg/mL in a 100 mL IV Bag

Route of Administration: Intravenous

Applicant Name: Exela Pharma Sciences, LLC.

Submission Reviewed:
Seq. No 0004 dated 01/17/2019
Seq. No 0001 dated 07/06/2018

Primary Biopharmaceutics Reviewer: Akm Khairuzzaman, PhD
Secondary Biopharmaceutics Reviewer: Banu Zolnik, PhD

Submission: Exela Pharma Science LLC is seeking approval for CYKLOKAPRON ™ (Tranexamic Acid) Injection, 10 mg/mL under the 505 (b)(2) regulatory path treatment of patients with hemophilia. The proposed drug product is a (b) (4) intravenous sterile solution in a 100 mL IV bag. The listed drug (LD) is NDA 19281 CYKLOKAPRON (tranexamic acid) Injection manufactured by Pharmacia and Upjohn.

Review Summary: The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the biowaiver request for the proposed product, and **2)** bridging between the proposed and LD products.

1) Biowaiver Request

Applicant's request for biowaiver based on 21 CFR §320.22(b) is not feasible due to differences in strength (10 mg/mL vs. 100 mg/mL) and the presence of sodium chloride in the proposed drug product (b) (4) However, the "bridge" between the proposed product and the listed drug product is established based on 21 CFR 320.24(b)(6).

2) Bridging

The Applicant submitted data which showed that there are no significant differences in physiochemical properties between the proposed drug product and the LD. Although there is a strength difference between the proposed drug product (10 mg/mL) and the LD (100 mg/mL), the proposed drug product will be administered at the same dose (10 mg/kg) as the LD. Therefore, the bridging between the proposed and Listed Drug products is established based on 21 CFR §320.24(b)(6).

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212020 for CYKLOKAPRON (Tranexamic Acid) Injection, 10 mg/mL, is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

CYKLOKAPRON, the Listed Drug (LD) product, was approved under NDA 19281 in December 1986. LD product is presented as a 100 mg/mL, 10 mL single-dose ampules, total dose in a vial is 1000 mg. The proposed drug product, Tranexamic Acid Injection, has the same active ingredient, dosage form, route of administration, and indications as LD product. However, Exela's Tranexamic Acid Injection contains sodium Chloride (b) (4) which is not present in LD and the concentration of Exela's Tranexamic Acid Injection is lower in the proposed drug product (10 mg/mL) compared to the LD (100 mg/mL). Therefore, due to these formulation differences, the biowaiver under 21 CFR § 320.22 (b)(1) is not feasible but bridge between the proposed drug product and LD could be established based on 21 CFR §320.24(b)(6).

According to the listed drug product's labeling[1], (NDA 19281/S-0303), the listed drug product may be mixed with most solution for infusion such as electrolyte solutions, carbohydrate solutions, amino acids solution, and dextran solutions. From these label instruction, it appears that the final concentration of the LD product may vary depending on the type of the infusion bag is used. Therefore, the following comparative physicochemical characteristics support to establish a bridge between the proposed and LD product:

- Final concentration prior to intravenous injection,
- pH,
- Osmolality,
- Assay, and
- Impurities

During the review of the NDA, below comments conveyed to the Applicant in an information in an IR letter dated 12/18/2018:

1. The FDA does not agree with your request for biowaiver based on 21 CFR §320.22(b) due to the fact that the test drug product has lower concentration (10 mg/mL) than that of the listed drug product (100 mg/mL) and contains sodium chloride (b) (4) However, we consider that the "bridge" between your proposed product and the listed drug product could be based on 21 CFR 320.24(b)(6). For this purpose, provide the following information with justification/supportive data:
    a. Comparative physicochemical data (such as final concentration prior to intravenous injection, pH, osmolality, color and clarity) for at least 3 lots of the listed drug product after reconstitution/dilution and 3 production lots of the proposed drug product. The measurements should be done in triplicate for each lot tested. Include justification for why you believe that any observed differences in the physicochemical properties of the test and listed drug products would not impact the pharmacokinetics, efficacy, and safety relative to the listed drug product.

