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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 Investigate and take appropriate actions against Enoxaparin Sodium injection Manufactured for: NorthStar Rx, manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. supplied as graduated pre-filled syringe (ANDA no. 205660).

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 appropriate actions with regards to generic enoxaparin sodium injection (ANDA no. 205660), manufactured for: Northstar Rx LLC Memphis, TN 38141 ("Northstar") and manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. The Northstar RX's product (30mg/0.3ml, 40mg/0.4ml, 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml) ("Techdow"). Enoxaparin sodium injection (ANDA no. 205660), manufactured for ("Northstar Product") poses potential patient safety risks due to a possibility of inaccurate dosing.

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. 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 Northstar Product poses patient safety risk because dosage demarcations are obfuscated on the product's syringes. As discussed below, the Northstar 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 product labels. The Northstar 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 Northstar Product 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 Northstar Product manufactured by: 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: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. 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 and single-dose prefilled syringes 30 mg per 0.3 mL, 40 mg per 0.4 mL.[1]

1. FDA should make a prompt assessment of enoxaparin sodium injection supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. 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 for its ability to deliver accurate dosing, given that the graduation demarcations on the pre-filled syringe are covered by the product label.

2. FDA should investigate that enoxaparin sodium injection supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. supplied as graduated pre-filled syringe of strength prefilled syringes 30 mg per 0.3 mL, 40 mg per 0.4 mL. FDA should implement appropriate change controls are established in quality system and necessary FDA approval is taken for the proposed changes.

3. FDA to ensure that enoxaparin sodium injection supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. comply with the all necessary standards for Barcode and 2D barcode. FDA. FDA should further ensure that serialized product release to market are complying with grading standards.

4. Should the enoxaparin sodium injection supply by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. be found to be non-confirming product, FDA

should promptly ask Northstar Rx LLC and Shenzhen Techdow Pharmaceutical Co., Ltd.to initiate a class-1, patient level recall for all non-confirming enoxaparin sodium injection products supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd.

5. Should FDA decide that a recall is not necessary, FDA should request that Northstar and Techdow. perform a human factor study and for its enoxaparin sodium injection 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml and demonstrate product comparability to RLD and its ability to deliver an accurate dosing as per product label.

6. Should enoxaparin sodium injection be found non-confirming or if Northstar or Techdow fail to promptly provide a human factor study, FDA should change the rating of product supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. from AP to BX and ask to submit a new label information.

7. FDA should investigate if 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 Enoxaparin Sodium Injection product on the market.

8. FDA should investigate if the product label and type of syringe of the approved ANDA, at the time of ANDA approval, for pre-filled syringe 30mg/0.3ml and 40mg/0.4ml. It should be consistent with product label of the Enoxaparin Sodium Injection product on the market as currently it is available as graduated pre-filled syringe and label indicates syringes are non-graduated. Differences in the user interface of Enoxaparin sodium injection supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd.as compared to the reference listed drug (RLD) pose potential risks of altering the safety profile and inappropriate for clinical use.

9. 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 the current manufacturer.

B) STATEMENTS OF THE GROUNDS

I. Factual Background:

Enoxaparin sodium injection is available as prefilled syringes in two concentrations, as shown in;

100 mg per mL concentration:

- Single-dose prefilled syringes: 30 mg per 0.3 mL, 40 mg per 0.4 mL

- Single-dose graduated prefilled syringes: 60 mg per 0.6 mL, 80 mg per 0.8 mL, 100 mg per mL

150 mg per mL concentration:

- Single-dose graduated prefilled syringes: 120 mg per 0.8 mL, 150 mg per 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: 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml and 150mg/ml. As per the product label, 30mg/0.3ml, 40mg/0.4ml are available as non-graduated pre-filled syringe however product available in market supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. is having graduation available.

