CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214520Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 5, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214520
Product Name, Dosage Form, and Strength:	taurolidine and heparin catheter lock solution[a], 40.5 mg/3 mL and 3,000 USP Units/3 mL (13.5 mg/mL and 1,000 USP Units/mL) 67.5 mg/5 mL and 5,000 USP Units/5mL (13.5 mg/mL and 1,000 USP Units/mL)[b]
Applicant/Sponsor Name:	CorMedix, Inc. (CorMedix)
TTT ID #:	2023-4791-2
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), container labels and carton labeling received on October 3, 2023 for taurolidine and heparin catheter lock solution. The Division of Anti-Infectives (DAI) requested that we review the revised PI, container labels and carton labeling for taurolidine and heparin catheter lock solution (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[c]

[a] Applicant provided the established name as "taurolidine and heparin catheter lock solution." The Office of Pharmaceutical Quality (OPQ) will make a final determination of the established name during the NDA review.
[b] Applicant provided the strength presentations as "taurolidine 40.5 mg/3 mL (13.5 mg/mL) and heparin 3,000 USP Units/3 mL (1,000 USP Units/mL)" and "taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)." OPQ will make a final determination of the strength presentation during the NDA review.
[c] Myers, D. Label and Labeling Review Memo for taurolidine and heparin catheter lock solution (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 SEP 22. TTT ID No.: 2023-4791-1.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 3, 2023

Prescribing Information (PI) (Images not shown) received on October 3, 2023

- Clean (Draft) PI available from the following link: \\CDSESUB1\EVSPROD\nda214520\0150\m1\us\14lbl\1dl\3dlt\11413-nda-214520revised-dr.docx.
- Track changes PI available from the following link: \\CDSESUB1\EVSPROD\nda214520\0150\m1\us\14lbl\1dl\2adlt\11412-nda-214520revised-dr.docx.

Container labels

(b) (4)

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/s/

DEBORAH E MYERS
10/05/2023 11:23:52 AM

VALERIE S VAUGHAN
10/05/2023 11:37:14 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 22, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214520
Product Name, Dosage Form, and Strength:	taurolidine and heparin catheter lock solution[a], 40.5 mg/3 mL and 3,000 USP Units/3 mL (13.5 mg/mL and 1,000 USP Units/mL) 67.5 mg/5 mL and 5,000 USP Units/5mL (13.5 mg/mL and 1,000 USP Units/mL)[b]
Applicant/Sponsor Name:	CorMedix, Inc. (CorMedix)
TTT ID #:	2023-4791-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 24, 2023 for taurolidine and heparin catheter lock solution. The Division of Anti-Infectives (DAI) requested that we review the revised container labels and carton labeling for taurolidine and heparin catheter lock solution (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[c]

[a] Applicant provided the established name as "taurolidine and heparin catheter lock solution." The Office of Pharmaceutical Quality (OPQ) will make a final determination of the established name during the NDA review.
[b] Applicant provided the strength presentations as "taurolidine 40.5 mg/3 mL (13.5 mg/mL) and heparin 3,000 USP Units/3 mL (1,000 USP Units/mL)" and "taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)." OPQ will make a final determination of the strength presentation during the NDA review.
[c] Myers, D. Label and Labeling Review for taurolidine and heparin catheter lock solution (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 17. TTT ID No.: 2023-4791.

2 DISCUSSION AND CONCLUSION

In response to our container label recommendations, we note that CorMedix included in their submission that they have *"…relocated the manufacturer information to the side panel as well as removed* [redacted] *" and the "* [redacted] *" statements from the Principal Display Panel (PDP). In regards to the Agency's recommendation for removing the 2-D matrix barcode and serial number from the side panel of the vial container labels, we are concerned doing so will result in a disruption and impediment of accurately capturing administration of the medication in a health care provider's electronic health records system since it is common clinical practice for health care providers to scan the 2-D matrix barcode and serial number prior to dispensing and administration. As a result, while CorMedix greatly appreciates the suggestion, we did not make this change."*[d]

On September 11, 2023, based on CorMedix's response above, we sent an information request (IR) seeking clarification regarding what would occur if the 2-D matrix barcode was scanned first. For example, if the serial number would populate in the location intended for the drug's national drug code (NDC) considering that the NDC, not the serial number, is often used as verification during the medication use process and is an important safety feature.[e]

On September 14, 2023, CorMedix submitted their response to the Agency's IR dated September 11, 2023, providing clarification that the NDC will be included in the 2-D matrix barcode. Additionally, CorMedix notes that the Agency, through its Drug Supply Chain Security Act (DSCA) guidance, permits the voluntary inclusion of a 2-D matrix code on a product's immediate container, provided the product remains compliant with all other labeling requirements, including the linear barcode requirements under 21 CFR §201.25.[f] Furthermore, CorMedix respectfully requests an explanation for why the Agency is concerned with the presence of the 2-D matrix barcode, specifically the relevance of the scanning order for the linear versus the 2-D matrix barcode. CorMedix specifically states, "the information provided after the scan would be the same."[g]

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[d] Cover Letter: NDA 214520: Response to FDA Information Request for Updates to Carton-Container Labeling. Berkeley Heights (NJ): CorMedix Inc.; 2023 AUG 24. Available from: \\CDSESUB1\EVSPROD\nda214520\0146\m1\us\2cover\12-cover-letter-resub-3-fd.pdf.

[e] Park, K. FDA Communication: Information Request (IR) – DMEPA IR (Response requested by 9/18/2023) for taurolidine and heparin catheter lock solution (NDA 214520). Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2023 SEP 11. NDA 214520. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806f2d7c.

[f] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

[g] Labeling: CorMedix Response to FDA DMEPA Information Request NDA 214520. Berkeley Heights (NJ): CorMedix Inc.; 2023 SEP 14. Available from: \\CDSESUB1\EVSPROD\nda214520\0148\m1\us\14lbl\1dl\1dccl\11411-cormedix-dmepa-vial-.pdf.

We acknowledge CorMedix's response dated September 14, 2023, to our IR dated September 11, 2023, and find the aforementioned proposal to include the 2-D matrix barcode, which would additionally include the NDC, is acceptable from a medication error perspective.

Beyond the aforementioned, we identified areas with the container labels and carton labeling that can be improved from a medication error perspective. Thus, we provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 3 (Table 1) for CorMedix, Inc.

3 RECOMMENDATIONS FOR CORMEDIX, INC.

Clarification that the 2-D matrix barcode on the container label will contain the National Drug Code addresses the Agency's previous concern and we have no additional question(s) relating to what information the 2-D matrix barcode will include. However, we recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for CorMedix, Inc.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	As currently presented, the warning box on the principal display panel(s) (PDP) does not include that this product is not intended for use as a lock flush. However, Section 2 *Dosage and Administration* of the prescribing information (PI) includes the statement "Do not use TRADENAME as a catheter lock flush product."	Including the warning that this product is not intended for use as a catheter lock flush may be helpful to mitigate the risk of wrong technique in use medication errors. Additionally, warning information should be consistent across all elements of the labeling (e.g., container label, carton labeling, PI). Thus, inclusion of a statement, such as "Do not use as a catheter lock flush" aligns the warning box on the PDP(s) with Section 2 *Dosage and Administration* of the PI.	To further help to mitigate the risk of wrong technique in use medication errors and assure alignment with the PI, revise the warning box on the PDP to include the statement "Do not use as a catheter lock flush." For example, within the warning box include the text: For Instillation in Central Venous Catheters Not for systemic administration Do not use as a catheter lock flush To ensure sufficient space to improve readability, on the container labels, we recommend relocating the storage statement to the side panel *or* if space limitations, removing the storage statement from the container

Table 1. Identified Issues and Recommendations for CorMedix, Inc.			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			labels, as allowed per 21 CFR 201.10(i). For the carton labeling, see additional recommendations in #2.
2.	As currently presented, the "Limited Population" statement lacks an asterisk following the statement referencing the reader to the footnote text associated with the statement "*See prescribing information for Tradename for information about the limited population."	Without the asterisk following the "Limited Population" statement, the important information included in the footnote could be missed.	Add an asterisk (*) following the "Limited Population" statement on the container labels and carton labeling. We acknowledge that the container label lacks adequate space to include the footnote text associated with the statement "*See prescribing information for Tradename for information about the limited population." However, inclusion of the asterisk following the "Limited Population" statement on the container label references the reader to the associated footnote on the carton labeling. Additionally, we recommend including the statement "*See prescribing information for Tradename for information about the limited population" on the PDP to better associate it with the "Limited Population" statement. To increase space to accommodate the revision, we recommend: • removing the (b) (4) from the PDP, as it already appears on

Table 1. Identified Issues and Recommendations for CorMedix, Inc.			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			other panels of the carton labeling • removing the (b) (4) from the PDP, as it already appears on other panels of the carton labeling and • reducing redundancy by combining the carton net quantity statement (i.e., Contains 10 single-dose vials) with the package type term in the lower right corner (e.g., "Contains 10 Single-dose vials. Discard unused portion." *OR* "10 x 3 mL Single-Dose vials. Discard unused portion.").
Carton Labeling			
1.	As currently presented, the product identifier is missing the human readable national drug code (NDC).	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number,	We recommend that you add the human readable NDC to the product identifier.

Table 1. Identified Issues and Recommendations for CorMedix, Inc.			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. For additional details, See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).[h]	

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[h] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

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VALERIE S VAUGHAN
09/22/2023 10:45:13 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 21, 2023

To: Kristine E. Park, Regulatory Project Manager
Division of Anti-Infectives Products (DAIP)

Gregory Mak, Clinical Reviewer, DAIP
Mukilan Natarajan, Clinical Reviewer, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

From: Qumerunnisa Syed, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Samuel Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (taurolidine and heparin) catheter lock solution, for central venous catheter instillation use

NDA: 214520

Background:
In response to DAI's consult request dated June 14, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for TRADENAME (taurolidine and heparin) catheter lock solution, for central venous catheter instillation use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 07, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on August 24, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Qumerunnisa Syed at 301-796-8897 or Qumerunnisa.syed@fda.hhs.gov.

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/s/

QUMERUNNISA B SYED
09/21/2023 03:47:05 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 17, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214520
Product Name, Dosage Form, and Strength:	taurolidine and heparin catheter lock solution,[a] 40.5 mg/3 mL and 3,000 USP Units/3 mL (13.5 mg/mL and 1,000 USP Units/mL) 67.5 mg/5 mL and 5,000 USP Units/5mL (13.5 mg/mL and 1,000 USP Units/mL)[b]
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CorMedix, Inc (CorMedix)
FDA Received Date:	May 15, 2023 and July 19, 2023
TTT ID #:	2023-4791
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

[a] Applicant provided the established name as "taurolidine and heparin catheter lock solution." The Office of Pharmaceutical Quality (OPQ) will make a final determination of the established name during the NDA review.

[b] Applicant provided the strength presentations as "taurolidine 40.5 mg/3 mL (13.5 mg/mL) and heparin 3,000 USP Units/3 mL (1,000 USP Units/mL)" and "taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)." OPQ will make a final determination of the strength presentation during the NDA review.

1 REASON FOR REVIEW

As part of the approval process for taurolidine and heparin catheter lock solution, the Division of Anti-Infectives (DAI) requested that we review the proposed taurolidine and heparin catheter lock solution prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND/REGULATORY HISTORY

CorMedix previously submitted NDA 214520 on June 30, 2020. However, NDA 214520 received a Complete Response on February 26, 2021. Subsequently, CorMedix resubmitted NDA 214520 on February 25, 2022. However, NDA 214520 received a second Complete Response on August 4, 2022.[c]

On May 15, 2023, CorMedix submitted their Resubmission[d] to provide their responses to the deficiencies included in the Agency's Complete Response Letter (CRL) dated August 4, 2022.

On June 15, 2023, CorMedix notified the Agency that they are seeking approval for both a 3 mL and 5 mL product packaging configuration.[e]

On June 20, 2023, the Agency provided CorMedix confirmation that we considered their May 15, 2023, resubmission a complete class 2 response to the Agency's CRL dated August 4, 2022.[f]

On June 29, 2023, the Agency sent an IR to CorMedix noting that two sperate prescribing information (PI) documents were submitted (dated May 15, 2023), one for the 3 mL and one for the 5 mL product packaging.[g] Since both proposed commercial drug product volumes and packaging presentations have similar safety profiles and use, the Agency recommended that CorMedix submit a single PI covering both packaging presentations (i.e., 3 mL and 5 mL volumes).

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[c] Park, K. Communication: Complete Response Letter for taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5 mL (1,000 Units/mL) catheter lock solution. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2022 AUG 22. NDA 214520. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80679c63.

[d] Cover Letter: NDA 214520: Resubmission. Berkeley Heights (NJ): CorMedix Inc.; 2023 MAY 15. Available from: \\CDSESUB1\EVSPROD\nda214520\0136\m1\us\2cover\12-cover-letter-resubmissi.pdf.

[e] CorMedix Response to FDA Request for Additional Information NDA 214520. Berkeley Heights (NJ): CorMedix Inc.; 2023 JUN 15. Available from: \\CDSESUB1\EVSPROD\nda214520\0139\m1\us\11iaincum\1qia\1111-cormedix-ir-response-.pdf.

[f] Park, K. FDA Communication: Acknowledge – Class 2 Resubmission for NDA 214520. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2023 JUN 20. NDA 214520. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806d722d.

[g] Park, K. FDA Communication: NDA 214520 - Information Request. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2023 JUN 29. NDA 214520. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806da68c.

On July 19, 2023, CorMedix responded[h] to the Agency's IR dated June 29, 2023, submitting their updated combined PI for the 3 mL and 5 mL single-dose vials.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 DISCUSSION

Prior to the issuance of the August 4, 2022 CRL, we reviewed the proposed container label and carton labeling submitted on June 30, 2020,[i] December 30, 2020,[j] February 12, 2021,[k] and February 25, 2022.[l] However, we note that our container label and carton labeling recommendations dated May 26, 2022, were not communicated to CorMedix prior to the CR issued on August 4, 2022. Thus, we considered our previous recommendations to see if they are

[h] Cover Letter: NDA 214520: Response to FDA Request for Updated Prescribing Information. Berkeley Heights (NJ): CorMedix Inc.; 2023 JUL 19. Available from: \\CDSESUB1\EVSPROD\nda214520\0140\m1\us\2cover\12-cover-letter-updated-co.pdf.

[i] Myers, D. Label and Labeling Review for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 06. RCM No.: 2020-477.

[j] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 06. RCM No.: 2020-477-1.

[k] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 16. RCM No.: 2020-477-2.

[l] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAY 26. OSE RCM No.: 2022-434.

applicable for this current review. Furthermore, the Applicant's proposal to add an additional volume size (i.e., 3 mL) warranted additional considerations.

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for CorMedix, Inc.