Applicant's Response:

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019281s030lbl.pdf

Exela's (b) (4) product performed comparable to the LD when diluted per the package insert to a concentration of 10 mg/mL in Sodium Chloride (0.9%) Injection. All assessed solutions of Exela's (b) (4) product and the diluted LD were clear, colorless solutions. The osmolality values for Exela's (b) (4) product and the LD were similar and ranged from 291 mOsm/kg to 319 mOsm/kg. All samples were within Exela's proposed specification range of (b) (4) mOsm/kg. The pH values for Exela's (b) (4) product and the LD were similar and ranged from 6.6 – 7.3. All samples were within Exela's proposed specification range of (b) (4) The assay values for Exela's (b) (4) product and the LD were similar and ranged from 104.7 – 98.9. All samples were within Exela's proposed specification of (b) (4) %. The total impurity values for Exela's (b) (4) product and the LD were similar and ranged from 0.0 – 0.1%. All samples met Exela's proposed specification of NMT (b) (4) %.

Reviewer's Evaluation: Since the proposed drug product exhibited the same physicochemical properties with that of the listed product, and the drug product is in a solution state, this sufficiently establish a bridge and there is no risk that this new formulation can impact the pharmacokinetics, efficacy, and safety relative to the listed drug product. **Acceptable.**

Akm Khairuzzaman

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Banu Zolnik

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Sherita McLamore

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MICROBIOLOGY

Product Background: 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.

NDA: 212020

Drug Product Name/Strength: Tranexamic Acid (b) (4) Injection, 10 mg/ml

Route of Administration: Intravenous Infusion

Applicant Name: Exela Pharma Sciences, LLC.

Manufacturing Site: Exela Pharma Sciences ("Exela"), 1325 William White Place Lenoir, NC 28645

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): **N/A**

Review Summary: **The drug product is (b) (4) .**

List Submissions Being Reviewed: 07/06/2018, 09/14/2018, 12/14/2018, 1/17/2019, 02/08/2019, 02/28/2019, 03/04/2019, 03/13/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks:

- **An Information Request was sent to the applicant on 08/27/2018 and a response was received on 09/14/2018.**
- **Information Requests were sent to the applicant on 11/30/2018 and 12/18/2018 and responses were received on 12/14/2018 and 01/17/2019, respectively.**
- **An Information Request was sent to the applicant on 02/01/2019 and a response was received on 02/08/2019.**

- **Information Requests were sent to the applicant on 12/18/2018 and 02/20/2019 and responses were received on 02/28/2019 and 03/04/2019, respectively.**
- **An Information Request was sent to the applicant on 03/07/2019 and a response was received on 03/13/2019. The original deficiency is italicized below.**

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance- N/A

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** A clear and colorless, sterile, non-pyrogenic, preservative-free solution, pH (b) (4), containing 1000 mg of API, supplied as a (b) (4) ml target fill volume in 100 ml IV bag, and given as an intravenous infusion

- **Drug product composition –**

Component	Quality Standard	Function	Amount		
			% w/v	mg/ml	per unit
Tranexamic acid	USP	Drug substance	1%	10 mg/ml	1000 mg/100 ml
Sodium chloride	USP	(b) (4)	0.7%	7 mg/ml	700 mg/ml
WFI	USP		q.s. to 100%	q.s. to 1 ml	q.s. to 100 ml

- **Description of container closure system –**

Product Description	IV bag	IV bag closure
Tranexamic Acid (b) (4) Injection, 10 mg/ml, 100 ml IV Bag	(b) (4)	(b) (4)

Note to reviewer: (b) (4)
(b) (4)

Reviewer's Assessment: ***Adequate***

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(b) (4)

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 212020 (CYKLOKAPRON (Tranexamic Acid) Injection, 10 mg/mL)

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments	L		Acceptable	Similar to the reference drug.

	• Site				
pH- (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	(b) (4)	Acceptable	Controls are in place during stability testing. Continue stability monitoring post approval
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place

Sherita McLamore

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LABELING

A preliminary labeling review is provided below. Labeling is still under evaluation by the OND Review Team.

I. Package Insert

Highlights of Prescribing Information

------DOSAGE FORMS AND STRENGTHS------

Injection: 1,000 mg of tranexamic acid in 100 mL (10 mg per mL) sterile, unpreserved, colorless solution in a single-dose bag for intravenous use

Full Prescribing Information

2. Section 2 Dosage and Administration

2.1 Recommended Dosage

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. Infuse no more than 10 mL per minute to avoid hypotension. 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.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use Tranexamic Acid in Sodium Chloride Injection if particulate matter or coloration is seen."

