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January 24, 2024

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Requesting FDA to promptly investigate and take appropriate actions against Enoxaparin Sodium injection of Sandoz supplied as graduated pre-filled syringe (ANDA no. 077857)

Dear Sir or Madam:

On behalf of Adventapharma DWC LLC ("Adventa"), the undersigned submits this Citizen Petition pursuant to the Federal Food, Drug and Cosmetic Act (the "FD&C Act") and in accordance with 21 C.F.R. §§ 10.25, 10.30, 10.31 and 314.70 to request that the Commissioner of Food and Drugs Administration investigate and take prompt appropriate actions with regards to generics enoxaparin sodium injection (ANDA no. 077857) manufactured by Shenzhen Techdow Pharmaceutical Co. Ltd, Guangdong, China and supplied by Sandoz Inc. ("Sandoz"). Generic enoxaparin sodium injection supplied by Sandoz is sold in the following dosages: 30mg/0.3ml, 40mg/0.4ml, 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml (collectively the "Sandoz Product"). The Sandoz Product poses patient safety risk due to possibility of inaccurate dosing on its enoxaparin sodium injection manufactured by Shenzhen Techdow Pharmaceutical Co. Ltd, Guangdong, China. The petition sets forth the potential risk associated with The Sandoz Product.

By way of background, enoxaparin sodium injection is an injectable drug that is sold in a pre-packaged syringe for optimal dosing in accordance with its label. *See, e.g.*, Sandoz Label, available at: http://www.accessdata.fda.gov/spl/data/f4e78371-47e9-4512-a435-de184591fbb7/f4e78371-47e9-4512-a435-de184591fbb7.xml (last accessed January 21, 2024). As with all syringes, that syringe includes specific demarcations or markings that are useful for

inter alia (i) determining the proper amount to give a patient and/or (ii) optimizing dosage. When a syringe's demarcations are blocked or obfuscated, the dosing and amounts become unclear and, thereby pose a safety risk.

The Sandoz Product poses patient safety risk because dosage demarcations are obfuscated on the Sandoz syringes. As discussed below, the Sandoz Product includes labeling that covers the syringe's demarcations. In other words, the label is superimposed on the syringe's graduations, which are essential for accurate dosing. Clear visibility of syringe demarcations is particularly important in this instance because certain indications requiring an adjustment of the dose in accordance with body weight as set forth in Tables 2 and 3 of the Sandoz Product labels. The Sandoz Product's obfuscation of syringe demarcations will, inevitably, lead to errors, particularly when adjusting the dose. Accordingly, the visibility of syringe markings is necessary to ensure patient safety. Please refer Annexure I which includes photographs of current marketed product of Sandoz showing how the product labeling obfuscates the syringe demarcations.

The FDA has a responsibility to protect the public health by ensuring that all products marketed in the United States are safe and effective. The Sandoz Product manufactured by Shenzhen Techdow Pharmaceutical Co. Ltd, Guangdong, China ("Techdow") poses a safety risk to patients and it should be promptly investigated and appropriate actions to be decided by agency.

A) ACTIONS REQUESTED

Petitioner respectfully requests that FDA take prompt appropriate action on generic enoxaparin sodium injection supplied by Sandoz and manufactured by Techdow and supplied as graduated pre-filled syringe of strength 100mg/ml supplied as 60 mg/0.6 ml, 80 mg/0.8ml and 100 mg/ml and strength 150mg/ml supplied as 120mg/0.8 ml, 150 mg/ml.[1]

1. FDA should make a prompt assessment of Sandoz's enoxaparin sodium injection 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml for its ability to deliver accurate dosing, given that the graduation on the pre-filled syringe are covered by the product label.

2. Should the Sandoz Enoxaparin Sodium Injection is found to be non-confirming product, the FDA should promptly request that Sandoz initiate a class-1, patient level recall for all non-confirming Enoxaparin sodium injection products from Sandoz supplied as graduated pre-filled syringe of strength 100mg/ml supplied as 60 mg/0.6 ml, 80 mg/0.8ml and 100 mg/ml and strength 150mg/ml supplied as 120mg/0.8 ml, 150 mg/ml, where the product label obfuscates or in any way covers the syringe demarcations.

3. Should the FDA decide that a recall is not necessary, FDA should request that Sandoz perform a human factor study for its Enoxaparin sodium injection 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml and demonstrate product comparability to the RLD and demonstrate the Sandos Product's ability to deliver an accurate dosing as per product

[1] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=38f60bd8-b518-4098-a808-b8f5a3ae6a3a#section-1

label.

4. Should the Sandoz Product be found non-confirming and if such a study is not promptly performed and provided to the FDA, FDA should change the rating of the Sandoz Product from AP to BX and request that Sandoz submit new label information.

