CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212020Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

<table>
<tr><th colspan="2">Clinical Pharmacology Review</th></tr>
<tr><td>NDA</td><td>NDA 212020 (SDN 001, eCTD 0001)</td></tr>
<tr><td>Type/Category</td><td>505(b)2 submission</td></tr>
<tr><td>Submission Date</td><td>07/06/2018</td></tr>
<tr><td>PDUFA</td><td>05/05/2019</td></tr>
<tr><td>Brand Name</td><td>TRANEXAMIC ACID IN SODIUM CHLORIDE Injection</td></tr>
<tr><td>Generic name</td><td>Tranexamic acid</td></tr>
<tr><td>Formulation and Strength</td><td>1000 mg of tranexamic acid in 100 mL (10 mg per mL) solution in a single-dose bag for intravenous use</td></tr>
<tr><td>Route of Administration</td><td>IV injection</td></tr>
<tr><td>Applicant</td><td>Exela Pharma Sciences, LLC</td></tr>
<tr><td>Approved Indications</td><td>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</td></tr>
<tr><td>Approved Dosing Regimen</td><td>Before Extraction: Administer 10 mg/kg body weight of Tranexamic Acid in Sodium Chloride Injection intravenously with replacement therapy.
After Extraction: Administer 10 mg/kg body weight 3-4 times daily for 2-8 days.
<u>Patients with Varying Degrees of Renal Impairment:</u>
<table>
<tr><th>Serum Creatinine (mg/dL)</th><th>Tranexamic Acid in Sodium Chloride Injection Intravenous Dosage (for both before and after extraction)</th></tr>
<tr><td>1.36 to 2.83 (120 to 250 micromol/L)</td><td>10 mg/kg twice daily</td></tr>
<tr><td>2.83 to 5.66 (250 to 500 micromol/L)</td><td>10 mg/kg daily</td></tr>
<tr><td>>5.66 (>500 micromol/L)</td><td>10 mg/kg every 48 hours or 5 mg/kg every 24 hours</td></tr>
</table></td></tr>
<tr><td>OCP Divisions</td><td>Division of Clinical Pharmacology V (DCPV)</td></tr>
<tr><td>OND Division</td><td>Division of Hematology Products (DHP)</td></tr>
<tr><td>OCP Primary Reviewer</td><td>Liang Li, Ph.D.</td></tr>
<tr><td>OCP Team Leader</td><td>Guoxiang (George) Shen, Ph.D.</td></tr>
</table>

EXECUTIVE SUMMARY

The Applicant submitted a New Drug Application (NDA) for Tranexamic Acid in Sodium Chloride Injection, 10 mg/mL in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The basis for this submission is NDA 019281 (Pharmacia and Upjohn Co.) for the Reference Listed Drug (RLD), CYKLOKAPRON® (tranexamic acid) injection 100 mg/mL, approved on 12/30/1986. Tranexamic Acid in Sodium Chloride Injection developed by the Applicant has the same ingredients as those in the RLD with

the exception of Sodium Chloride, USP, which is not present in RLD's product. The Applicant's product is intended to be a Ready to Use product and is manufactured at a lower concentration (10 mg/mL) compared to the RLD (100 mg/mL). The recommended route of administration, dosage and instructions for administration of the proposed product are identical to those of the RLD. No new clinical pharmacology information was included in this application. The proposed labeling included the same content as listed in the CYKLOKAPRON® labeling. However, the proposed labeling was modified in accordance 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).

RECOMMENDATION

This original 505(b)(2) application is approvable from a clinical pharmacology perspective.

Signatures:

Liang Li, Ph.D.	Guoxiang (George) Shen, Ph.D.
Reviewer	Team Leader
Division of Clinical Pharmacology V	Division of Clinical Pharmacology V

Cc: OHOP: RPM - K Kolibab; MTL - K Robie Suh; MO - Q Ryan

DCP-V: Deputy DD - B Booth; DD - A Rahman

FDA PROPOSED CLINICAL PHARMACOLOGY LABELING MODIFICATIONS

<table>
<tr><th>Section</th><th>Applicant's proposal</th><th>FDA's recommendation</th><th>Rationale</th></tr>
<tr>
<td>HIGHLIGHTS &