5 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the product strength is not included.	The "strength or potency of the dosage form in metric system" is required by 21 CFR 201.57(c)(17)(i).	Add the proposed product strengths. For example, • 3 mL single-dose vial containing taurolidine 40.5 mg/3 mL (13.5 mg/mL) and heparin 3,000 USP Units/3 mL (1,000 USP Units/mL) • 5 mL single-dose vial containing taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)

6 RECOMMENDATIONS FOR CORMEDIX, INC

Table 3. Identified Issues and Recommendations for CorMedix, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	As currently presented, there is inadequate	Lack of adequate differentiation may	We recommend using different colors, boxing, or some other

Table 3. Identified Issues and Recommendations for CorMedix, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	differentiation between the 3 mL vial and the 5 mL vial.	contribute to wrong dose (e.g., inadequate volume) medication errors.	means to ensure adequate differentiation between the volumes (i.e., "3 mL" and "5 mL") for the container labels and carton labeling. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).[m]
2.	As currently presented, the expiration date format is defined as "YYYY-MM-DD." However, it is unclear how the month will be expressed.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors. For example, presenting the month as 'MA' or 'JU' does not clearly communicate whether 'MA' or 'JU' is for the months of March or May and June or July, respectively.	Clarify how you intend to express the month within the expiration date statement. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are

[m] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 3. Identified Issues and Recommendations for CorMedix, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
3.	As currently presented, the storage statement on the container labels and carton labeling does not align with the storage information included in the prescribing information. For example, the statements, "Do NOT freeze" and "Vials must be stored in the commercial carton, prior to the instillation in the central venous catheters" are missing from the storage statement.	Improperly storing this product (e.g., not protecting from freezing or not storing vials in commercial carton prior to installation) could lead to deteriorated drug medication errors.	Ensure the storage statements are consistent across the labels and labeling. Because the vial container labels may be too small to include all of the storage information, ensure the carton labeling includes all storage information that is included in the prescribing information.
Container Labels			
1.	The container label principal display panels (PDPs) are crowded, which decreases the readability of critical information.	Crowded labels may contribute to critical information being overlooked. For example, inclusion of the (b) (4) on the PDP takes the readers' attention away from critical product information on the PDP. Moreover, lines or blocks of text should be separated by sufficient blank space to avoid crowding or clutter.	To reduce crowding of the PDP and improve readability, we recommend placing noncritical information on the side panel of the container label rather than on the PDP. Consider removing the 2-D matrix barcode and serial number from the side panel of the vial container labels and subsequently relocating the (b) (4) to the side panel.

Table 3. Identified Issues and Recommendations for CorMedix, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Errors. Food and Drug Administration* (May 2022)[n] for additional information. Additionally, as currently presented, the 2-D matrix barcode and serial number are notated on the side panel of the vial container labels. However, the vial container labels do not require the product identifier, given the smallest saleable unit is the carton of 10.	Additionally, to further reduce crowding of the PDP and improve readability you may consider removing the "(b) (4)" *and* the "(b) (4)" statements per 21 CFR 201.10(i) and USP Chapter <7> standards.
General – Carton Labeling			
1.	We note a grammatical error within the net quantity statement of the 5 mL carton containing 10 vials. Revise "vial" to "vials" so that the net quantity statement states "Contains 10 single-dose vials".		
2.	Consider including the National Drug Code (NDC) on the principal display panel of each carton. Additionally, to further differentiate between the NDCs of the 3 mL and 5 mL product we recommend increasing the prominence of the drug code (middle digits) by increasing their font size in comparison to the remaining digits and putting them in bold type font. As an example: XXXXX-**XXX**-XX.		

[n] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for taurolidine and heparin catheter lock solution that CorMedix, Inc submitted on July 19, 2023.

Table 4. Relevant Product Information for taurolidine and heparin catheter lock solution	
Initial Approval Date	N/A
Active Ingredient	taurolidine and heparin
Indication	To reduce the incidence of catheter-related bloodstream infections (CRBSIs) in patients with kidney failure receiving chronic hemodialysis (HD) through a central venous catheter (CVC). This drug is indicated for use in a limited and specific population of patients. Limitations of Use The safety and effectiveness have not been established for use in populations other than patients with kidney failure receiving chronic HD through a CVC.
Route of Administration	Instill into the CVCs only (not intended for systemic administration) Do not use as a catheter lock flush product.
Dosage Form	catheter lock solution (CLS)
Strength	3 mL single-dose vial (b) (4) taurolidine 40.5 mg/3 mL (13.5 mg/mL) and heparin 3,000 USP Units/3 mL (1,000 USP Units/mL) 5 mL single-dose vial (b) (4) taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5mL (1,000 USP Units/mL)
Dose and Frequency	Withdraw a sufficient volume of CLS from the vial using a sterile needle and syringe to fill (b) (4) catheter lumens. Prior to initiation of the next HD session, the CLS must be aspirated from the catheter and discarded. Discard any unused portion remaining in the vial.
How Supplied	3 mL single-dose vial carton containing 10 vials 5 mL single-dose vial carton containing 10 vials
Storage	Vials must be stored at a controlled room temperature of 20°C to 25°C (68°F to 77°F). Do not freeze. Vials must be stored in the commercial carton, prior to the instillation in the central venous catheters.
Container Closure	Stopper: (b) (4), Grey, 13 mm Cap: aluminum seal, 13 mm, flip-off

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 28, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "NDA 214520" and "IND 113764." Our search identified four previous reviews[o,p,q,r], and we considered our previous recommendations to see if they are applicable for this current review.

[o] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAY 26. OSE RCM No.: 2022-434.

[p] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 16. OSE RCM No.: 2020-477-2.

[q] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 06. OSE RCM No.: 2020-477-1.

[r] Myers, D. Label and Labeling Review for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 06. OSE RCM No.: 2020-477.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[s] along with postmarket medication error data, we reviewed the following taurolidine and heparin catheter lock solution labels and labeling submitted by CorMedix, Inc.

- Container labels received on May 15, 2023
- Carton labeling received on May 15, 2023
- Prescribing Information (PI) (Image not shown) received on July 19, 2023
    - Combined Clean (Draft) PI available from the following link: \\CDSESUB1\EVSPROD\nda214520\0140\m1\us\14lbl\1dl\3dlt\11413-nda-214520revised-dr.docx.
    - Combined Track changes PI available from the following link: \\CDSESUB1\EVSPROD\nda214520\0140\m1\us\14lbl\1dl\3dlt\c19bf03bd2.docx.

F.2 Label and Labeling Images

Container labels

[s] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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DEBORAH E MYERS
08/17/2023 09:23:42 AM

VALERIE S VAUGHAN
08/17/2023 09:26:59 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Memorandum

Date:	July 28, 2023
Reviewer:	Sarah Kang, PharmD, MSP, BCPS Division of Pharmacovigilance II (DPV II)
Team Leader:	Mallika Mundkur, MD, MPH DPV II
Product Name:	Heparin
Subject:	Hyperkalemia
Application Type/Number:	See Appendix A
Applicant/Sponsor:	See Appendix A
TTT Record ID:	2023-3883
SS ID #:	1005071

We would like to acknowledge Allison Lardieri, PharmD, BCPPS for her valuable feedback and assistance with this memorandum.

EXECUTIVE SUMMARY

In this pharmacovigilance memorandum, requested by the Division of Nonmalignant Hematology (DNH), the Division of Pharmacovigilance (DPV) II documents prior work and regulatory activity relating to the association between heparin and the adverse event of hyperkalemia. This memorandum includes a summary of a comprehensive 2015 DPV review on this topic. Also included within this memorandum is a high-level assessment of literature published since the completion of the 2015 DPV review. (b) (4) On February 24, 2023, DNH opened a Newly Identified Safety Signal (NISS) (SSID 1005071) for heparin and hyperkalemia.

Although we can confirm that reports of hyperkalemia associated with heparin use continue to be published, we do not have new labeling recommendations based upon our review of the medical literature for this memorandum compared to recommendations made in the 2015 DPV review.

1 INTRODUCTION

In this pharmacovigilance memorandum, requested by the Division of Nonmalignant Hematology (DNH), the Division of Pharmacovigilance (DPV) II documents prior work and regulatory activity relating to the association between heparin and the adverse event of hyperkalemia. This memorandum includes a summary of a comprehensive 2015 DPV review on this topic. Also included within this memorandum is a high-level assessment of literature published since the completion of the 2015 DPV review. (b) (4) [redacted] On February 24, 2023, DNH opened a Newly Identified Safety Signal (NISS) (SSID 1005071) for heparin and hyperkalemia.

1.1 BACKGROUND

Previous DPV review and NDA 201370 (heparin sodium injection - Pfizer)

- On July 21, 2011, FDA approved NDA 201370 (heparin sodium injection - Pfizer)
- On June, 26, 2013, DPV completed a Food and Drug Administration Amendments Act (FDAAA) Section 915 Non-New Molecular Entity Safety Summary review for NDA 201370. In this review, DPV identified one FAERS case of hyperkalemia with heparin use and planned to provide a separate analysis (Tobenkin et al. 2013).
- On May 6, 2015, DPV completed a review of hyperkalemia with heparin use. In this review, DPV evaluated FAERS and published literature from 2005 to 2015, and identified 13 cases (FAERS [12] and literature [1[a]]) of serious hyperkalemia with heparin use. Reported serum potassium elevation ranged from 5.8 to 8.7 mEq/L. One case reported a fatal outcome[b] not directly related to hyperkalemia and four cases reported electrocardiogram (EKG) abnormalities that coincided with cardiac arrest, arrhythmias, ventricular fibrillation and pulseless ventricular tachycardia. Eight cases reported risk factors for hyperkalemia (i.e., renal dysfunction, diabetes). DPV concluded that they identified cases reporting serious risks (e.g., abnormal cardiac conduction, arrhythmias, and cardiac arrest) associated with hyperkalemia secondary to heparin use from FAERS and the published medical literature. Based on well-documented cases of hyperkalemia associated with heparin use and potential serious risks associated with hyperkalemia, **DPV recommended the addition of hyperkalemia under the ADVERSE REACTIONS section of heparin product labeling (Tobenkin et al. 2015).**
- On June 8, 2015, the Division of Hematology Products (DHP) consulted the Division of Cardiovascular and Renal Products (DCRP) to provide input on the question of whether the strength of evidence presented in the OSE review was sufficient to revise heparin labeling (McMullen 2015).
- On June 9, 2015, the DHP memo stated that "there is insufficient information to assess any relationship with heparin. DHP will not pursue further in the absence of sufficient evidence to assess" (Leaman and Kane 2015).

[a] (Thomas et al. 2008)
[b] The patient died likely due to septic shock and multi-organ failure

- [redacted] (b) (4)
-
-

NDA 018609 (heparin sodium in 0.9% sodium chloride injection - Baxter)

- On July 15, 2021, the applicant for NDA 018609 (Baxter) submitted a Changes Being Effected labeling supplement (CBE)- 58, which included an addition of hyperkalemia under the WARNINGS AND PRECAUTIONS section. As part of its justification for the labeling change, the applicant included three articles[d] to support the addition of hyperkalemia (Baxter 2021).
- On January 3, 2022, CBE-58 was approved with the addition of hyperkalemia under the WARNINGS AND PRECAUTIONS section.

NDA 019952 (heparin sodium in 5% dextrose injection – B. Braun)

- On January 20, 2023, the applicant for NDA 019952 (B. Braun) submitted a PAS-48, which included an addition of hyperkalemia under the WARNINGS AND PRECAUTIONS section. The applicant's reason for the labeling change was to be consistent with competitor labeling (BBraun 2023).

Biologic plausibility

Drugs can cause hyperkalemia by multiple mechanisms (e.g., interfere with potassium homoeostasis or aldosterone secretion, increase potassium supply) and are a primary cause or contributing factor of hyperkalemia in 35 to 75% of hospitalized patients (Ben Salem et al. 2014). Drugs that can induce hyperkalemia, based on their underlying mechanism, include beta-blockers, calcium channel blockers, digoxin, aldosterone antagonists, potassium sparing diuretics, trimethoprim, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drug and heparin (Ben Salem et al. 2014).

Hyperkalemia with heparin use has been recognized for some time in the medical literature. Heparin is a potent, reversible inhibitor of aldosterone synthesis (Oster et al. 1995). Decreased aldosterone leads to less potassium excretion, and thus can induce hyperkalemia (Oster et al. 1995, Verma et al. 2010). Hyperkalemia may occur in 7 to 8% of patients treated with heparin (Oster et al. 1995), and the risk is increased in patients with renal failure, diabetes, metabolic acidosis, or concomitant use of drugs that can induce hyperkalemia (e.g., potassium salts, ACE inhibitors) (Oster et al. 1995, Simon et al. 2023).

[c] (Leehey et al. 1981, Monreal et al. 1989)
[d] (Edes and Sunderrajan 1985, Aull et al. 1990, Oster et al. 1995)

1.2 REGULATORY HISTORY

FDA approved multiple heparin products since 1939. **Table 1** summarizes the approval information for heparin products that are currently available in the United States. Note, this table only includes approved NDA heparin products. See Appendix A for a list of approved ANDA heparin products.

Table 1. Approval information for heparin products (NDAs)

NDA	Applicant	Approval year	Product name	Route of administration	Labeling
017029	Fresenius Kabi	1972	Heparin sodium injection	IV and subcut	(FreseniusKabi 2021)
017037	Hikma	1972	Heparin sodium injection	IV and subcut	(Hikma 2020)
017651	Fresenius Kabi	1978	Heparin sodium injection	IV and subcut	(FreseniusKabi 2020)
018609	Baxter	1982	Heparin sodium in 0.9% Sodium Chloride injection (2 units/mL)	IV infusion	(Baxter 2022)
018916	Hospira	1984	Heparin sodium in Sodium Chloride injection	IV	(Hospira 2020)
019339	Hospira	1985	Heparin sodium in 5% Dextrose Injection	IV	(Hospira 2018)
019952	B. Braun	1992	Heparin sodium in 5% Dextrose Injection	IV	(BBraun 2016a)
019953	B. Braun	1992	Heparin sodium in 0.9% Sodium Chloride injection (2 units/mL)	IV infusion	(BBraun 2016b)
201370	Pfizer	2011	Heparin sodium injection	IV and subcut	(Pfizer 2019b)

Abbreviations- IV: intravenous, NDA: New Drug Application, Subcut: subcutaneous

1.3 RELEVANT PRODUCT LABELING

Only one currently marketed heparin product, NDA 018609 (heparin sodium in sodium chloride injection), includes a statement regarding hyperkalemia under the WARNINGS AND PRECAUTIONS as well as ADVERSE REACTIONS sections of product labeling (Baxter

2022). Of note, enoxaparin labeling includes the risk of hyperkalemia under the ADVERSE REACTIONS section (Sanofi 2021). No other heparin injection products approved in the United States describe the risk of hyperkalemia within their product labeling.

NDA 018609 (Baxter)

5.6 Hyperkalemia

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly in patients with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium, or taking potassium sparing drugs. The risk of hyperkalemia appears to increase with duration of therapy but is usually reversible upon discontinuation of heparin.

Measure plasma potassium in patients at risk of hyperkalemia before starting heparin therapy and periodically in all patients treated for more than 5 days or earlier as deemed fit by the clinician.

6.1 Postmarketing Experience

Metabolism and Nutrition Disorders: Hyperkalemia

Enoxaparin

6.2 Postmarketing Experience

Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward the development of hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparing drugs, administration of potassium, hematoma in body tissues).

8.7 Renal Impairment

In patients with renal failure, treatment with enoxaparin has been associated with the development of hyperkalemia [see Adverse Reactions (6.2)].

2 METHODS AND MATERIALS

In addition to reviewing DARRTS for information regarding prior work on this safety issue, DPV conducted a high-level search of the literature for recent publications relating to heparin and hyperkalemia. This search strategy and results summary are provided in more detail below. We did not conduct a formal assessment of causality.

2.1 LITERATURE SELECTION CRITERIA

DPV selected publications reporting one or more individual cases of hyperkalemia with heparin identified as the culprit drug. We adopted the definition of hyperkalemia from the 2015 DPV review (serum potassium level above 5 mEq/L). We excluded publications that reported a contributory role of a concomitant medication (e.g., temporal association and positive dechallenge).

2.2 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategy described in **Table 2**.

Table 2. Literature Search Strategy	
Date of search	May 30, 2023
Database	Embase, PubMed
Search terms	Embase 'heparin'/mj/exp AND 'hyperkalemia'/mj/exp PubMed (("heparin"[MeSH Terms] OR "heparin"[All Fields] OR "heparine"[All Fields] OR "heparins"[All Fields] OR "heparin s"[All Fields] OR "heparinate"[All Fields] OR "heparinated"[All Fields] OR "heparines"[All Fields] OR "heparinic"[All Fields] OR "heparinisation"[All Fields] OR "heparinised"[All Fields] OR "heparinization"[All Fields] OR "heparinize"[All Fields] OR "heparinized"[All Fields] OR "heparinizing"[All Fields]) AND ("hyperkalaemia"[All Fields] OR "hyperkalemia"[MeSH Terms] OR "hyperkalemia"[All Fields] OR "hyperkalemias"[All Fields]))
Years included in search	2015-2023
Other criteria	Humans

3 RESULTS

The published medical literature search retrieved 29 articles. After accounting for duplicate publications and applying the selection criteria in **Section 2.1**, we included seven publications describing seven cases of hyperkalemia with heparin use in this case series (see **Figure 1**).