5. FDA should investigate whether the product label of the approved ANDA, at the time of ANDA approval, for graduated pre-filled syringe 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml is consistent with product label of the Sandoz Production of the market.

6. In case the approved product label for Enoxaparin sodium injection is not consistent with the label on the commercial product then FDA should investigate the change control and QA oversight and GMP compliance of Sandoz's current manufacturer (including Techdow).

B) STATEMENTS OF THE GROUNDS

I. Factual Background:

Enoxaparin Sodium Injection is available as prefilled syringes in two concentrations, as shown in Table 1, below.

Table 1: Summary of available Enoxaparin Sodium Injection in the United States

100 mg/mL Concentration	
– *Single-Dose Prefilled Syringes*	30 mg/0.3 mL, 40 mg/0.4 mL
– *Single-Dose Graduated Prefilled Syringes*	60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL
150 mg/mL Concentration	
– *Single-Dose Graduated Prefilled Syringes*	120 mg/0.8 mL, 150 mg/1 mL

Enoxaparin sodium injection is available in seven strengths namely, 30mg/0.3ml, 40mg/0.4ml, 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml. Out of the seven strengths, five strengths are supplied in graduated pre-filled syringe namely, 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml.

The current indications for Enoxaparin sodium injection are described below: Enoxaparin Sodium Injection is a low molecular weight heparin (LMWH) indicated for:

- Prophylaxis of deep vein thrombosis (DVT) in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness
- Inpatient treatment of acute DVT with or without pulmonary embolism
- Outpatient treatment of acute DVT without pulmonary embolism
- Prophylaxis of ischemic complications of unstable angina and non–Q-wave myocardial infarction (MI)
- Treatment of acute ST-segment elevation myocardial infarction (STEMI) managed medically or with subsequent percutaneous coronary intervention (PCI)

Certain indications for enoxaparin sodium injection require a dosing based on per kilogram body weight basis. **Table 2 and 3** provides a summary of indications that require a dosing on per kilogram bodyweight basis. To deliver this accurate dose, Enoxaparin sodium injection is offered as graduated pre-filled syringes for 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml. The graduation on the pre-filled syringe and associated demarcations are designed for patients to receive accurate dosing (on per kg body weight basis) and it is critical to achieve the desired clinical efficacy and safety of the Enoxaparin Sodium Injection.

Table 2: Summary of approved indications for Enoxaparin Sodium Injection and requirements for a graduated syringe to deliver the accurate dose in Adult dosage[1]

Indication	Dosage Regimen
Abdominal Surgery	40 mg administered subcutaneously once daily
Hip or Knee Replacement Surgery	30 mg every 12 hours administered by subcutaneous injection 40 mg once a day subcutaneously may be considered for hip replacement surgery for up to 3 weeks.
Medical Patients During Acute Illness	40 mg once a day administered by subcutaneous injection
Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism	1 mg/kg every 12 hours administered Subcutaneously 1.5 mg/kg once a day administered subcutaneously at the same time every day for inpatient (hospital) treatment of patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism

Unstable Angina and Non-Q-Wave Myocardial Infarction	1 mg/kg administered subcutaneously every 12 hours
Treatment of Acute ST-Segment Elevation Myocardial Infarction	Single intravenous bolus of 30 mg plus a 1mg/kg subcutaneous dose followed by 1mg/kg administered subcutaneously every 12 hours (maximum 100 mg for the first two doses only, followed by 1 mg/kg dosing for the remaining doses) in patients with acute ST-segment elevation myocardial infarction.

Table 3: Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30 mL/minute)[2]

Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered subcutaneously once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered subcutaneously once daily
Prophylaxis in medical patients during acute Illness	30 mg administered subcutaneously once daily
Inpatient treatment of acute deep vein Thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered subcutaneously once Daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered subcutaneously once Daily
Prophylaxis of ischemic complications of unstable angina and non–Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered subcutaneously once Daily
Treatment of acute ST-segment elevation myocardial infarction in patients <75 years of age, when administered in conjunction with aspirin	30 mg single intravenous bolus plus a 1 mg/kg subcutaneous dose followed by 1 mg/kg administered subcutaneously once daily
Treatment of acute ST-segment elevation myocardial infarction in geriatric patients ≥75 years of age, when administered in conjunction with aspirin	1 mg/kg administered subcutaneously once Daily (no initial bolus)

[2] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=38f60bd8-b518-4098-a808-b8f5a3ae6a3a#section-1

Out of total seven strengths, five strengths are available as graduated pre-filled syringe as 60mg/0.6 ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8 ml, 150mg/ml.[3]

The current generic enoxaparin sodium injection supplied by Sandoz are offered as graduated the following pre-filled syringes: 60mg/0.6ml, 80mg/0.8ml, 100mg/ml 120mg/0.8ml and 150mg/ml.