2.2 Recommended Dosage for Patients with Varying Degrees of Renal Impairment</td>
<td>Patients with Moderate to Severe Renal Impairment:
<table>
<tr><th>Serum Creatinine (µmol/L)</th><th>Tranexamic Acid Intravenous Dosage</th></tr>
<tr><td>120 to 250 (1.36 to 2.83 mg/dL)</td><td>10 mg/kg twice daily</td></tr>
<tr><td>250 to 500 (2.83 to 5.66 mg/dL)</td><td>10 mg/kg daily</td></tr>
<tr><td>>500 (>5.66 mg/dL)</td><td>10 mg/kg every 48 hours or 5 mg/kg every 24 hours</td></tr>
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<tr><td>>5.66 (>500 micromol/L)</td><td>10 mg/kg every 48 hours or 5 mg/kg every 24 hours</td></tr>
</table>
</td>
<td>1. Recommend editing as the serum creatinine cutoffs noted in table are not the typical criteria for the "moderate to severe" renal impairment.
2. Recommend reformatting to present serum creatinine in units more commonly used in clinical practice first.</td>
</tr>
<tr>
<td>5.4 Hepatic Impairment</td>
<td>The dose of TRANEXAMIC ACID (b) (4) INJECTION should be reduced in patients with renal insufficiency because of the risk of accumulation [see Dosage and Administration see Dosage and Administration (2)].</td>
<td>Recommend deletion</td>
<td>Per 21CFR201.57, "This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification)." This information is relevant to section 8.6 and Dosage and Administration.</td>
</tr>
<tr>
<td>7 DRUG INTERACTIONS</td>
<td>No studies of interactions between TRANEXAMIC ACID (b) (4) INJECTION and other drugs have been conducted.</td>
<td>Recommend deletion and replace with the following:

7.1 Prothrombotic Medical Products
Avoid concomitant use of Tranexamic Acid in Sodium Chloride Injection with medical products that are prothrombotic because concomitant use can further</td>
<td>According to the "Guidance for Industry—Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications", The DRUG INTERACTIONS section includes a description of the clinical</td>
</tr>
</table>

		increase the risk of thromboembolic adverse reactions associated with tranexamic acid *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)]*. 7.2 Chlorpromazine Concurrent use of chlorpromazine and Tranexamic Acid in Sodium Chloride Injection may result in increased risk of bleeding.	implications of clinically significant interactions with other drugs (including prescription and over-the-counter drugs), classes of drugs, dietary supplements, and foods and practical instructions for preventing or managing them. Recommendations for dose adjustments of co-administered drugs are included in this section. The lack of studies is not relevant to this section. Include in Highlights under Drug Interactions.
8.6 Renal Impairment	No proposed language	Reduce the dosage of Tranexamic Acid in Sodium Chloride Injection in patients with renal impairment, based on the patient's serum creatinine *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.	Include in Highlights under Use in Specific Populations . Also recommend including supporting data under Specific Populations heading under 12.3.
12.2 Pharmacodynamics	Tranexamic acid in concentrations up to 10 mg per mL blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects. (b) (4), tranexamic acid in concentrations of 10 mg and 1 mg per mL blood prolongs the thrombin time.	Tranexamic acid in concentrations of 1 mg/mL and 10 mg/mL prolongs the thrombin time. An antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to seven or eight hours. Tranexamic acid in concentrations up to 10 mg/mL blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from healthy subjects.	Recommend moving with edits to communicate more impactful information earlier in section.
12.3 Pharmacokinetics	The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin. After an intravenous dose of 1 g, the plasma concentration time curve shows a triexponential decay with a half-life of about 2 hours for the terminal elimination phase. The initial volume of distribution is about 9 to 12 liters. Urinary excretion is the main route of elimination via glomerular filtration. Overall renal	<u>Distribution</u> The initial volume of distribution is about 9 to 12 liters. The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin. <u>Elimination</u> After an intravenous dose of 1 g, the plasma concentration time curve shows a triexponential decay with a half-life of about 2 hours for the terminal	This section has been revised per guidance *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*.

	clearance is equal to overall plasma clearance (110 to 116 mL/min) and more than 95% of the dose is excreted in the urine as the unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg per kg body weight. An antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to seven or eight hours. Tranexamic acid diffuses rapidly into joint fluid and the synovial membrane. In the joint fluid the same concentration is obtained as in the serum. The biological half-life of tranexamic acid in the joint fluid is about three hours. The concentration of tranexamic acid in a number of other tissues is lower than in blood. In breast milk the concentration is about one hundredth of the serum peak concentration. Tranexamic acid concentration in cerebrospinal fluid is about one tenth of that of the plasma. The drug passes into the aqueous humor, the concentration being about one tenth of the plasma concentration.	elimination phase. *Excretion* Urinary excretion is the main route of elimination via glomerular filtration. Overall renal clearance is equal to overall plasma clearance (110 to 116 mL/min) and more than 95% of the dose is excreted in the urine as the unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg body weight. Specific Populations *Renal Impairment* The effect of renal impairment on the disposition of Tranexamic Acid in Sodium Chloride Injection has not been evaluated. Urinary excretion following a single intravenous injection of tranexamic acid declines as renal function decreases. Following a single 10 mg/kg intravenous injection of tranexamic acid, the 24-hour urinary fractions of tranexamic acid with serum creatinine concentrations 1.4 – 2.8, 2.8 – 5.7, and greater than 5.7 mg/dL were 51, 39, and 19%, respectively. The 24-hour tranexamic acid plasma concentrations for these patients demonstrated a direct relationship to the degree of renal impairment. Therefore, dose adjustment is needed in patients with renal impairment *[*see *Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*. Drug Interaction Studies No studies of interactions between Tranexamic Acid in Sodium Chloride Injection and other drugs have been conducted.	

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/

LIANG LI
03/28/2019 03:06:10 PM

GUOXIANG SHEN
03/28/2019 03:21:26 PM