Figure 1. Literature Case Selection

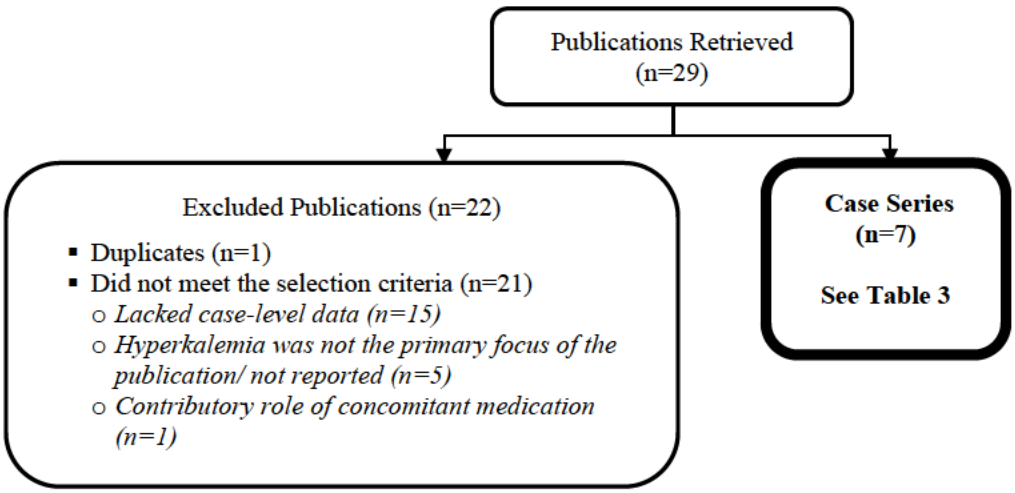

Table 3 summarizes the seven cases of hyperkalemia reported with heparin for this case series.

Appendix B contains a line listing of the seven cases in this case series.

Table 3. Descriptive Characteristics of Hyperkalemia With Heparin in This Case Series, Medical Literature Published between 2015 and 2023 (N=7)	
Publication type	
Article	3
Conference abstract/poster	4
Age (year)	
Range	22-77
Median	69
Sex	
Female	2
Male	5
Country*	
Foreign	4
United States	3
Route of heparin administration	(n=6)
Intravenous†	5
Subcutaneous	1
Risk factors for hyperkalemia‡	(n= 4)
Acute kidney injury	4
Diabetes	2
Concomitant ACE inhibitor use	1
Severe hypoxemia/shock	1
Peak serum potassium level range (mEq/L)	(n=5§) 5.8 - 6.7

Table 3. Descriptive Characteristics of Hyperkalemia With Heparin in This Case Series, Medical Literature Published between 2015 and 2023 (N=7)	
EKG change reported	0
Positive rechallenge	1
Positive dechallenge	5
Outcome	
Death	2

* The primary author location was used if the country of source was not stated in Embase

† Includes three cases that reported "therapeutic" heparin, heparin treatment for thrombosis and heparin for hemodialysis without specified route

‡ A case may include more than one risk factor.

§ Five cases reported serum potassium levels reported in mmol/L or mEq/L. Serum potassium 1 mmol/L = 1 mEq/L. Of the remaining two cases that are not included here, one case reported 5.6 without specifying units, and one case reported 5.9 mg/dL.

| One case reported that hyperkalemia resolved after heparin discontinuation and treatment with fludrocortisone.

Appendix C includes a summary and commentary for these cases.

4 DISCUSSION

The previous 2015 DPV review of FAERS and the published medical literature supported an association between heparin and hyperkalemia based on temporal association, positive rechallenge, and biologic plausibility. Current heparin labeling for NDA 018609 (heparin sodium in sodium chloride injection- Baxter) lists hyperkalemia under the WARNINGS AND PRECAUTIONS section. PAS-48 for NDA 019952 (heparin sodium in 5% dextrose injection-B. Braun), which includes an addition of hyperkalemia is currently under review. Our findings from review of the published medical literature since 2015 are consistent with the 2015 DPV review findings and the current heparin labeling (NDA 018609) regarding an association between heparin use and hyperkalemia.

Although we identified a limited number of cases reporting hyperkalemia with heparin use between 2015 and present, hyperkalemia with heparin use is well documented in published medical literature. and heparin has been available for almost 85 years. Therefore, healthcare providers may be less likely to publish or report these adverse events with heparin.

5 CONCLUSION

Hyperkalemia associated with heparin use continues to be reported in the medical literature. We do not have new labeling recommendations based upon this review compared to recommendations made in the 2015 DPV review.

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7 APPENDICES

7.1 APPENDIX A. APPLICATION TYPE/ NUMBER AND APPLICANTS FOR HEPARIN PRODUCTS INCLUDED IN THIS MEMORANDUM (FDA 2023)

Application Type/ Number	Product name (strength)	Applicant
NDA 201370*†	Heparin sodium injection (1,000 units/mL, 5000 units/mL) Heparin sodium preservative free (1,000 units/mL)	Pfizer
NDA 017029*†	Heparin sodium injection (1,000 units/mL, 10,000 units/mL, 20,000 units/mL) Heparin sodium preservative free (1,000 units/mL, 10,000 units/mL)	Fresenius Kabi USA
NDA 017037*†	Heparin sodium injection (1000 units/mL, 5000 units/mL, 10,000 units/mL)	Hikma Pharmaceuticals USA
NDA 017651*†	Heparin sodium injection (5000 units/mL)	Fresenius Kabi USA
NDA 018609	Heparin sodium in 0.9% Sodium Chloride injection (2 units/mL)	Baxter Healthcare
NDA 019953*†	Heparin sodium in 0.9% Sodium Chloride injection (2 units/mL)	B Braun Medical
NDA 019339	Heparin sodium in 5% Dextrose Injection (50 units/mL, 100 units/mL)	Hospira
NDA 019952*†	Heparin sodium in 5% Dextrose Injection (40 units/mL, 50 units/mL, 100 units/mL)	B Braun Medical
NDA 018916*†	Heparin sodium in Sodium Chloride injection (2 units/ml, 50 units/mL, 100 units/mL)	Hospira
ANDA 214804	Heparin sodium injection (1,000 units/mL)	Be Pharmaceuticals
ANDA 205323	Heparin sodium injection (1000 units/mL, 5000 units/mL)	Gland Pharma
ANDA 090571	Heparin sodium injection (1000 units/mL, 5000 units/mL, 10,000 units/mL)	Hospira
ANDA 203851	Heparin sodium injection (1000 units/mL, 5000 units/mL, 10,000 units/mL)	Mylan Laboratories
ANDA 211005	Heparin sodium injection (1000 units/mL)	Nanjing King-Friend Biochemical Pharmaceutical
ANDA 211007	Heparin sodium injection (1000 units/mL, 5000 units/mL, 10,000 units/mL)	Nanjing King-Friend Biochemical Pharmaceutical
ANDA 090808	Heparin sodium injection (1000 units/mL, 5000 units/mL, 10,000 units/mL)	Sagent Pharmaceuticals
ANDA 091682	Heparin sodium injection (1000 units/mL, 5000 units/mL)	Sandoz

Application Type/ Number	Product name (strength)	Applicant
ANDA 202957	Heparin sodium injection (1000 units/mL, 5000 units/mL)	Shenzhen Techdow Pharmaceutical
ANDA 208827	Heparin sodium injection (5000 units/ 0.5 mL)	B Braun Medical
ANDA 088100†	Heparin sodium injection (5000 units/mL)	Hospira
ANDA 206552	Heparin sodium injection (5000 units/mL)	Fresenius Kabi USA
ANDA 212061	Heparin sodium injection (5000 units/mL)	Nanjing King-Friend Biochemical Pharmaceutical
ANDA 202733	Heparin sodium injection (5000 units/mL)	Shenzhen Techdow Pharmaceutical
ANDA 214839	Heparin sodium injection (10,000 units/mL)	Be Pharmaceuticals
ANDA 201002	Heparin sodium injection (10,000 units/mL)	Sandoz
ANDA 203198	Heparin sodium injection (10,000 units/mL, 20,000 units/mL)	Shenzhen Techdow Pharmaceutical
ANDA 203852	Heparin sodium injection (20,000 units/mL)	Mylan Laboratories
ANDA 211004	Heparin sodium injection (20,000 units/mL)	Nanjing King-Friend Biochemical Pharmaceutical
ANDA 090809	Heparin sodium injection (20,000 units/mL)	Sagent Pharmaceuticals
ANDA 212441	Heparin sodium in 0.9% Sodium Chloride injection (2 units/mL)	Fresenius Kabi USA
ANDA 090810	Heparin sodium preservative free (1,000 units/mL)	Sagent Pharmaceuticals
ANDA 202732	Heparin sodium preservative free (1,000 units/mL)	Shenzhen Techdow Pharmaceutical
ANDA 089522	Heparin sodium preservative free (10,000 units/mL)	Hospira
ANDA 212060	Heparin sodium preservative free (10,000 units/mL)	Nanjing King-Friend Biochemical Pharmaceutical

***** Reference Listed Drugs (RLD): a drug product approved under section 505(c) of the FD&C Act for which FDA has made a finding of safety and effectiveness

† Reference Standard (RS): the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval of an ANDA

7.2 APPENDIX B. LINE LISTING OF HYPERKALEMIA AND HEPARIN USE CASE SERIES

	Publication	Publication year	Country Derived*	Age (years)	Sex	Fatal outcome
1.	Kargar, F, A Zahedmehr, Z Shafii, T Babaee, S Banar, Y Rezaei and S Hosseini (2023). "Heparin-Induced Hyperkalemia Following Heart Surgery: A Case Report." Iranian Heart Journal 24(2): 104-107.	2023	Iran	69	Female	Yes
2.	Nlandu, YM, YM Engole, MI Mboliassa, TM Sakaji, PU Kobo, PM Boloko, PK Mafuta, JP Tsangu, K Van Echkout, JM Kanku, G Kalifa, R Ahmed and JB Bukabau (2022). "Ineffectiveness of Intermittent Hemodialysis in a Critically Ill COVID-19 Patient: A Case of Persistent Heparin-Induced Hyperkalemia." Case Rep Nephrol 2022: 8613656.	2022	United Kingdom	72	Male	Yes
3.	Kovacs, J, S Talib, A Khashan, B Garsondiya and MP Carson (2022). "A 77-Year-Old Man with Heparin-Induced Aldosterone Suppression Causing Hyperkalemia." Am J Case Rep 23: e937017.	2022	USA	77	Male	No
4.	Baleguli, V, M Herrera, R Mahmood and E Raybon-Rojas (2021). "HEPARIN-INDUCED RENAL TUBULAR ACIDOSIS MASQUERADING AS HYPERKALEMIA IN A PATIENT WITH SARS-COV-2." Chest 160(4, Supplement): A967.	2021	Netherland	72	Male	No
5.	Talib, U and P Lee (2019). "HEPARIN-INDUCED HYPERKALEMIA: THE UN-NOTICED SHADOW." Chest 156(4, Supplement): A1958.	2019	USA	66	Male	No
6.	Vangoitsenhoven, R, PJ Martens and C Mathieu (2017). "Heparin-induced hyperkalemia-an underestimated cause of hyperkalemia." Acta Clinica Belgica: International Journal of Clinical and Laboratory Medicine 72: 21-22.	2017	Belgium	22	Female	No
7.	Ganesh, M, A Mangla, I Paintsil and F Iskander (2015). "Heparin and hyperkalemia-an uncommon cause of a common effect." Journal of General Internal Medicine 30: S406.	2015	USA	60	Male	No

*The primary author location was used if the country of source was not stated in Embase

7.3 APPENDIX C. LITERATURE CASE NARRATIVE SUMMARY (N=7)

7.3.1 Fatal Outcome (n=2)

Kargar et al/2023/article/Iran/death (Kargar et al. 2023)

A 69-year-old-female with a medical history of triple-vessel coronary artery disease underwent coronary artery bypass grafting (CABG) surgery.

- Preoperative transthoracic echocardiography showed a moderate reduction in the left ventricular ejection fraction (40%) with mild regurgitation in the mitral and aortic valves. The preoperative serum sodium, potassium and creatinine were 137 mEq/L, 4.2 mEq/L and 1.5 mg/dL, respectively.
- The patient underwent CABG and the serum potassium level at the end of the operation was 4.2 mEq/L. The patient was transferred to the intensive care unit (ICU) and started on heparin intravenous (IV) infusion and heparin routine use (to wash arterial and central lines). EKG was normal.
- Six hours after ICU admission, serum potassium level was 5.8 mEq/L. Other lab tests (e.g., arterial blood gas, blood glucose) were within normal ranges. The patient did not receive any "causative agent of hyperkalemia" perioperatively.
- The serum potassium level progressively increased to an unspecified level despite diuresis, relatively stable renal function and hyperkalemia treatment with IV glucose, furosemide, and insulin infusion.
- The patient expired on the night of the operation due to "hyperkalemia heart dysfunction unresponsive to medical treatment"

Reviewer comments:
This case reported hyperkalemia in an elderly patient who underwent CABG surgery and received heparin (during surgery and in the ICU). Hyperkalemia did not respond to medical treatments, and the patient died from "hyperkalemia heart dysfunction" on the night of the surgery. The authors noted that "all etiologies of hyperkalemia were ruled out," and the patient did not receive other medications with a risk of hyperkalemia perioperatively; however, they did not provide further detail regarding timeline of serum potassium level, EKG change and hyperkalemia treatment leading up to the death.

Nlandu et al/2022/article/ United Kingdom/ death (Nlandu et al. 2022)

A 72-year-old male with a medical history of type II diabetes mellitus, hypertension, unspecified arrhythmia for the past 10 years presented with coronavirus disease 2019 (COVID-19) infection. Home medications included repaglinide, irbesartan, hydrochlorothiazide, manidipine[e] and flecainide.

- For COVID-19, the patient was treated with azithromycin, rivaroxaban, vitamin C, vitamin D, prednisone, and oxygen at home for 6 days.
- Due to worsening dyspnea, the patient was admitted to the hospital. The chest computerized tomography scan showed "very significant COVID-19 pneumonia stage 5" without pulmonary embolism. The patient also had elevated cardiac and inflammatory biomarkers, and respiratory alkalosis with hypoxemia. The patient did not have kidney

[e] calcium channel blocker for treatment of hypertension (Cheer and McClellan 2001)

dysfunction or hyperkalemia (serum potassium level was 4 mmol/L [reference range 3.0 – 5.0]).

- At the time of hospital admission, the patient was treated with noninvasive ventilation with a high level of oxygen, dexamethasone, vitamin C, vitamin D, empiric antibiotics (ceftriaxone with ofloxacin as the "first line," and imipenem, amikacin, and vancomycin as the "second line"), and enoxaparin[f] 1 mg/kg subcutaneously every 12 hours.
- On hospital day 11, the patient experienced severe hypoxemia, shock, and acute kidney injury (AKI). The patient required intubation with mechanical ventilation and started on norepinephrine and dobutamine.
- On hospital day 14 (also reported as day 15), due to worsening AKI with hypervolemia and hyperkalemia refractory to medical treatment (e.g., insulin-dextrose, beta 2 agonist and sodium polystyrene sulfonate), hemodialysis was started. Serum potassium levels were 5.1 and 6.6 mmol/L on hospital days 14 and 15, respectively.
- On an unknown day, irbesartan was stopped. Hyperkalemia associated with hyponatremia persisted despite daily hemodialysis combined with medical treatment.
- Between hospital days 16 and 20, serum potassium and sodium levels ranged from 5.9 to 6.4 mmol/L and 134 to 137 mmol/L, respectively.
- The authors noted unfractionated heparins were used for anticoagulation during hemodialysis.
- On hospital day 22, the patient was transferred abroad.
- Next day, the patient died "in context of a severe hypoxemia."