Tranexamic Acid in Sodium Chloride Injection should NOT be mixed with blood. The drug is a synthetic amino acid and should NOT be mixed with solutions containing penicillin.
The premix flexible plastic container bag contains no preservative; discard any unused portion.

2.2 Recommended Dosage for Patients with Varying Degrees of Renal Impairment

The recommended dosage of Tranexamic Acid in Sodium Chloride Injection in patients with varying degrees of renal impairment is described in Table 1 *[see Use in Specific Populations (8.6)]*.

Table 1. Recommended Dosage in Patients with Varying Degrees of Renal Impairment*

Serum Creatinine (mg/dL)	Tranexamic Acid in Sodium Chloride Injection Intravenous Dosage
1.36 to 2.83 (120 to 250 micromol/L)	10 mg per kg twice daily
2.83 to 5.66 (250 to 500 micromol/L)	10 mg per kg daily

>5.66 (>500 micromol/L)	10 mg per kg every 48 hours or 5 mg per kg every 24 hours

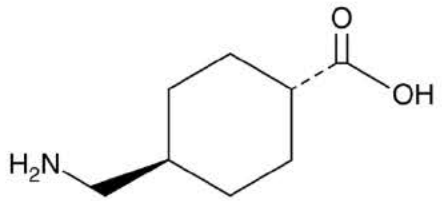
*Dose reduction is recommended for all doses, both before and after tooth extraction.

3. ***Section 3 Dosage Forms and Strengths***

Injection: 1,000 mg of tranexamic acid in 100 mL (10 mg per mL), colorless solution in a single-dose bag for intravenous use.

4. ***Section 11 Description***

Tranexamic acid is trans-4-(aminomethyl)cyclohexanecarboxylic acid, an antifibrinolytic agent. Tranexamic acid is a white crystalline powder. The structural formula is



Empirical Formula: $C_8H_{15}NO_2$ Molecular Weight: 157.2

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.

5. ***Section 16 How Supplied/Storage and Handling***

Tranexamic Acid in Sodium Chloride Injection is 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).

Discard any unused portion.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	X
Available units	X
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	X
Special handling (e.g., protect from light)	X
Storage conditions	X
Manufacturer/distributor name (21 CFR 201.1(h)(5))	X

6. ***Section 17 Patient Counceling Information***

Manufactured and Distributed by:

Exela Pharma Sciences, LLC
1245 Blowing Rock Blvd
Lenoir, NC 28645

Reviewer's Assessment of Package Insert: Adequate.

The PI is still under discussion and evaluation. Final assessmen will be documented in an Addendum to this review.

II. Container Labels:

Images of labels and labeling received on 07-Mar-2019:

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information provided in the Intravenous Bag label	Information provided in the Carton Case label(s)	Information provided in the Intravenous Bag Overwrap
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	X	X	X
Dosage strength	X	X	X
Net contents	X	X	X
"Rx only" displayed prominently on the main panel	X	X	X
NDC number (21 CFR 207.35(b)(3)(i))	X	X	X
Lot number and expiration date (21 CFR 201.17)	X	X	X
Storage conditions	X	X	X
Bar code (21CFR 201.25)	X	X	X
Name of manufacturer/distributor	X	X	X
And others, if space is available			

Recommendations for Exela Pharma Sciences, LLC, **as per DMEPA review dated 21-Mar-2019:**

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.*

Reviewer's Assessment of Carton case, Container Intravenous Bag, and Overwrap: Pending.

Overall Labeling Assessment: Pending evaluation by OND Review Team. Please also refer to the Label and Labeling Review in DARRTS dated 21-Mar-2019 from the Division of Medication Error Prevention and Analysis (DMEPA), prepared by Casmir Ogbonna, PharmD.

Primary Drug Product Reviewer Name and Date:

Danuta Gromek-Woods, Ph.D

25-Mar-2018

Secondary Reviewer Name and Date:

Anamitro Banerjee, Ph.D.
25-Mar-2018

Danuta Gromek-Woods

Digitally signed by Danuta Gromek-Woods
Date: 3/29/2019 10:37:47AM
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Anamitro Banerjee

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Date: 3/29/2019 06:03:22PM
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Sherita McLamore

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