CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212020Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	15-Apr-2019
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212020
Type of Application	505(b)(2)
Applicant	Exela Pharma Sciences, LLC
Date of Receipt	06-Jul-18
PDUFA Goal Date	06-May-19
Proposed Proprietary/Established Names	Tranexamic Acid
Dosage forms / Strength	Injection/10 mg/mL
Route of Administration	Intravenous
Proposed Indication(s)	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.
Recommended:	**APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Qin Ryan, M.D., Ph.D.)
- Clinical Pharmacology (Liang Li, Ph.D.)
- Pharmacology/Toxicology (Matthew Thompson, Ph.D.)
- Ophthalmology (Wiley Chambers, M.D.)
- Division of Pediatric and Maternal Health (Carrie Ceresa, Pharm D., MPH)
- DEMPA (Casmir Ogbonna, Pharm. D.)
- Drug Product (Danuta Gromek-Woods, Ph.D.)
- Drug Substance (Sharron Kelly, Ph.D.)
- Microbiology (Renee Marcisin, Ph.D.)
- Manufacturing Facilities (Aditi Thakur, Ph.D.)
- Manufacturing Process (Djelila Mezaache, Ph.D.)
- Biopharmaceutics (Akm Khairuzzaman, Ph.D.)

1. Introduction

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 synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. It 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 hemorrhage. In the presence of tranexamic acid, the lysine receptor binding sites of plasmin fibrin are occupied, preventing binding to fibrin monomers, thus preserving and stabilizing fibrin's matrix structure. Tranexamic Acid is a small molecule with 2 asymmetric centers that was originally approved by the FDA for the treatment of patients with hemophilia for short-term to reduce hemorrhage and reduce the need for replacement therapy during and following tooth extraction.

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. The Exela formulation differs from the innovator product in the strength, (b) (4) the unit dose volume, and container closure. The proposed Exela drug product is presented as a ready to use, (b) (4) 10 mg/mL solution in a 100 mL fill in single-dose, 100 mL IV bag, while the innovator product is presented as a 100 mg/mL solution in 10 mL ampules/vials and requires further dilution.

No clinical studies were performed with the proposed drug product, Tranexamic Acid Injection, 10 mg/mL as this submission relies on the agency's findings for CYKLOKAPRON (Tranexamic Acid) Injection (NDA 19281) for safety and efficacy. Accordingly, approval of NDA 212020 from clinical, non-clinical and clinical pharmacology perspectives will be primarily based on publicly available information for CYKLOKAPRON. CYKLOKAPRON which was manufactured by Pharmacia and Upjohn Company, originally approved in 1986, is the Listed Drug (LD) for this application.

2. Background

This application presents a new formulation of tranexamic Acid. Tranexamic acid is a synthetic lysine amino acid derivative that diminishes the dissolution of hemostatic fibrin by plasmin. The lysine receptor binding sites of plasmin for fibrin are occupied, preventing binding to fibrin monomers in the presence of tranexamic acid thereby preserving and stabilizing fibrin's matrix structure. Tranexamic Acid was approved under NDA 19280 CYKLOKAPRON (tranexamic acid injection); NDA 19281 CYKLOKAPRON (tranexamic acid tablets) and NDA 22430 Lysteda (tranexamic acid tablets). NDAs 19280 and 22430 are currently active. NDA 19281 is discontinued.

The recommended dose of Tranexamic Acid in Sodium Chloride Injection is the same as the Listed Drug, 10 mg per kg body weight intravenously. This dose is to be administered as a single dose, immediately before tooth extractions and may be administered for 2 to 8 days the same dose three to four times daily, intravenously following tooth extraction.

NDA 212020 contains no clinical data but instead relies upon information in the public domain and on the Agency's determination of safety and efficacy for the listed drug, CYKLOKAPRON which was previously approved for marketing under NDA 19280.

3. Product Quality

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, but 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) As the drug product is formulated as clear solution (b) (4) 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 further 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 that requires dilution. The recommended route of administration, dosage and instructions for administration of the proposed product are identical to those of the Listed Drug.

The drug product is self-preserving and contains no antimicrobial preservatives. The applicant requested a waiver of *in vivo* bioequivalence of the drug product; however, it was concluded that a waiver of the requirement to conduct *in vivo* bioequivalence studies could not be granted 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.
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).

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)

In support of the proposed 24-month expiry, the applicant provided 24 months of primary stability data. In addition to the primary stability data, the applicant included photostability and (b) (4) data. 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 product 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 included 4 manufacturing, testing, and packaging facilities:

- Exela Pharma Sciences, LLC.
- (b) (4)
-
-
-

All sites were listed as ready for inspection and all were found acceptable for the responsibilities listed in the application.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities reviewers) recommends **APPROVAL** for NDA 212020.