Reviewer comments:
This case reported hyperkalemia in a critically ill elderly patient with risk factors for hyperkalemia (i.e., diabetes, AKI, severe shock which can lead to metabolic acidosis, and irbesartan use). It is unclear if enoxaparin was continued in the setting of AKI. Irbesartan was discontinued due to hyperkalemia, however, hyperkalemia persisted despite hemodialysis and medical treatment. In this case, the authors mentioned "heparin-induced hyperkalemia," however, they also noted that the patient received heparin during hemodialysis, which was initiated after onset of hyperkalemia. The patient died from "severe hypoxemia."

7.3.2 Non-Fatal Outcomes (n=5)

Kovacs et al /2022/article/United States (Kovacs et al. 2022)

A 77-year-old male with a medical history of type 2 diabetes, benign prostatic hyperplasia, chronic kidney disease (Stage 3B), and nephrectomy for renal cancer presented with COVID-19, acute respiratory distress with elevated serum troponin and AKI (serum creatinine 2.4 mg/dL; glomerular filtration rate 28 mL/min/1.73 m^2).

- At the time of admission, the patient's serum potassium level was 5.1 mmol/L (reference range 3.6 - 5.1). The patient was started on "high-dose" heparin infusion for potential underlying hypercoagulable state in the setting of COVID-19 infection.
- On hospital day 4, serum potassium level was 5.6 mmol/L, and heparin was stopped. The patient did not receive other medications known to cause serum potassium elevation.

[f] Authors stated that therapeutic anticoagulation was used due to high risk of thromboembolic events in severe COVID-19 patients.

- On hospital day 5, serum potassium level was 6.2 mmol/L, and the patient was treated with sodium polystyrene sulfonate, insulin, and dextrose.
- On hospital day 6, serum potassium was 5.5 mmol/L. Due to a concern of pulmonary embolism (worsening tachycardia, respiratory distress, and nonspecific elevations of D-dimer of 15.71 mg/dL), "high-dose" heparin was restarted. In the evening, the patient's serum potassium level increased to 6.0 mmol/L. Heparin was discontinued and serum potassium level "quickly" normalized to 4.8 mmol/L and remained within normal limits.

Reviewer comments
This case reported hyperkalemia in an elderly patient with risk factors for hyperkalemia (i.e., diabetes and AKI with underlying chronic kidney disease). Initial hyperkalemia appeared 3 days after "high-dose" heparin initiation. This case reported both positive rechallenge and dechallenge. Although a list of concomitant medications was not provided, this case noted that the patient did not receive other medications with a risk of hyperkalemia.

Baleguli et al /2021/poster/Netherland (Baleguli et al. 2021)
A 72-year-old male with a medical history of chronic kidney disease and leukemia (in remission) presented with COVID-19 infection. The patient was admitted to the ICU for acute hypoxic respiratory failure and started on dexamethasone, remdesivir, azithromycin, ceftriaxone, enoxaparin,[g] zinc and vitamin C.

- On hospital day 10, the patient was intubated.
- On hospital day 14, serum creatinine peaked at 3.51 mg/dL.
- On unknown day, the patient developed hyperkalemia presumed to be secondary to AKI. Serum potassium level was not reported.
- Unspecified, but more than 10 days after hospitalization, argatroban was started due to a concern of heparin induced thrombocytopenia (HIT), but stopped for bleeding.
- On unknown day, heparin (unspecified route) was started when HIT antibody results were obtained.
- On hospital day 21, serum potassium peaked at 6.7 mmol/L. The patient was treated with calcium gluconate, insulin, dextrose 50% injection, patiromer 8.4 g without improvement in potassium levels.
- On unknown day, heparin was discontinued. Subsequently, serum potassium levels improved.

Reviewer comments:
This case reported hyperkalemia in a critically ill elderly patient with risk factors for hyperkalemia (i.e., AKI with underlying chronic kidney disease). It is unclear if enoxaparin was continued in the setting of AKI or if initial hyperkalemia resolved prior to heparin initiation. This case reported positive dechallenge.

Talib and Lee/ 2019/poster/United States (Talib and Lee 2019)
A 66-year-old "wheelchair-bound" male with a medical history of chronic indwelling suprapubic catheter presented with AKI and multi-drug resistant urinary tract infection (treated with

[g] the authors did not specify dose or indication for enoxaparin use.

imipenem). The patient received subcutaneous heparin every eight hours for deep vein thrombosis prophylaxis.

- On hospital day 8, the patient developed right lower extremity deep vein thrombosis and was treated with "therapeutic" unfractionated heparin while bridging to warfarin.
- On hospital day 10, serum potassium level was 5.9 mg/dL. Hyperkalemia did not improve with sodium polystyrene sulfonate. EKG was normal and the patient's vital signs remained stable.
- On hospital day 11, international normalized ratio (INR) was therapeutic, and heparin was discontinued. This resulted in immediate normalization of the potassium.

Reviewer comments
This medical resident poster reported hyperkalemia in an elderly patient with a risk factor for hyperkalemia (i.e., AKI). Hyperkalemia was not reported while on subcutaneous heparin for prophylaxis, but occurred 2 days after therapeutic heparin initiation, suggesting a potential dose-response relationship. This case reported positive dechallenge.

Vangoitsenhoven et al./2017/conference abstract/Belgium (Vangoitsenhoven et al. 2017)
A 22-year-old female with a medical history of cystic fibrosis and recent lung transplantation was started on unfractionated heparin for an extensive thrombosis of the pulmonary veins, left atrium, vena cava superior and right atrium.

- Five days after heparin initiation, the patient developed hyperkalemia (5.6 mmol/L),
- On an unknown day, serum potassium level progressed to 6.1 mmol/L while the plasma sodium declined to 134 mmol/L.
- On an unknown day, adrenal insufficiency was excluded by normal ACTH-stimulation test, and the patient had plasma aldosterone within normal range [110 ng/mL (normal range 12 – 150 ng/mL)] and plasma renin activity in the lower normal range [0.8 ng/mL/h (normal range 0.5 – 2.6 ng/ mL/h)].
- On an unknown day, unfractionated heparin was switched to low-molecular-weight heparin. The patient was treated with fludrocortisone 0.05 mg per day, and hyperkalemia resolved.

Reviewer comments:
This case reported a patient who experienced hyperkalemia 5 days after starting therapeutic heparin in the setting of normal aldosterone level. Hyperkalemia resolved after heparin was switched to low- molecular-weight heparin and treatment with fludrocortisone. Concomitant medications were not provided.

Ganesh et al. /2015/conference abstract/United States (Ganesh et al. 2015)
A 60-year-old male without previous medical history, presented with a 3-month history of intermittent fever, productive cough, hemoptysis and 30-pound weight loss and was found to have tuberculosis.

- The patient was started on unspecified anti-tuberculosis therapy. The patient also received subcutaneous heparin for venous thromboembolism prophylaxis.
- On hospital day 3, the patient's routine labs showed serum potassium level of 5.5 (unspecified units). There were no EKG changes and the patient's renal function remained "normal."

- On hospital day 4, serum potassium remained high at 5.6 (unspecified units). Other causes of hyperkalemia, including renal failure, adrenal insufficiency, medications such as non-steroidal anti-inflammatory drugs, ACE inhibitors, and volume depletion were ruled out. Heparin was discontinued and switched to a pneumatic compression device.
- The next morning, hyperkalemia resolved with serum potassium level at 4.6 (unspecified units).

Reviewer comments:
This case reported a patient who experienced hyperkalemia 3 days after starting a prophylactic dose of heparin. This case reported positive dechallenge. The authors excluded potential roles for concomitant medications and other causes of hyperkalemia (e.g., renal failure, adrenal insufficiency).

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 26, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214520
Product Name and Strength:	Defencath (taurolidine and heparin) catheter lock solution, 67.5 mg/5 mL and 5,000 USP Units/5 mL (13.5 mg/mL and 1,000 USP Units/mL)
Applicant/Sponsor Name:	CorMedix Inc. (CorMedix)
OSE RCM #:	2022-434
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

On February 25, 2022, CorMedix submitted their Resubmission[a] to provide their responses[b] to the deficiencies included in the Agency's Complete Response Letter (CRL) dated February 26, 2021.[c] Thus, the Division of Anti-Infectives (DAI) requested that we review the proposed prescribing information (PI), container label, and carton labeling for Defencath (Appendix A) to determine if they are acceptable from a medication error perspective.

[a] Cover Letter: NDA Resubmission for Defencath (taurolidine and heparin) NDA 214520. Berkeley Heights (NJ): CorMedix Inc.; 2022 FEB 25. Available from: \\CDSESUB1\evsprod\nda214520\0120\m1\us\2cover\12-cover-letter-final.pdf.
[b] CorMedix Inc. Responses to Complete Response received February 26, 2021 for Defencath (taurolidine and heparin) NDA 214520. Berkeley Heights (NJ): CorMedix Inc.; 2022 FEB 25. Available from: \\CDSESUB1\evsprod\nda214520\0120\m1\us\12oc\4rca\1124-request-for-lpad-revi.pdf.
[c] Park, K. Communication: Complete Response Letter for Defencath (taurolidine and heparin) NDA 214520. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2021 FEB 26. NDA 213645. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805d5c41.

2 BACKGROUND/REGULATORY HISTORY

On March 25, 2022, the Agency provided CorMedix confirmation that we considered their February 25, 2022, resubmission a complete class 2 response to the Agency's CRL dated February 26, 2021.[d]

3 DISCUSSION

Prior to the issuance of the February 26, 2021 CRL, we reviewed the proposed container label and carton labeling submitted on June 30, 2020,[e] December 30, 2020,[f] and February 12, 2021.[g] Our review of the container label and carton labeling submitted on February 12, 2021, did not identify any additional areas of vulnerability that may lead to medication errors and thus, we provided no additional recommendations at that time.

However, the CRL dated February 26, 2021, included the following container label and carton labeling recommendation:

> **CARTON AND CONTAINER LABELING**
>
> Submit draft carton and container labeling revised as follows:
>
> As currently presented, the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXX-XX) on both the proposed container label and carton labeling dated February 12, 2021. However, we note that Section 16, *How Supplied/Storage and Handling* of your proposed PI includes the NDC 72990-(b) (4). Therefore, replace the current placeholders (NDC XXXXX-XXX-XX) with the intended NDCs on the container label and carton labeling and submit for our review.

We acknowledge that CorMedix has replaced the previously denoted placeholder (i.e., NDC XXXXX-XXX-XX) with the National Drug Code (NDC) 72990-(b) (4), as proposed in Section 16, *How Supplied/Storage and Handling* of their proposed prescribing information (PI), on both their proposed container label and carton labeling. However, the NDC associated with the linear barcode on the carton labeling remains denoted by a placeholder (i.e., "XXXXX XXXXX").

Additionally, we note that the current human readable NDC (i.e., 72990-(b) (4)) included on the carton labeling (carton containing (b) (4) single-dose vials) is identical to the NDC (i.e., 72990-(b) (4)) included on the container label (individual vial). A carton containing more than one unit should have a different package code (last 2 digits of NDC) than that of the containers within the carton.

We also note that the proposed container label denotes an "*Area for Serial, Lot, Expiration and 2D Code*". While we find CorMedix's proposed location and inclusion of the lot number and

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[d] Park, K. FDA Communication: Acknowledge – Class 2 Resubmission for taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5 mL (1,000 Units/mL) catheter lock solution) NDA 214520. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2022 MAR 25. NDA 214520. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8065231b.

[e] Myers, D. Label and Labeling Review for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 06. RCM No.: 2020-477.

[f] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 06. RCM No.: 2020-477-1.

[g] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 16. RCM No.: 2020-477-2.

expiration date acceptable, we note that they did not define their intended expiration date format.

Furthermore, we note that as currently presented on the container label and carton labeling, the statement "Single-Dose Vial - Discard Unused Portion" lacks prominence.

Therefore, we include our identified issues, rationale for concern, and recommendations to mitigate risk of medication error in Table 1 below.

4 CONCLUSION

Our evaluation of the proposed carton labeling received on February 25, 2022, identified additional areas of vulnerability with the proposed container label and carton. Therefore, we provide our identified issues, rationale for concern, and recommendations to mitigate risk of medication error in Table 1 below, for CorMedix Inc. to implement prior to approval of this NDA.

5 RECOMMENDATIONS FOR CORMEDIX INC.

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the statement "Single-Dose Vial - Discard Unused Portion" lacks prominence.	Overlooking this information could lead to unused amounts being "saved" for future use and result in use of deteriorated drug product medication errors.	We recommend that you bold the font of the statement "Single-Dose Vial - Discard Unused Portion" to increase the prominence of this important information.
Carton Labeling			
1.	As currently presented, the current human readable national drug code (NDC) (i.e., 72990-(b) (4)) included on the carton labeling (carton containing(b) (4) single-dose vials) is identical to the NDC (i.e., 72990-(b) (4)) included on the	The NDC assigned to a carton containing more than one unit should have a different package code (last 2 digits) than that of the individual containers within the carton.	Revise the package code (last two digits of the NDC) on either the carton labeling or the container label to provide differentiation between the individual vials and the carton containing(b) (4) single-dose vials. Additionally, ensure the revised NDC is updated in Section 16, *How Supplied /Storage and*

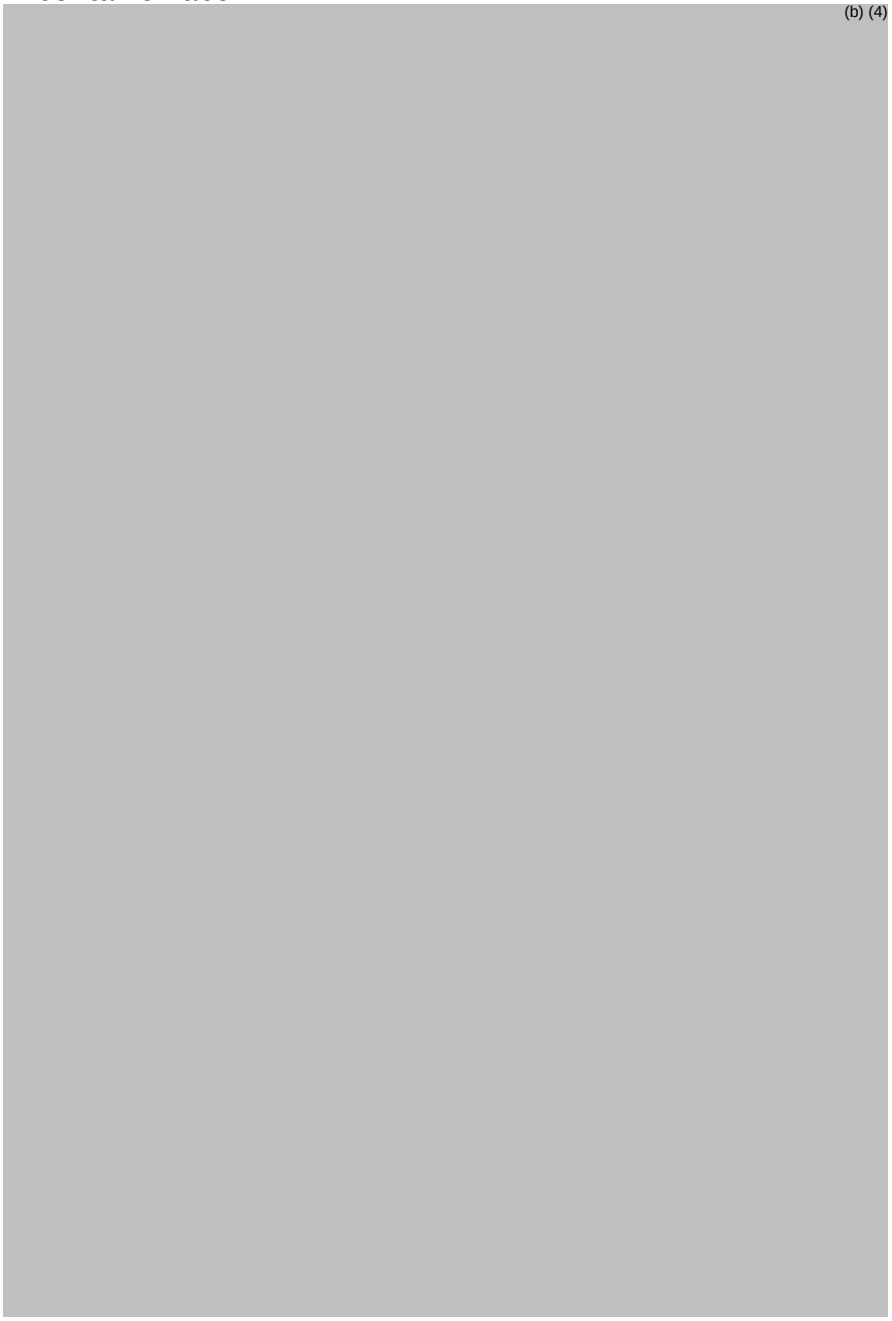
Table 1. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	container label (individual vial).		*Handling* of the Prescribing Information.
2.	As currently presented, the NDC associated with the linear barcode on the carton labeling is denoted by a placeholder (i.e., "XXXXX XXXXX").		Replace the current placeholder (i.e., "XXXXX XXXXX") associated with the linear barcode with the intended NDC.
Container Label			
1.	We acknowledge your denoted *"Area for Serial, Lot, Expiration and 2D Code"* on your proposed container label. While we find your proposed location and inclusion of the lot number and expiration date acceptable, we note that you did not define your intended expiration date format.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the human-readable expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 25, 2022