The current indications for Enoxaparin sodium injection are mentioned 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)

Several of the approved 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 requires 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 and demarcations on the pre-filled syringe are designed for patients to receive accurate dosing (on per kg body weight basis) and it is critical to achieved 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
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 1 mg/kg subcutaneous dose followed by 1 mg/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)[1]

Indication	Dosage Regimen
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

[1] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=014c6710-f2c4-fd1e-e063-6394a90ae525

Indication	Dosage Regimen
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)

As per the product label, 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.[2]

The current generic enoxaparin sodium injection (in all strengths) supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. are offered as graduated pre-filled syringes. These products are supplied as graduated pre-filled syringe is having transparent barcode on the graduations of prefilled syringes.

Because the barcode covers the graduation on the prefilled syringes, a practitioner using the drug lacks the ability to provide an accurate dosing of enoxaparin sodium injection on the basis of kilogram body weight basis for the indications defined in Table 2 and 3. This can lead to the potential for dosing errors. Indeed, the visibility of these markings is necessary to accurately measure doses. Accordingly, the Northstar Products pose potential risks of altering the safety profile and inappropriate for clinical use.

II. FDA is Working to Reduce Medication Errors

A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer," according to the National Coordinating Council for Medication Error Reporting and Prevention.

Medication errors can occur throughout the medication-use system. Such as, when prescribing a drug, upon entering information into a computer system, when the drug is being prepared or dispensed, or when the drug is given to or taken by a patient.

The U.S. Food and Drug Administration (FDA) receives more than 100,000 U.S. reports each year associated with a suspected medication error. FDA reviews the reports and classifies them to determine the cause and type of error. The reports come from drug manufacturers, and healthcare professionals and consumers through MedWatch, the Agency's safety information and adverse event reporting program. Serious harmful results of a medication error may include:

- Death

[2] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=014c6710-f2c4-fd1e-e063-6394a90ae525

- Life threatening situation
- Hospitalization
- Disability
- Birth defect

After drugs are approved for marketing in the United States, FDA monitors and evaluates medication error reports. FDA may require a manufacturer to revise the labels, labelling, packaging, product design or proprietary name to prevent medication errors. FDA may also issue communications alerting the public about a medication error safety issue, by way of Drug Safety Communications, Drug Safety Alerts, Medication Guides and Drug Safety Podcasts.

FDA also put into place rules requiring barcodes on certain drug and biological product labels. Barcodes allow healthcare professionals to use barcode scanning equipment to verify that the right drug -- in the right dose and right route of administration -- is being given to the right patient at the right time. This system is intended to help reduce the number of medication errors that occur in hospitals and other healthcare settings.[3]

All legally required marking shall be printed on the package in a legible font in an area which does not intrude into the symbol region, including quiet zones, and shall not affect the scan ability of the symbol.

Quiet Zone is an area free of printing, preceding and following all standard bar code symbols, that is required for the decoding process.[4]

Enoxaparin sodium injection supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd. supplied as graduated pre-filled syringe is having transparent barcode on the graduations of prefilled syringes.

Bar codes on the graduation of pre-filled syringes are likely to cause inaccurate bar code scanning (which will impede the ability to verify that the right drug in the right dose and right route of administration is used) and interferes with the visibility of graduation which is an essential element for accurate dosing.

The nonconforming product for enoxaparin sodium injection should be recalled because the graduation markings are covered by bar code, which could cause the healthcare professional or user to administer the wrong dose.

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[3] https://www.fda.gov/drugs/information-consumers-and-patients-drugs/working-reduce-medication-errors
[4] THE HEALTH INDUSTRY BAR CODE (HIBC) SUPPLIER LABELING STANDARD FDA-2011-N-0090-0274_attachment_4

III. Recommended recall type and recall strategy:[5]

Considering the potential for dosing errors due to lack of clear visibility of demarcations/ markings attributed from covering by label 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.

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.

IV. 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.

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

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 Deshmukh

Jay R. Deshmukh

Annexure I: Photographs of current marketed product supplied by: Northstar Rx LLC manufactured by: Shenzhen Techdow Pharmaceutical Co., Ltd.