6. Clinical Pharmacology

The Excela product is a reformulation of CYKLOKAPRON and the applicant is relying on the Agency's previous findings of safety and efficacy as described in the approved labeling for the LD. The clinical pharmacology reviewer confirms that there was no new clinical pharmacology information included in this application and recommends approval of NDA 212020 from a clinical pharmacology perspective.

7. Non-Clinical Pharmacology/Toxicology

The pharm/tox reviewer states that the Applicant is relying on the FDA's previous findings of safety and effectiveness for the Listed Drug and that there is no nonclinical information included in the submission. The reviewer indicates that the dosing is consisted with the LD and recommends approval of NDA 212 020 from a Pharmacology/Toxicology perspective.

8. Clinical/Statistical-Efficacy

Exela did not conduct any human clinical studies and therefore efficacy was based on the Prescribing Information for CYKLOKAPRON. The clinical reviewer recommends approval of NDA 212020 for the aforementioned indications if pharmacological equivalence is supported adequately.

9. Safety

Safety was based on the Prescribing Information for the Listed Drug, CYKLOKAPRON.

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

The labeling review was completed by DMEPA, Clinical, Non-Clinical, Clinical Pharmacology, Ophthalmology, Division of Pediatric and Maternal Health and CMC. With the exception of the Dosage and Administration section on the dilution of the drug product, How Supplied, Description, and Storage and Handling sections of the labeling, the proposed labeling for the Excela product contained effectively the same in content as the listed drug's, CYKLOKAPRON, labeling.

Clinical Recommendations:
The DHP clinical reviewer made modifications to update and improve the label based recommended on literature and clinical practice guidelines. The clinical reviewer recommended that the new product label be updated to comply with PLR formatting and that information regarding tranexamic acid effect in late pregnancy and outcomes comply with requirements of PLLR.

Ophthalmology Consult: The Ophthalmology clinical team was consulted in conjunction with the review of NDA 212020. The Ophthalmology team was asked to review section 4 of the package insert and advise on the contraindication (b) (4) (see Ophthalmology Medical Officer review dated 3/19/19). From the available human clinical information the Ophthalmology review team concluded that the retinal findings in cats, dogs and rats are not consistent with findings in humans and that there is no evidence of retinal degeneration in humans after years of treatment. Accordingly, the following labeling recommendations were forwarded to the Applicant:

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 post-marketing 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

DMEPA Recommendations:
The DMEPA completed the initial review on 2/13/19 in which the reviewer identified several deficiencies in the label and labeling that required resolving. These recommendations were conveyed to applicant and the applicant responded and provided a revised label and carton labeling. The final recommendations from DMEPA are included below*:*

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.

Clinical Pharmacology Recommendations:
The Clinical Pharmacology reviewer noted that there was no new clin/pharm information included in this application and that the proposed labeling included the same content as the LD with modifications consistent with current labeling practices and Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016).

Non-Clinical Recommendations:
The non-clinical reviewer notes that with the exception of Pregnancy and Lactation Labeling Rule (PLLR) compliance, the label is comparable to that of the Listed Drug. Additionally, the reviewer notes that under section 12.1 of the label where the general mechanism of action for tranexamic acid is described, the text used in the Listed Drug label comparing tranexamic acid to other products was removed based on 21 CFR 201.56(a)(2).

CMC Recommendations:
No additional comments noted

ADL Recommendations:

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

Highlights, Adverse Reactions	(b) (4)	Revised to provide a list (b) (4) (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) (b) (4)
Highlights, Drug Interactions	No subsection is proposed.	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	(b) (4)	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.	*Corrected the nonproprietary name.* (b) (4) (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.

See review dated 01/30/19 for additional recommendations included in the USPI

Division of Pediatric and Maternal Health (DPMH) Consult:
The following consult question was forwarded to the Division of Pediatric and Maternal Health: Please review the PLLR conversion and two clinical information amendments related to PLLR (see section 1.11.3). DPMH included revised sections, 5.4, 7.1, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see review dated 2/28/19).

Overall Labeling Recommendation:
The applicant accepted the changes recommended by the agency and submitted revised labeling. The labeling for the Exela Tranexamic acid product is acceptable with no additional recommendations.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, CYKLOKAPRON. The Exela product differs from the listed drug in the strength, excipients (b) (4) used, and the unit dose volume. The Exela product has the same active ingredient is the same dosage form and has the same routes of administration and final concentration of tranexamic acid following dilution as the Listed Drug. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

As there are no outstanding issues precluding the approval of this application and based on the recommendations form all review disciplines, the CDTL recommends **APPROVAL** of NDA 212020**.**

- **Risk Benefit Assessment**

Please refer to NDA 19281.

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/s/

SHERITA D MCLAMORE
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