Prescribing Information (PI) (Images not shown) received on February 25, 2022:

- Cleaned proposed (Draft) PI available at the following link: \\CDSESUB1\evsprod\nda214520\0120\m1\us\14lbl\1dl\3dlt\11413-nda-214520revised-dr.docx.
- Annotated Comparison with Listed Drug available at the following link: \\CDSESUB1\evsprod\nda214520\0120\m1\us\14lbl\1dl\2adlt\11412-nda-214520revised-dr.docx.

Container label



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ADDENDUM TO CDRH REVIEW
NDA 214520

Based on the toxicological risk assessment on the detected leachables from the two test catheters and the balanced adverse events between the two clinical study arms during the LOCK-IT-100 clinical trial on the patients following exposure to multiple types of catheters, the use of these marketed catheters with Defencath is not likely to raise an unacceptable toxicity concern to the patients from a biocompatibility perspective. From a mechanical integrity standpoint, tensile testing was performed on two test catheters. The company did not perform cumulative, repeated systematic mechanical strength and life testing on other marketed catheters. Multiple catheter types were studied in the LOCK-IT-100 trial and we are not restricting Defencath to use in only the two catheters with bench testing for the labeling.

Douglas Silverstein -S

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Date: 2021.02.25 12:33:13 -05'00'

Douglas M. Silverstein, M.D.

Carolyn Y. Neuland -S

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Carolyn Y. Neuland, Ph.D., A.D., THT3A1

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Addendum to CDRH review

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 16, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214520
Product Name and Strength:	Defencath (taurolidine and heparin) catheter lock solution, 13.5 mg/mL and 1,000 USP Units/mL
Total Product Strength:	57.5 mg/5 mL and 5,000 Units/mL
Applicant/Sponsor Name:	CorMedix Inc. (CorMedix)
OSE RCM #:	2020-477-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Division Director (Acting):	Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 12, 2021 for Defencath. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Defencath (Appendix A) to determine they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review, as well as comments from our Office of Pharmaceutical Quality (OPQ) colleagues.[a,b]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Myers, D. Label and Labeling Review Memo for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 06. RCM No.: 2020-477-1.
[b] Park, K. FDA Communication: NDA 214520 (Defencath) - Labeling/PMR Information Request (please respond by 02/12/2021): FDA, CDER, OND, DAI (US); 2021 JAN 05. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805cfc64.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DEBORAH E MYERS
02/16/2021 02:08:23 PM

LUBNA A MERCHANT
02/16/2021 02:14:48 PM

Division of Cardiology and Nephrology
Consultation for the Division of Anti-Infectives

From: Shen Xiao, M.D., Ph.D., Medical Officer
Division of Cardiology and Nephrology

Through: Aliza Thompson, M.D., M.S., Deputy Director
Division of Cardiology and Nephrology

To: Kristine Park, PhD, Project Manager
Division of Anti-Infectives

This memo serves to close out the consult for NDA 214520 (Neutrolin solution for prevention of catheter-related bloodstream infections in patients with end-stage renal disease receiving hemodialysis through a central venous catheter) dated June 29, 2020.

Reason for consult:
On June 1, 2020, CorMedix Inc submitted the clinical portion of NDA 214520 for Neutrolin solution for prevention of catheter-related bloodstream infections in patients with end-stage renal disease receiving hemodialysis through a central venous catheter. On June 29, 2020, the Division of Anti-Infectives submitted a consult to the Division of Cardiology and Nephrology requesting assistance with the review of the primary efficacy endpoint, as well as input on the numerically higher proportion of catheter removal and loss of patency events in the Neutrolin arm.

DCN response:
Drs. Xiao and Thompson attended meetings for NDA 214520 and participated in discussions as needed.

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/s/

SHEN XIAO
01/31/2021 04:59:07 PM

ALIZA M THOMPSON
01/31/2021 05:02:34 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Memorandum

Date: Jan 26, 2021

Subject: ICCR NDA 214520 – Biocompatibility Consult

Device: Neutrolin Catheter Lock Solution

To: Peter Kim, M.D.
CDER

Through: Douglas Silverstein, M.D., Lead reviewer
CDRH/OPEQ/OHT3/DHT3A

From: Qin Zhang, Ph.D., DABT
CDRH/OPEQ/OHT3/DHT3A

Sponsor: CorMedix Inc.

PURPOSE OF REVIEW

I am requested to review the biocompatibility information in the submission on the compatibility study of Neutrolin drug with hemodialysis catheters.

INTENDED USE

The Neutrolin drug product is intended for the prevention of catheter-related bloodstream infections (CRBSIs) in patients with end-stage renal disease receiving hemodialysis through a central venous catheter.

DEVICE DESCRIPTION

The Neutrolin drug is instilled into the lumens of hemodialysis central venous catheters following hemodialysis treatment in order to make the catheter lumen hostile to bacterial and fungal growth and resistant to clot formation.

The drug contains antimicrobial and anticoagulant substances, its composition of the Neutrolin CLS, 5.0ml/via is listed in the following table:

Table 1: Ingredients and Composition of Neutrolin® CLS, 5.0 mL vial

Ingredient	Concentration	Quantity per mL	Function	Reference to Specification
Taurolidine	1.35% wt/vol	13.5 mg	Antimicrobial	NEU01-API-TAU-002
Heparin Sodium USP	1000 U/mL	1000 units	Anticoagulant	NEU01-API-HEP-001
Anhydrous Citric Acid	2.61% wt/vol	26.1 mg	Buffer	NEU01-RWM-CIT-001
Sodium Hydroxide (b) (4)	Not Applicable	QS to pH (b) (4)	pH Adjustment, (b) (4)	NEU01-RWM-NAO-002
Water for Injection	Not Applicable	(b) (4)		NEU01-RWM-WFI-002

To evaluate the compatibility of the Neutrolin drug product with hemodialysis catheters, the sponsor provided several chemical leachable/extractable study reports as summarized below:

Study 1:

The sponsor conducted the chemical extractable study (#10-6116-N15) on the following selected catheters: MedComp Split Cath (polyurethane) and MedComp Hemo-Cath LT (silicone). The catheters were filled with Neutrolin lock solution or saline lock solution at room temperature for 24 hrs. Then the treated catheters were extracted separately in water and hexane at 37°C for 72hrs. The testing was performed at (b) (4) in accordance with ISO 10993-18 standard. The extractables from the water and hexane were analyzed using a variety of analytical techniques including ICP/MS, LC/MS and GC/MS analysis. The extractables from the Neutrolin lock solution and saline lock solution treatment were analyzed using ICP/MS and GC/MS only. The extract compounds from two catheters were listed in Table 3-8 for comparison.

Study 2:

The sponsor provides a chemical extractable study report (#EXT-20-008-R) performed at (b) (4). The test article is the selected catheter only as listed in the table below.

Table 1: List of catheters tested

Catheters	Model	Catalogue	Material
MedCOMP (without port C-A)	Hemo-Cath Silicone Double Lumen Basic Set	MC101243	Silicone
Merit (without port C-B)	Centros Flo LT HD Catheter 15F	CENFP19K/A	Polyurethane

The catheter was extracted with water, ethanol and hexane solvents for 72hrs at 37°C. The extractables from the water and hexane were analyzed using a variety of analytical

techniques including ICP/MS, LC/MS and GC/MS analysis. The extract compounds were listed in Table 5 & 6.

In the chemical extractable study report provided above, the catheters were extracted with a various of polarity solvents only. The Neutrolin lock solution was not used to extract the catheters for its compatibility evaluation. Therefore, the results from this chemical extractable study is not sufficient to evaluate the interaction between the drug and catheters. The evaluation will focus on the leachable study of the catheters following incubation with the lock solution as provided in study 3 below:

Study 3:

The sponsor provides the chemical leachable study report (#LEA-20-007-R) performed by (b) (4). The same report is also provided in Attach CDRH 1.2 in sponsor's response to FDA Additional Information Request below:

In response to CDRH comment related to device-drug compatibility concerning device derived contaminants released as leachates in the drug, you provided extraction study performed on two catheters, Medcomp Split Cath III and Medcomp Hemo Cath. You state that (b) (4) *were released in both polar and non-polar extracts, post- Neutrolin exposure in both catheters. The report shows that the extraction studies were conducted after the catheters were dwelled for 24 hours in the Neutrolin lock solution, and subsequently the Neutrolin dwelled catheters were extracted with saline or hexane. In the report, we were not able to locate if the device related residuals in the Neutrolin lock solutions were assessed as part of the assessment. Please address the following concerns*:

a. *Please provide test data that identifies and quantifies catheter-derived residues in the Neutrolin lock solutions up to the claimed use time of the catheters. You are recommended to use the catheters intended for clinical use with the Neutrolin lock solutions. As part of your assessment you should consider the claimed dwell time in the assessment of residues in the subject Neutrolin lock solutions*.

b. Based on the residue analysis of catheter residues in the Neutrolin lock solution you should provide risk analysis to show that the levels of catheter residues are safe and do not interfere with the drug formulation.

The study was conducted by instilling the hemodialysis catheters with the Neutrolin solution at 37℃ for 3 days and 7 days to simulate the clinical dwell time. The catheters were pre-hydrated for 24 hr at room temperature with saline for 24hr. The potential volatile, semi-volatile, non-volatile and metal elements leachables in saline and Neutrolin solution were analyzed by LC/MS, GC/MS and ICP/MS analytical techniques. Given that all the leachable compounds out of saline and lock solution are analyzed, the extraction conditions and analytical methods are considered reasonable for comparison of leachables. The models of catheter used in the study are the same as the chemical extractable study as shown in the table below:

Table 1: List of catheters to be tested

Catheters	Model	Catalogue	Material
MedCOMP (C-A)	Hemo-Cath Silicone Double Lumen Basic Set	MC101243	Silicone
Merit (C-B)	Centros Flo LT HD Catheter 15F	CENFP19K/A	Polyurethane

We are unclear if these two test catheters are FDA previously cleared device or not. The following question was sent to the sponsor via email on 01/21/2021:

You have provided a leachable study report conducted on two models of catheters MC101243 (MedCOMP) and CENFP19K/A (Merit). However, we are not able to locate the 510(k) numbers for these two catheters. Please clarify whether the test catheters are FDA previously cleared devices. If so, please provide the FDA cleared 510(k) numbers. If not, please evaluate biocompatibility on the final, sterile catheters in accordance with the FDA CDRH's biocompatibility guidance (https://www.fda.gov/media/85865/download).

In response to the above information request, the sponsor provided the FDA clearance number of test catheter in the following table:

Manufacturer	Name	510(k) Number
MedCOMP	Hemo-Cath LT	K113487
Merit	Centros Flo LT HD Catheter	K092597

Thus, I do not have further concerns on the biocompatibility of the test catheter. The leachable results obtained from each catheter type following incubation with the saline and lock solution are summarized in Section 6 of the report. As listed in the table below, three volatile or semi-volatile leachable compounds were observed using polyurethane catheters (Merit) in both saline and lock solution extraction, no increased levels of volatile/semi-volatile leachable components were observed with silicone catheters (MedComp).

Name	Concentration (µg/mL = ppm)				
	Hydration NaCl 0.9% Time (hours)		Neutrolin (b) (4)		Time (days)
	0	24	0	3	7
(b) (4)					

In the response to FDA Additional Information Request, the sponsor provides a toxicological risk assessment on the detected leachables from the catheters leaching into Neutrolin solution in Attachment CDRH 1.5. There are two compounds identified in both saline and lock solution extraction with higher amounts in lock solution extraction than saline. The (b) (4) was identified in the lock solution extraction only. The assessment was conducted in accordance with principles outlined in ISO 10993-17

standard. The sponsor derived the tolerable intake value from the NOAEL data through literature toxicity study review. I agree with the sponsor that the amounts of each detected compound are not likely to pose an unacceptable toxicity risk to the patients. Since the toxicological risk assessment is focused on the evaluation of systemic toxicity, the local tissue effects of these compounds are not included in the assessment. For those compounds that are detected in both saline and lock solution extracts, the assessment can be focused on the systemic toxicity based on its higher amounts of these compounds. For the new detected compound of (b) (4) in lock solution extract, the sponsor did not evaluate the potential local response such as irritation, sensitization and hemolysis. Through my review of literature, the study showed that this chemical did not produce skin irritation and sensitization reactions following direct skin exposure in guinea pigs ((b) (4)). In the toxicity study conducted in animals, there were no effects on clinical pathology at doses of (b) (4) mg/kg for females and (b) (4) mg/kg for males. Based on the available data, the detected amounts of compounds form the test catheters into the lock solution are not expected to pose an unacceptable toxicity risk to the exposed patients when used as intended.

RECOMMENDATIONS/CONCLUSIONS:

1. **For the selected test catheter model MC101243 (MedCOMP) and CENFP19K/A (Merit), the sponsor evaluated the leachables out of the test catheters into the Neutrolin lock solution. Based on the toxicological risk assessment, I agree that the amounts of detected leaching compounds into Neutrolin lock solution from the test catheters are not likely to raise an unacceptable toxicity concern to the exposed patients.**

   In addition to the two test catheters, there are many other catheters tested in the clinical study. Given these catheters have been cleared on the market and there are no concerns raised on the toxicity adverse effects from the clinical trial, I agree to allow the use of DEFENCATH to the two tested catheters and those marketed catheters that have been tested in the clinical study.