The graduation on Sandoz prefilled syringes for 60mg/0.6ml, 80mg/0.8ml, 100mg/ml 120mg/0.8ml and 150mg/ml strengths are obfuscated because they are covered by the product label. Accordingly, the label covers the graduation on the pre-filled syringes. This obfuscation of graduation on above strengths limits the ability to see the syringe graduation and accurately dose the Sandoz Product.

The Sandoz Product's obfuscated syringes, inevitably, could lead to miscalculation and inaccurate dose administration to patients. Accidental overdosage following administration of enoxaparin sodium injection may lead to bleeding complications. Alternatively, if the dose administered is less than prescribed, the patient may be subject to developing blood clotting conditions.

The FDA defines a nonconforming product as a product that does not meet its specified requirements. Nonconformance can occur in both product and process. For example, a nonconformance can include manufacturing defects, inadequacies in labeling, or packaging discrepancies.[4]

The Sandoz Product, as explained above, is nonconforming because the graduation demarcations are covered by product label, which could cause the healthcare professional or user to administer the wrong dose. For example, a practitioner will be unable to provide accurate dosing of Enoxaparin sodium injection based on kilogram body weight. Accordingly, the Sandoz Product should be recalled.

II. Recommendations to Minimize Medication Errors[5]

In 2000, the Institute of Medicine (IOM) published a report entitled To Err Is Human: Building a Safer Health System. The report stated that from 44,000 to 98,000 deaths occur yearly due to medical errors, making medical errors the eighth leading cause of death in the United States.

The report identified medication errors as the most common type of error in health care. Seven thousand (7,000) deaths annually were attributed to medication errors.
In the report, IOM recommended that FDA:

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[3] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=38f60bd8-b518-4098-a808-b8f5a3ae6a3a#section-1
[4] https://www.fda.gov/files/about%20fda/published/Nonconforming-Product---Transcript.pdf
[5] Safety Considerations for Product Design to Minimize Medication Errors Guidance for Industry U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) April 2016 Drug Safety (https://www.fda.gov/media/84903/download)

Develop and enforce standards for the design of drug packaging and labeling that will maximize safety in use

In addition to the IOM recommendations, the Secretary of Health and Human Services published a report entitled Bringing Common Sense to Health Care Regulation: Report of the Secretary's Advisory Committee on Regulatory Reform (November 2002). This report recommended that FDA adopt safe labeling practices for all FDA-regulated products to improve patient safety and decrease preventable adverse events.

In July 2006, the IOM published a report entitled Preventing Medication Errors. In this report, the IOM cited labeling and packaging issues as the cause of 33 percent of medication errors, this effort is also consistent with FDA's May 10, 1999, report to the FDA Commissioner titled Managing the Risks from Medical Product Use, which underscored the importance of providing an adequate risk assessment associated with the use of drug products, including a mandate to reduce medication errors from proprietary name confusion. Contains Nonbinding Recommendations including 30 percent of fatalities from medication errors. The report stated that "[p]roduct naming, labeling, and packaging should be designed for the end user — the provider in the clinical environment and/or the consumer." The report also urged the Agency to incorporate principles of cognitive and human factors engineering in its review process to address issues concerning information presentation in labelling and naming.

III. Dosing Errors Reported to FDA Adverse Event Reporting System (FAERS) Public Dashboard:[6]

We investigated reported cases of dosing errors using the FDA Adverse Event Reporting System (FAERS) Public Dashboard. The results of our investigation are summarized in Annexure II. We found that there were a number of dosing errors reported to FAERS.

IV. Recommended recall type and recall strategy: [7]

Considering the potential for dosing errors due to lack of clear visibility of demarcations attributed to labels covering the syringes, we recommended below class of recall and depth of recall strategy as defined in FDA's "Recalls, Corrections and Removals (Devices)"

Class I - a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. Dose accuracy is essential for product like Enoxaparin Sodium Injection.

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[6] https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis

[7] https://www.fda.gov/medical-devices/postmarket-requirements-devices/recalls-corrections-and-removals-devices

- Depth of recall: Depending on the product's degree of hazard and extent of distribution to both in patients and out patients, the recall strategy is recommended at consumer or user level, including any intermediate wholesale or retail level.

V. Conclusion

For the reasons described above, Petitioner respectfully requests FDA to grant the actions requested in this citizen petition.

C) ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

D) ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), Petitioner will submit economic information upon the request by the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date 24 January 2024. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from my organization, Adventa. I verify under penalty of perjury that the foregoing is true and correct as of the data of the submission of this petition.

Sincerely,

/s/ Jay R. Deshmukh

Jay R. Deshmukh

Annexures

Annexure I: Photographs of current marketed product of Sandoz where label covers the demarcations

Annexure II: Dosing Errors Reported to FDA Adverse Event Reporting System (FAERS) Public Dashboard