2. **For any other silicon or polyurethane catheters that have been cleared on the market, the manufacturer needs to evaluate the biocompatibility of the proposed drug with the catheters since we evaluate the biocompatibility of a device not only on the materials but also on the processing of the materials, added chemicals (e.g, plasticizers, fillers, additives, cleaning agents, adhesive and molding release agents), potential chemical interactions between materials during processing, manufacturing methods (including the sterilization process) and the manufacturing residuals that may be imparted on the final device. Even though the catheters are made of the same raw materials (e.g., silicone, polyurethane), the leachable profiles into the lock solution from each catheter might be different. The drug should be used in the catheter for which the potential leachables into the lock solution do not present a toxicity risk to the patients.**

Qin Zhang -S
Digitally signed by Qin Zhang -S
Date: 2021.01.26 13:24:56 -05'00'

Review Sign-Off

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/s/

MEKLIT N WORKNEH
01/26/2021 02:07:03 PM

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
OFFICE OF PRODUCT EVALUATION AND QUALITY

FROM: Richard J. Williams, Biomedical Engineer,
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TO: Kristine Park, Ph.D.
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DATES: 12/31/20 & 1/23/21 (FOLLOW-UP RESPONSE)

SPONSOR: CORMEDIX INC.
300 Connell Drive – Suite 4200
Berkeley Heights NJ 07922

DOCUMENT/STUDY: NDA 214520 – DEFENCATH (TAUROLIDINE AND HEPARIN CATHETER LOCK SOLUTION)

SPONSOR CONTACT: Dr. Phoebe Mounts, Esq.
Executive Vice President and General Counsel
E-MAIL: pmounts@cormedix.com
TELEPHONE: (b) (6)

BACKGROUND

The Primary Reviewer (CDER) has requested an engineering review from CDRH for the use of a new drug DEFENCATH in hemodialysis catheters. The Sponsor [CorMedix Inc.] has submitted an original NDA requesting permission to market their drug [DEFENCATH] which is a sterile catheter lock solution consisting of taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL) in a (b) (4) container. The Sponsor intends to label this drug combination for use in any FDA-cleared central venous hemodialysis catheters.

Central venous catheters, or CVCs (for hemodialysis) are generally classified into two varieties based on their use – either for short-term use, i.e., <30 days or, long-term use, i.e., ≥30 days. Those short-term catheters are maintained in the patient and removed up to 30 days before a new one is used or an alternate method of blood access is employed. The long-term catheters have a slightly different design and are maintained as long as possible with careful monitoring of the patient. The Sponsor has chosen to systematically test two company's catheters. These are a representative MedComp catheter made of silicone and a representative Merit catheter made of polyurethane that have been cleared for marketing through the 510(k) submission process.

The Sponsor focused on the interaction of the commercial packaging (a 3-component container system including a glass vial, an elastomeric closure, and a sealing cap) on the drug properties, but it is not clear if the Sponsor evaluated properly and completely, the effects of the drug on the central venous catheters which function also as a temporary storage 'container' and pathway for blood/fluids. In addition, these catheters are partially implanted devices where the distal end is within the vasculature and the proximal end resides outside the body.

For hemodialysis catheters, the manufacturer who intends to market such a device of this generic type must conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, and obtain a substantial equivalence determination from FDA prior to marketing the device. (See also 21 CFR 807.81 and 807.87.)

As part of the premarket notification requirements under section 510(k) of the Act, we ask the manufacturers of hemodialysis catheters to provide a description of the performance aspects We recommend that the Sponsor include a brief description of the nonclinical tests submitted, referenced, or relied on in their 510(k) submission. If the Sponsor follows a suggested test method, they may cite the method rather than describing it. If they modify a suggested test method, they may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, they may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, or (2) describe the acceptance criteria they will apply to their test results.

1/23/21 (FOLLOW-UP)

The Sponsor provided a follow-up response dated to the two questions in the below section entitled

'SUGGESTED COMMENTS/CLARIFICATIONS FOR THE SPONSOR'

The Consulting reviewer is providing high-level comments only.

SPONSOR INFORMATION SUPPORTING PROPOSED LABELING

The Sponsor was asked to respond to the following two items sent on December 9, 2020.

1. You have provided the in-catheter stability data for two types of catheters, MedComp and Merit, in the submission dated August 28, 2020. We note a reported significant loss of solution volume by 168 hours of instilling the solution into the catheters. Even by 72 hours, the extracted volume decreased from the initial 2.6 mL to 1.5 ml, and from 3.8 ml to 2.1 mL, for MedComp and Merit catheters, respectively. In addition, the taurolidine and heparin assay results at 72 hours (127.4% and 121.2%, respectively) (b) (4) the assay acceptance criteria ((b) (4) %). We acknowledge other information submitted in the NDA (e.g., extractable/leachable studies, catheter tensile strength report, etc.) to demonstrate compatibility of the drug product with catheters.

   Please explain and provide a justification for how these data support the compatibility of the proposed drug product with a wide range of catheters used for hemodialysis in clinical practice. Note that this information may have implications on labeling for this product such as limiting the use to only catheters tested in the catheter compatibility studies and for which acceptable results were obtained.

2. Although the results of extractable and leachable studies were provided, you should clarify whether the MedComp and Merit catheters still meet their 510(k) cleared physical, mechanical and dimensional specifications and continue to be in conformance with the performance standards and acceptance criteria during the acceptable in-use period with the proposed drug product. Please provide validated performance testing with the dwelling of the proposed drug product within the claimed catheters to show that they conform to the original catheter specifications as cleared in the 510(k) or, provide adequate scientific justification that the catheters are in conformance with the original device specifications as cleared in the 510(k), during in-use conditions

The Sponsor supplied responses to the above deficiencies on December 16, 2020. From CorMedix's response to FDA's December 9, 2020 request for additional information, the Sponsor provided information relevant to labeling and catheter testing.

The Sponsor claims that all testing was conducted in a silicone and a polyurethane catheter. They claim these two catheter types represent the overwhelming majority of catheters used in the hemodialysis community, as discussed on two prior occasions, in the October 2, 2019 meeting and submitted again in Information Request 2, based on a review of the approvals in the 510(k) database (product code MSD) and the record of catheters used in the LOCK-IT-100 clinical trial. In the trial, most subjects used polyurethane catheters, with a smaller subset using silicone

catheters. The results of the 510(k) database search [by the Sponsor] and the record of catheters from LOCK-IT-100 were provided in this submission in Attachments 2 and 3. Because the Sponsor proposes no limitations in the heparin catheter lock solution labeling, they did not limit enrollment in the study by catheter brand or model, to permit the inclusion of a breadth of catheter types currently in clinical use, which will allow the study results to be widely applicable to hemodialysis catheters.

Further, the Sponsor states that the catheter tensile strength test 'strongly supports' the compatibility of DEFENCATH with hemodialysis catheters. Unlike the in-catheter stability test, which tested a short-term exposure to DEFENCATH, the tensile strength test evaluated exposure to the product for up to 30 days. The results of the testing, included initially in the third 'rolling' review submission and included in Attachment 4 for ease of review, demonstrated that exposure to DEFENCATH had no impact on the tensile strength of the catheter. If there was a question of disruption of catheter integrity, one would expect that this would have been seen in the tensile strength study, which applies a great deal of force on the catheter, specifically to test its integrity.

The Sponsor states tests for both extractables and leachables from silicone and polyurethane catheters were conducted with DEFENCATH. The extractables study, also submitted on June 15, 2020, found a 'small' number of extractable compounds, and no elemental impurities. Extractable compounds were more frequently see in ethanol and hexane extracts, which are much more severe than water, which is more akin to the formulation of DEFENCATH. The Sponsor states that neither study found 'significant' destruction of the catheter resulting from DEFENCATH exposure.

The Sponsor claims catheter tensile strength test (done according to ISO 10555-1) 'strongly supports' the compatibility of DEFENCATH with hemodialysis catheters. Unlike the in-catheter stability test, which tested a short-term exposure to DEFENCATH, the tensile strength test evaluated exposure to the product for up to 30 days. The results of the testing, included initially in the third rolling review submission and included in Attachment 4 for ease of review, demonstrated that exposure to DEFENCATH had no impact on the tensile strength of the catheter. If there was a question of disruption of catheter integrity, one would expect that this would have been seen in the tensile strength study, which applies 'a great deal of force' on the catheter, specifically to test its integrity.

The Sponsor believes that the most compelling data to support the compatibility of DEFENCATH with hemodialysis catheters is the LOCK-IT-100 clinical trial. This trial, which enrolled over 800 subjects, was conducted at 70 hemodialysis centers, and was a true clinical use study (consistent with the regulation of DEFENCATH as a drug product). The Sponsor claims the catheters were manipulated repeatedly during the hemodialysis session, as is common clinical practice. The average time in study was 173 days in the DEFENCATH arm, but more telling is the range, as subjects ranged from 4 days to 863 days in the study in the DEFENCATH arm. These actual exposure times to DEFENCATH 'far exceed' any exposure that would result from any standard laboratory study. This prolonged exposure period, combined with the repeated manipulation of the catheter, represents a worst-case stress test for the catheters. The Sponsor states that despite this exposure, there were no reports of device breakage in the DEFENCATH arm, yet two episodes of breakage occurred in the heparin control arm (See CSR pg. 84, provided in the NDA Module 5).

The Sponsor claims that a large number of sites further supports the compatibility of the drug with hemodialysis catheters, as such a diverse set of medical professionals manipulating the catheter with similar but likely different techniques increases the reliability of the results and applicability to the hemodialysis community as a whole.

REVIEWER DISCUSSION

CDRH uses the testing procedures (where applicable) in the '***Guidance for Industry and FDA Staff Hemodialysis Blood Tubing Sets - Premarket Notification [510(k)] Submissions***' issued on April 23, 2008 for central venous catheter (CVC) evaluation. CVCs are subject to similar stresses and testing environment (in part) to hemodialysis blood tubing sets. In CDRH, we recommend performing the tests on three or more catheters of each model the Sponsor intends to market. Of the following list of tests, the Reviewer believes those mechanical tests underlined below would apply to the CVCs interacting with DEFENCATH.

• pressure leak testing demonstrating that the blood tubing can withstand pressures up to 1.5 times the maximum labeled positive and negative pressures;

• endurance testing of the pump segment at maximum labeled blood flow rates and pressures;

• endurance testing, under both positive and negative pressures, of any injection ports (if applicable), using the largest recommended gauge needle identified in the labeling;

• priming volume assessment;

• tensile testing of joints and tubing segments;

• the ability of pressure transducers to withstand leakage when subjected to pressures up to 2 times the maximum labeled pressure, e.g., "strikethrough"

• performance testing of the device's clamps to demonstrate that they can successfully occlude the blood tubing;

• hemocompatibility (i.e., mechanical hemolysis) for a new or significantly altered hemodialysis tubing design that affects the pattern of blood flow; and

• performance testing to evaluate the ability of the tubing to resist kinking after repeated clamping, particularly in the post-pump tubing segment.

The Sponsor has systematically tested the drug in two catheters - one silicone and one polyurethane marketed by MedComp and Merit (as well as their proposed container). From an engineering standpoint, they have performed tensile testing on these catheters after controlled exposures to DEFENCATH. In addition, the Sponsor has performed a clinical study (LOCK-IT-100) employing DEFENCATH where approximately 800 (although only 400 mentioned in another location in the Sponsor's response; see page 2 of 4 vs. page 4 of 4, respectively) subjects were enrolled at 70 hemodialysis clinics under supposed real-life conditions without any claimed breakage.

The Reviewer would agree with the Sponsor that the forces encountered for tensile failures showed the catheters were within the limits specified in ISO 10555-1:2013(E) *Intravascular Catheters – Sterile and Single-Use Catheter Part 1: General Requirements.* The Reviewer wonders why the Sponsor did one test only – tensile - while neglecting others we normally require for approval. The Sponsor should investigate the effects on the tensile strength when all leachables are extracted, and aging has occurred according to maximum shelf life.

The Reviewer notes that the potential exists for different properties for each and every formulation of silicone or polyurethane, therefore, it remains unclear whether the Sponsor could simply lump all silicone and polyurethane catheters into this category. The Reviewer does not have extensive knowledge about the stability of a type of material as a function of the many potential formulations. It is the Reviewer's opinion that we cannot accept a blanket statement that just because a group of catheters did not suffer a known failure under a variety of conditions, that all catheters would respond similarly. The Reviewer recommends that an expert chemist/materials engineer evaluate this area. Again, they have only used two formulations of which there could be hundreds used.

CONCLUSIONS AND RECOMMENDATIONS

The Primary Reviewer has asked CDRH to provide an engineering review in regard to the proposed labeling for use of a potential new drug (DEFENCATH catheter lock solution) in central venous catheters (CVC) for hemodialysis. The Sponsor would like their labeling to reflect that DEFENCATH can be used in any pre-existing legally marketed CVCs.

The Reviewer realizes that there could be hundreds of formulations of polyurethane and silicone used to construct CVCs with each formulation intended to impart certain performance characteristics the manufacturer is seeking. Therefore, each could theoretically respond differently to the mechanical tests performed after contact with DEFENCATH.

The Reviewer would agree with the Sponsor that most CVCs marketed today would be composed of either silicone or polyurethane which is implanted in the vasculature. However, these catheters may be composed of other components, such as the connectors, which are often made of another material. Depending on the catheter's design, it is possible that the catheter lock solution may contact these other components of the catheter and therefore, should be evaluated for any other material/drug interaction that could compromise the CVCs performance and safety.

In addition, the Sponsor has not covered catheters (indwelling tubing) made of materials other than silicone and polyurethane, although they seem to acknowledge that some may be made of another material. This Reviewer is not aware of the scope of these - particularly older models still available.

It is not clear that the Sponsor adequately tested cumulative effects on the strength of materials properties over long-term use of the catheters which will be subject to this lock solution repeatedly over an unspecified time period. The effects cannot be known for certain.

Although the Sponsor states that they tested the drug at 70 clinical sites in 800(?) subjects with various models, ages and lengths of catheters, without apparent damage, they have not provided any important

details with regards to the catheters. Therefore, we cannot confirm the value of this information to support their labeling position.

The Sponsor only performed a single tensile strength test while these catheters for CDRH Premarket [510(k)] Review are normally subject to additional tests as there are more than one avenue of failure in these products. CDRH recommends that these catheters exposed to DEFENCATH also include pressurization tests and kink resistance. DEFENCATH exposure could have an effect on the outcome of these tests.

Has the Sponsor clearly stated that they have used the worst case scenario for testing? That is, have they used catheters at the end of their shelf life? I did not see that in their pre-conditioning but I am not sure I have seen all the information. The use of end of shelf-life samples could have a bearing on both the performance of the catheter mechanically speaking as well as having biocompatibility issues.

In conclusion, the Reviewer believes that the Sponsor cannot make a blanket safety claim that DEFENCATH can be used with all CVCs based on the two models tested.

The Engineering Reviewer initially had the following comments/clarifications (1 & 2 underlined) for the Lead Reviewing Office. These were relayed to the Sponsor through a January 12, 2021 interaction.

SUGGESTED COMMENTS/CLARIFICATIONS FOR THE SPONSOR:

1. You have provided testing of two central venous catheters instilled with DEFENCATH and heparin to document catheter integrity test results for two commercially available hemodialysis catheters - one of a silicone formulation made by MedComp P/N MC101242 and one of a polyurethane formulation made by Merit P/N CENFP19K. Please clarify whether the 'Peak Tensile Strength' tests supplied in Attachment #4 from your December 16, 2020 interactive response were performed on worst case catheter samples including those aged to the end of their labeled shelf-life.

The Sponsor's response to this deficiency was received on January 15, 2021 and is provided below in **Bold** text while any Engineering Reviewer's comments follow in *Italics*.

> **The Peak Tensile Strength Test was conducted in accordance with ISO 10555, an FDA recognized standard, which recommends testing up to 30 days. DEFENCATH is intended to be placed in the catheter at the end of a dialysis session, and removed prior to the start of the next dialysis, which is typically 3 days later. Therefore, given that the DEFENCATH product will likely only be in the catheter for 3 days, an exposure of 30 consecutive days for the tensile strength represents a worst-case scenario.**
>
> **Testing specifically using aged catheters in a laboratory setting was not performed. It is not discussed in the ISO 10555 protocol for Peak Tensile Testing, and despite multiple meetings including the October 2019 meeting attended by members of CDRH where catheter testing was discussed, the use of aged catheters was never raised by the Agency. Furthermore, there was no indication after the 30-day exposure that prolonged exposure**

to DEFENCATH results in any disruption of catheter integrity. Additionally, as CorMedix does not manufacture catheters, it would be difficult to assess what an appropriate shelf life for a catheter would be, as various factors such as materials and formulation dictate the value, and these differ widely across brands.

In an attempt to determine the average shelf life of approved hemodialysis catheters, CorMedix reviewed the 510(k) database, with limited success, as shelf life is not usually included in the 510(k) summary. We found one catheter, silicone, which had a shelf life of 3 years. To propose that CorMedix age a catheter for 3 years at this late stage of review is impracticable and overly burdensome. Even artificial aging would require months of work, in addition to the time it would take to conduct the testing, and we cannot purchase expired catheters as this would be adulterated goods. Further, artificially aging a catheter using thermal cycling, as discussed in the FDA guidance documents on intravascular catheters (which are not applicable to a drug product), could introduce unrealistic stresses on catheters that are typically stored at room temperature, which could in turn provide misleading data on the disruption of the integrity of the catheter. Given that there was no evidence of any disruption of catheter stability from the Peak Tensile Strength testing, which represented a worst-case scenario of exposure period, and actual performance experience in the LOCK-IT-100 clinical trial where catheters of any various ages were included, laboratory studies of aged catheters were not conducted for this product, nor does CorMedix believe such testing is justified, particularly at this late stage of NDA review.

The Sponsor states that the DEFENCATH is intended to be placed in the catheter and stored within it 3 consecutive days. The Sponsor has surmised that 10 of these sessions, or 3 x 10 = 30 total days is the worst-case situation. Therefore, given that the DEFENCATH product will likely only be in the catheter for 3 days, an exposure of 30 consecutive days for the tensile strength represents a worst-case scenario. The dialysis patient undergoing conventional hemodialysis could get treatment every three days or even more often. This translates to one month's use for the catheter.

In reality, the Reviewer believes this is not the worst case situation as the catheter may remain longer especially if it is a long-term catheter which is meant to be implanted greater than 30 days.

The Sponsor points out that specific testing of aged samples was not done, nor does it specify this testing in ISO 10555. In addition, the Sponsor claims they were never advised by CDRH representatives in multiple meetings about the need for this kind of testing (that is, on aged subjects). The Engineering Reviewer points out that the proper staff with knowledge of hemodialysis catheters may not have been there at the time of these meetings.

Contrary to what the Sponsor says, it would not be difficult to determine what is the appropriate shelf-life of a sample to be tested because this information is contained in the labeling for each catheter marketed in the US (at least at this point in time). They did determine that 3 years is a possible age. The Engineering Reviewer agrees with this and is considered the maximum shelf-life for these kinds of devices. The Reviewer does not know of a present manufacturer who has requested a shelf-life of greater than 3 years. However, the Sponsor thinks that they need to age it for testing, or otherwise

they could not obtain a sample for testing. The Reviewer does not agree they could not obtain an already aged sample for testing.

2. Although you provided tensile tests in Attachment #4 from your December 16, 2020 interactive response, FDA normally requires additional tests to validate the performance of central venous catheters. The installation and storage of a catheter lock solution, as well as repeatedly insulting the same catheter for an indefinite number of times can have a cumulative effect over time by affecting the catheter material properties – especially for long-term implanted catheters, i.e., ≥30 days. FDA believes these should be evaluated as well to verify suitability to catheters to be used with DEFENCATH. These tests include pressure leak testing demonstrating that the catheter tubing can withstand pressures up to 1.5 times the maximum labeled positive and negative pressures; and performance testing to evaluate the ability of the tubing to resist kinking after repeated clamping. These tests apply different kinds of stress other than tensile on the catheters. Please provide results for these tests after exposing the finished end-of-shelf life, sterile catheters with DEFENCATH for the worst case scenario or justification for not performing these additional tests.

The Sponsor's response to this deficiency is provided below in **Bold** text while CDRH Reviewer's comments are provided in *Italics*.

CorMedix respectfully disagrees that such additional catheter testing is appropriate for its drug product DEFENCATH. As noted in the December 16, 2020 submission, the product was the subject of a large, randomized, controlled trial, LOCK-IT-100. Instead of simulating the repeated instillation and removal, as the Agency suggests, CorMedix actually put catheters through that process in the clinic and added far more potential insult to the catheter than could ever be accomplished in a bench performance test. The catheters were not only subject to the instillation and removal of the catheter lock solution, but they were also subjected to the hours long, high flow pressure of hemodialysis, multiple times per week. The catheters were not put away in a storage container between testing but were subject to the wear and tear that actually comes with an implanted catheter used in a real patient in the real world. The purpose of providing data from a clinical trial is to demonstrate that leaks or kinks did not develop in the catheter with exposure to DEFENCATH during the rigors of hemodialysis, which far exceed those proposed by the Agency's bench testing recommendations.

Perhaps the most compelling reason that laboratory-based aged catheter testing is not justified comes from the results of the trial. In the LOCK-IT-100 clinical trial, catheters of all age and all types (with the exception of antimicrobial or heparin coated catheters) were accepted for enrollment. This breadth of catheters far exceeds any that could be reasonably tested in an artificial environment such as a lab-based study. Moreover, a review of the trial data indicates that catheters of ages exceeding 3 years were included in the clinical trial, as demonstrated in the table below. Not only were the catheters older, the exposure time in many cases far exceeded the 30 days that is dictated by most laboratory studies.

Notably, one catheter had been in the patient for 4 years at the time of enrollment and was exposed to DEFENCATH over an 844 day period, which are conditions that would never be accomplished in a lab-bench performance test. The following table provides data for 12 specific study subjects documenting the age of the catheter at the time of randomization to the DEFENCATH arm that ranges from 2.75 years to 4.95 years, which properly should justify not conducting a lab-based performance test of an aged catheter. Eight of these aged catheters were exposed to DEFENCATH in LOCK-IT-100 for more than 300 days.

Subject	Age of Catheter at Randomization	Time in Trial	Total Age of Catheter at Study Completion
Treatment Group: Defencath/Neutrolin			
(b) (6)	1,530 days (4.19 years)	844 days	2,374 days (6.50 years)
	1,005 days (2.75 years)	403 days	1,408 days (3.86 years)
	1,228 days (3.36 years)	351 days	1,579 days (4.33 years)
	1,168 days (3.20 years)	46 days	1,214 days (3.33 years)
	1,373 days (3.76 years)	324 days	1,697 days (4.65 years)
	1,273 days (3.48 years)	422 days	1,695 days (4.64 years)
	1,807 days (4.95 years)	179 days	1,986 days (5.44 years)
	1,556 days (4.25 years)	349 days	1,905 days (5.22 years)
	1,081 days (2.96 years)	450 days	1,531 days (4.19 years)
	1,419 days (3.89 years)	421 days	1,840 days (5.04 years)
	1,115 days (3.05 years)	284 days	1,399 days (3.83 years)
	1,214 days (3.33 years)	15 days	1,229 days (3.37 years)
Treatment Group: Heparin (Control Group)			
(b) (6)	1,678 days (4.60 years)	29 days	1,707 days (4.68 years)
	1,221 days (3.35 years)	55 days	1,276 days (3.50 years)
	2,030 days (5.56 years)	18 days	2,048 days (5.61 years)
	1,228 days (3.36 years)	273 days	1,501 days (4.11 years)
	1,009 days (2.76 years	270 days	1,279 days (3.50 years)

As discussed in the previous submission, CorMedix did not receive reports of catheter breakage, pressure leaks, or kinking despite using new and aged catheters and an exposure time that ranged from 4 to 863 days, across multiple catheter types and brands (as demonstrated in Attachment 3 of the December 16, 2020 submission). This testing is far more rigorous, and more importantly, clinically relevant, than a lab-based test meant to simulate clinical use.

The Engineering Reviewer understands the comments and clinical testing performed in an attempt to cover many formulations and brands of presently marketed hemodialysis catheters. In a pure systematical sense, this testing is not a guarantee for all on the market. Indeed, some catheters used in the clinical trial were even unknown. It appears that some were tested for an extended period of time even above the usual 3-year shelf life. It is unknown if the proper sample size was tested. Even though they have not done all the tests CDRH Renal Group recommends being performed, the

Reviewer would not have an issue with those catheters used beyond the three years in the clinical trial for those catheters where the names and model numbers could be determined.

SUBSEQUENT CONCLUSIONS

The Engineering Reviewer has examined the additional interactive response from the Sponsor received January 15, 2021 to support their proposed labeling position. From the new additional information, the Sponsor has still not shown, from a purely systematic testing perspective, that every central venous catheter for hemodialysis will respond safely and withstand the cumulative repeated effects of the use of DEFENCATH over the catheter's use period. They acknowledge limited bench testing with only two catheters – one silicone and one polyurethane in composition - just performing a tensile test according to ISO 10555.

Historically, CDRH's Guidance does not require catheters to be tested with each and every catheter lock solution they may encounter. New catheter lock solutions are rare (to the Reviewer's knowledge) and we mainly think along the line of heparin being used, which has been the case for years. This goes for catheters prior to the initiation of the Guidance document as well. It is believed that this is a shortfall of the present Guidance requirements. Instead, we ask the Sponsor/manufacturer of each new catheter to perform a set of mechanical tests with the catheter containing a blood analog fluid at 37 degrees C. Since DEFENCATH will be a new cleared catheter lock solution, it would seem logical for presently marketed, as well as new catheters, to be tested for compatibility with DEFENCATH by each manufacturer for evidence of any adverse effects.

Because of the present Guidance without the restriction of testing with a catheter lock solution, and because of the LOCK-IT-100 clinical study performed by the Sponsor on a variety of catheters, along with the existence of other real-world testing and marketing of 'Neutrolin' outside the United States, the Engineering Reviewer would be inclined to permit the use of DEFENCATH in the two catheters MedComp P/N MC101242 and Merit P/N CENFP19K identified as studied most prominently by the Sponsor. In addition, (although not familiar with how CDER labels drugs), the Reviewer would recommend inclusion of some statement similar to the following labeling restriction for all presently marketed polyurethane and silicone central venous catheters:

> *Before using DEFENCATH, it is recommended that each manufacturer of any polyurethane or silicone catheter being used should test their respective catheter with DEFENCATH in a real-time in-vitro test situation in conformance with the stated life of the catheter. The effects of DEFENCATH on the mechanical integrity of all catheters but the MedComp P/N MC101242 and Merit P/N CENFP19K is unknown.*

This completes my review.

Digital Signature Concurrence Table

Reviewer Sign-Off	*<<Richard J. Williams>>* Richard J. Williams -S 2021.01.25 21:55:26 -05'00'

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/s/

MEKLIT N WORKNEH
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Memorandum

Date: Jan 21, 2021

Subject: ICCR NDA 214520 – Biocompatibility Consult

Device: Neutrolin Catheter Lock Solution

To: Douglas Silverstein, M.D., Lead reviewer
CDRH/OPEQ/OHT3/DHT3A

From: Qin Zhang, Ph.D., DABT
CDRH/OPEQ/OHT3/DHT3A

Sponsor: CorMedix Inc.

PURPOSE OF REVIEW

I am requested to review the biocompatibility information in the submission on the compatibility study of Neutrolin drug with hemodialysis catheters.

INTENDED USE

The Neutrolin drug product is intended for the prevention of catheter-related bloodstream infections (CRBSIs) in patients with end-stage renal disease receiving hemodialysis through a central venous catheter.

DEVICE DESCRIPTION

The Neutrolin drug is instilled into the lumens of hemodialysis central venous catheters following hemodialysis treatment in order to make the catheter lumen hostile to bacterial and fungal growth and resistant to clot formation.

The drug contains antimicrobial and anticoagulant substances, its composition of the Neutrolin CLS, 5.0ml/via is listed in the following table:

Table 1: Ingredients and Composition of Neutrolin® CLS, 5.0 mL vial

Ingredient	Concentration	Quantity per mL	Function	Reference to Specification
Taurolidine	1.35% wt/vol	13.5 mg	Antimicrobial	NEU01-API-TAU-002
Heparin Sodium USP	1000 U/mL	1000 units	Anticoagulant	NEU01-API-HEP-001
Anhydrous Citric Acid	2.61% wt/vol	26.1 mg	Buffer	NEU01-RWM-CIT-001
Sodium Hydroxide (b) (4)	Not Applicable	QS to pH (b) (4)	pH Adjustment, (b) (4)	NEU01-RWM-NAO-002
Water for Injection	Not Applicable	(b) (4)		NEU01-RWM-WFI-002

To evaluate the compatibility of the Neutrolin drug product with hemodialysis catheters, the sponsor provided several chemical leachable/extractable study reports as summarized below:

Study 1:

The sponsor conducted the chemical extractable study (#10-6116-N15) on the following selected catheters: MedComp Split Cath (polyurethane) and MedComp Hemo-Cath LT (silicone). The catheters were filled with Neutrolin lock solution or saline lock solution at room temperature for 24 hrs. Then the treated catheters were extracted separately in water and hexane at 37°C for 72hrs. The testing was performed at (b) (4) in accordance with ISO 10993-18 standard. The extractables from the water and hexane were analyzed using a variety of analytical techniques including ICP/MS, LC/MS and GC/MS analysis. The extractables from the Neutrolin lock solution and saline lock solution treatment were analyzed using ICP/MS and GC/MS only. The extract compounds from two catheters were listed in Table 3-8 for comparison.

Study 2:

The sponsor provides a chemical extractable study report (#EXT-20-008-R) performed at (b) (4). The test article is the selected catheter only as listed in the table below.

Table 1: List of catheters tested

Catheters	Model	Catalogue	Material
MedCOMP (without port C-A)	Hemo-Cath Silicone Double Lumen Basic Set	MC101243	Silicone
Merit (without port C-B)	Centros Flo LT HD Catheter 15F	CENFP19K/A	Polyurethane

The catheter was extracted with water, ethanol and hexane solvents for 72hrs at 37°C. The extractables from the water and hexane were analyzed using a variety of analytical

techniques including ICP/MS, LC/MS and GC/MS analysis. The extract compounds were listed in Table 5 & 6.

In the chemical extractable study report provided above, the catheters were extracted with a various of polarity solvents only. The Neutrolin lock solution was not used to extract the catheters for its compatibility evaluation. Therefore, the results from this chemical extractable study is not sufficient to evaluate the interaction between the drug and catheters. The evaluation will focus on the leachable study of the catheters following incubation with the lock solution as provided in study 3 below:

Study 3:

The sponsor provides the chemical leachable study report (#LEA-20-007-R) performed by (b) (4). The same report is also provided in Attach CDRH 1.2 in sponsor's response to FDA Additional Information Request below:

In response to CDRH comment related to device-drug compatibility concerning device derived contaminants released as leachates in the drug, you provided extraction study performed on two catheters, Medcomp Split Cath III and Medcomp Hemo Cath. You state that (b) (4) *were released in both polar and non-polar extracts, post- Neutrolin exposure in both catheters. The report shows that the extraction studies were conducted after the catheters were dwelled for 24 hours in the Neutrolin lock solution, and subsequently the Neutrolin dwelled catheters were extracted with saline or hexane. In the report, we were not able to locate if the device related residuals in the Neutrolin lock solutions were assessed as part of the assessment. Please address the following concerns*:

a. *Please provide test data that identifies and quantifies catheter-derived residues in the Neutrolin lock solutions up to the claimed use time of the catheters. You are recommended to use the catheters intended for clinical use with the Neutrolin lock solutions. As part of your assessment you should consider the claimed dwell time in the assessment of residues in the subject Neutrolin lock solutions*.

b. Based on the residue analysis of catheter residues in the Neutrolin lock solution you should provide risk analysis to show that the levels of catheter residues are safe and do not interfere with the drug formulation.

The study was conducted by instilling the hemodialysis catheters with the Neutrolin solution at 37℃ for 3 days and 7 days to simulate the clinical dwell time. The catheters were pre-hydrated for 24 hr at room temperature with saline for 24hr. The potential volatile, semi-volatile, non-volatile and metal elements leachables in saline and Neutrolin solution were analyzed by LC/MS, GC/MS and ICP/MS analytical techniques. Given that all the leachable compounds out of saline and lock solution are analyzed, the extraction conditions and analytical methods are considered reasonable for comparison of leachables. The models of catheter used in the study are the same as the chemical extractable study as shown in the table below:

Table 1: List of catheters to be tested

Catheters	Model	Catalogue	Material
MedCOMP (C-A)	Hemo-Cath Silicone Double Lumen Basic Set	MC101243	Silicone
Merit (C-B)	Centros Flo LT HD Catheter 15F	CENFP19K/A	Polyurethane

We are unclear if these two test catheters are FDA previously cleared device or not. The following question was sent to the sponsor via email on 01/21/2021:

You have provided a leachable study report conducted on two models of catheters MC101243 (MedCOMP) and CENFP19K/A (Merit). However, we are not able to locate the 510(k) numbers for these two catheters. Please clarify whether the test catheters are FDA previously cleared devices. If so, please provide the FDA cleared 510(k) numbers. If not, please evaluate biocompatibility on the final, sterile catheters in accordance with the FDA CDRH's biocompatibility guidance (https://www.fda.gov/media/85865/download).

In response to the above information request, the sponsor provided the FDA clearance number of test catheter in the following table:

Manufacturer	Name	510(k) Number
MedCOMP	Hemo-Cath LT	K113487
Merit	Centros Flo LT HD Catheter	K092597

Thus, I do not have further concerns on the biocompatibility of the test catheter. The leachable results obtained from each catheter type following incubation with the saline and lock solution are summarized in Section 6 of the report. As listed in the table below, three volatile or semi-volatile leachable compounds were observed using polyurethane catheters (Merit) in both saline and lock solution extraction, no increased levels of volatile/semi-volatile leachable components were observed with silicone catheters (MedComp).

Name	Concentration (µg/mL = ppm)				
	Hydration NaCl 0.9% Time (hours)		Neutrolin (b) (4)		Time (days)
	0	24	0	3	7
(b) (4)					

In the response to FDA Additional Information Request, the sponsor provides a toxicological risk assessment on the detected leachables from the catheters leaching into Neutrolin solution in Attachment CDRH 1.5. There are two compounds identified in both saline and lock solution extraction with higher amounts in lock solution extraction than saline. The (b) (4) was identified in the lock solution extraction only. The assessment was conducted in accordance with principles outlined in ISO 10993-17

standard. The sponsor derived the tolerable intake value from the NOAEL data through literature toxicity study review. I agree with the sponsor that the amounts of each detected compound are not likely to pose an unacceptable toxicity risk to the patients. Since the toxicological risk assessment is focused on the evaluation of systemic toxicity, the local tissue effects of these compounds are not included in the assessment. For those compounds that are detected in both saline and lock solution extracts, the assessment can be focused on the systemic toxicity based on its higher amounts of these compounds. For the new detected compound of [redacted] (b) (4) in lock solution extract, the sponsor did not evaluate the potential local response such as irritation, sensitization and hemolysis. Through my review of literature, the study showed that this chemical did not produce skin irritation and sensitization reactions following direct skin exposure in guinea pigs ([redacted] (b) (4)). In the toxicity study conducted in animals, there were no effects on clinical pathology at doses of [redacted] (b) (4) mg/kg for females and [redacted] (b) (4) mg/kg for males. Based on the available data, the detected amounts of compounds form the test catheters into the lock solution are not expected to pose an unacceptable toxicity risk to the exposed patients when used as intended.

RECOMMENDATIONS/CONCLUSIONS:

Through my review of risk assessment, the sponsor provided on the leachables out of the test catheters into the Neutrolin lock solution, I agree that the amounts of detected leaching compounds into Neutrolin lock solution from the test catheters are not likely to raise an unacceptable toxicity concern to the exposed patients. This conclusion is applied to the selected test catheter model MC101243 (MedCOMP) and CENFP19K/A (Merit) only. In Attachment CDRH 1.3, the sponsor provides a list of 510(k) data base on the catheters made with silicone or polyurethane. However, we evaluate the biocompatibility of a device not only on the materials but also on the processing of the materials, added chemicals (e.g, plasticizers, fillers, additives, cleaning agents, adhesive and molding release agents), potential chemical interactions between materials during processing, manufacturing methods (including the sterilization process) and the manufacturing residuals that may be imparted on the final device. Even though the catheters are made of the same raw materials (e.g., silicone, polyurethane), the leachable profiles into the lock solution from each catheter might be different. I recommend the drug be used in the catheter for which the potential leachables into the lock solution do not present a toxicity risk to the patients following the compatibility testing.

Qin Zhang -S Digitally signed by Qin Zhang -S Date: 2021.01.21 15:00:15 -05'00'

Review Sign-Off

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MEKLIT N WORKNEH
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 6, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214520
Product Name and Strength:	Defencath (taurolidine and heparin) catheter lock solution, 13.5 mg/mL and 1,000 USP Units/mL
Total Product Strength:	(57.5 mg/5 mL and 5,000 USP Units/5 mL)
Applicant/Sponsor Name:	CorMedix Inc. (CorMedix)
OSE RCM #:	2020-477-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader (Acting):	Valerie Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 30, 2020, for Defencath. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Defencath (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review, as well as comments from our Office of Pharmaceutical Quality (OPQ) colleagues.[a,b]

2 CONCLUSION

The revised container label is unacceptable from a medication error perspective. We note on the revised container label the inclusion of (b) (4) which may be misinterpreted as the volume of the drug product contained within the vial. Additionally, as

[a] Myers D. Label and Labeling Review for Defencath (NDA 214520). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 06. RCM No.: 2020-477.
[b] Park, K. FDA Communication: NDA 214520 Revised Draft Labeling IR plus PMR/PMC Comment (please respond by 12/30/2020): FDA, CDER, OND, DAI (US); 2020 DEC 14. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805ba0c2.

previously recommended, per 21 CFR 201.51, the net quantity statement should be included on the container label. Thus, we provide our specific recommendations below in Section 3.

3 RECOMMENDATIONS FOR CORMEDIX INC.

A. As currently presented, your revised container label includes (b) (4) , which could be misinterpreted as the volume of the drug product contained within the vial. To minimize the potential for misinterpretation, we recommend removing the text, "(b) (4)," from the container label.

B. Additionally, as currently presented the net quantity statement is missing from your revised container label. In accordance with 21 CFR 201.51, the container label should include a net quantity statement. We recommend adding the net quantity statement to the principal display panel (PDP). You may choose to replace the "(b) (4)" text referenced in recommendation 3A above with the appropriate net quantity volume.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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VALERIE S VAUGHAN
01/06/2021 11:08:07 AM

Clinical Inspection Summary

Date	8 December 2020
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kristine Park, PhD, RAC, RPM Meklit Workneh, MD, MPH, Clinical Reviewer Hiwot Hiruy, MD, PhD, Clinical Team Leader Peter Kim, MD, MS, Cross-Discipline Team Leader Division of Anti-infectives (DAI)
NDA #	214520
Applicant	CorMedix, Inc.
Drug	Defencath (Neutrolin; taurolidine 1.35%, citrate 3.5%, and heparin 5,000 units/5 mL (1,000 U/mL))
NME	Yes
Proposed Indication	For the prevention of catheter-related bloodstream infections (CRBSIs) in patients with end-stage renal disease receiving hemodialysis through a central venous catheter
Consultation Request	31 July 2020
Summary Goal Date	1 January 2021
Action Goal Date	26 February 2021
PDUFA Date	28 February 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators, Drs. Murillo, Jamal, and Bien, were inspected in support of this NDA (NDA 214520). The inspection covered one clinical study, LOCK-IT-100. The study appears to have been conducted adequately, and the study data submitted, including the primary and key secondary efficacy endpoint data, appear acceptable in support of the respective indication.

II. BACKGROUND

NDA 214520 was submitted in support of the use of Defencath (Neutrolin; taurolidine 1.35%, citrate 3.5%, and heparin 5,000 units/5 mL (1,000 U/mL)) for the prevention of catheter-related bloodstream infections (CRBSIs) in patients with end-stage renal disease receiving

hemodialysis through a central venous catheter The key study supporting the application was the following:

- LOCK-IT-100, "A Phase 3, prospective, multicenter, double-blind, randomized, active control study to demonstrate the safety and effectiveness of Neutrolin in preventing catheter-related bloodstream infections in subjects receiving hemodialysis therapy as treatment for end stage renal disease"

This was a randomized, double-blind, active control, parallel-arm, multicenter study. The primary objective was to demonstrate the safety and efficacy of Neutrolin in preventing CRBSI in subjects receiving hemodialysis for the treatment of end stage renal disease when compared with Heparin USP 4,000 units/4 mL (1,000 units/mL).

- *Subjects:* A total of 806 subjects were randomized (403 received Neutrolin and 403 received heparin with benzyl peroxide preservative as a comparator)
- *Sites:* 70 sites in the United States
- *Study Initiation and Completion Dates:* 14 December 2015 (first subject enrolled) to 11 October 2018 (last subject study visit)
- *Database cutoff date:* 4 December 2017
- *Unblinding:* occurred on 22 December 2018

At the Baseline Visit, eligible subjects were randomized via an Interactive Voice Response System (IVRS) in a 1:1 ratio to receive one of the following catheter lock solutions:

- Neutrolin (taurolidine 1.35%, citrate 3.5%, and heparin 5,000 units/5 mL (1,000 units/mL)
- Heparin (Heparin sodium USP 1,000 units/mL, Benzyl alcohol 9.45 mg/mL and Sodium chloride 9.0 mg/mL)

Kits containing Neutrolin or Heparin vials were indistinguishable and only identifiable by their unique kit number. Kit numbers were assigned via IVRS, and study drug was instilled in the hemodialysis catheter on Day 1 (day of first administration of blinded, randomized therapy) following the index hemodialysis episode and subsequent hemodialysis sessions. All subjects received standard of care consistent with clinical practice guidelines recommended by Kidney Disease Outcomes Quality Initiative for the placement, care, and use of central venous catheters for hemodialysis therapy.

Subjects were followed from randomization until either the development of a CRBSI; catheter removal; death; transfer to a non-study site; termination of dialysis; or the end of the study, whichever occurred first. Study visits occurred on dialysis treatment days. Vital signs and labs were collected every four weeks at one of these dialysis visits. Infection monitoring was done prior to and during all dialysis sessions.

Assessment of CRBSI should have occurred if the subject demonstrated clinical signs or symptoms compatible with bacteremia, including any one of the following: change in body

temperature, fever, observed rigors; or any two of the following: hypotension, tachycardia, increased respiratory rate, or an obvious change in mental status; or on any other clinical sign or symptom consistent with an infection. Assessment of a CRBSI should also have occurred under the following circumstances: the prescription of systemic antibiotic or antifungal therapy unless there is a documented microbiological source other than CRBSI, and at the time of catheter removal unless the subject is receiving systemic antibiotic or antifungal therapy or has received such therapy in the previous week.

The primary efficacy endpoint was the time to CRBSI. The definition of CRBSI was that the same organism is grown from at least one blood culture from a peripheral site or bloodline sample and either the arterial or venous catheter hub (or the venous or arterial dialysis circuit blood lines if on dialysis), or the catheter tip if/when the catheter is ultimately removed

The key secondary endpoints of interest were as follows:

- Catheter Removal: Catheter removal for any reason, for example as a result of CRBSI, catheter malfunction, or the catheter is no longer needed for hemodialysis, during the follow up period of the trial.
- Loss of Catheter Patency: Loss of catheter patency following enrollment in the study. Loss of catheter patency is defined as required use of a tissue plasminogen activating factor (tPA) or removal of catheter due to dysfunction.

Rationale for Site Selection
The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

II. RESULTS (by site):

1. Abel Murillo, MD
   Site #011
   Advanced Interventional Pain Management and Research Clinic,
   17760 NW 2nd Ave
   Miami, FL 33169
   Inspection Dates: 5 to 7 October, 9 October, and 13 October 2020

At this site for Protocol LOCK-IT-100, 93 subjects were screened, 84 were enrolled, and 83 subjects completed the study. An audit of the study records for the 33 of the 84 enrolled subjects and for 4 of 9 subjects who were screen failures was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source data, medical records, and other regulatory documentation (e.g., Form FDA 1572s); primary and key secondary efficacy endpoint data (i.e., time to CRBSI, catheter removal, and catheter patency); adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up

letters.

There was no evidence of under-reporting of adverse events. The source records for the primary and key secondary efficacy endpoint data were reviewed and verified against the data listings provided by the sponsor for 33 of the 84 enrolled subjects. Primary and key secondary efficacy endpoint variables reviewed included dates of catheter assessment, dates of CRBSI symptoms first reported, symptoms present, blood cultures and sensitivities, catheter removal, loss of catheter patency, and reasons for catheter removal and loss of catheter patency. No discrepancies were noted.

2. Aamir Jamal, MD
   Site #003
   North America Research Institute
   1335 West Cypress Street, Suite 205
   San Dimas, CA 91773
   Inspection Dates: 17 to 25 August 2020

At this site for Protocol LOCK-IT-100, 68 subjects were screened, 50 were enrolled, and 42 subjects completed the study. A complete audit of the study records for 10 of the 50 enrolled subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source data, medical records, and other regulatory documentation (e.g., Form FDA 1572s); primary and key secondary efficacy endpoint data (i.e., time to CRBSI, catheter removal, and catheter patency); adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

Source records were reviewed to verify adverse event reporting and the primary and key secondary efficacy endpoint data against the data listings provided by the sponsor for all 50 enrolled subjects. There was no evidence of under-reporting of adverse events. Primary and key secondary efficacy endpoint variables reviewed included dates of catheter assessment, date of CRBSI symptoms first reported, symptoms present, blood cultures and sensitivities, catheter removal, loss of catheter patency, and reasons for catheter removal and loss of catheter patency. No discrepancies were noted.

3. Michael Bien, MD
   Site #008
   North America Research Institute
   1335 West Cypress Street, Suite 205
   San Dimas, CA 91773
   Inspection Dates: 26 August to 2 September 2020

At this site for Protocol LOCK-IT-100, 76 subjects were screened, 45 were enrolled, and 36 subjects completed the study. A complete audit of the study records for 10 of the 45 enrolled

subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source data, medical records, and other regulatory documentation (e.g., Form FDA 1572s); primary and key secondary efficacy endpoint data (i.e., time to CRBSI, catheter removal, and catheter patency); adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

Source records were reviewed to verify adverse event reporting and the primary and key secondary efficacy endpoint data against the data listings provided by the sponsor for all 45 enrolled subjects. There was no evidence of under-reporting of adverse events. Primary and key secondary efficacy endpoint variables reviewed included dates of catheter assessment, date of CRBSI symptoms first reported, symptoms present, blood cultures and sensitivities, catheter removal, loss of catheter patency, and reasons for catheter removal and loss of catheter patency. No discrepancies were noted.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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Phillip Kronstein, M.D.
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Kassa Ayalew, M.D., M.P.H
Branch Chief
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Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 214520
DAI /Project Manager/Kristine Park
DAI/Clinical Reviewer/Meklit Workneh
DAI/Clinical Team Leader/Hiwot Hiruy
DAI/Cross-Discipline Team Leader/Peter Kim
OSI/DCCE/Branch Chief/Kassa Ayalew
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OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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/s/

CHERYL A GRANDINETTI
12/08/2020 08:14:23 AM

PHILLIP D KRONSTEIN
12/08/2020 08:18:56 AM

KASSA AYALEW
12/08/2020 10:13:48 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 25, 2020

To: Kristine Park, PhD, RAC
Senior Regulatory Health Project Manager
Anti-Infectives Group 2
Division of Regulatory Operations for Infectious Diseases

Abimbola Adebowale
Associate Director for Labeling
Division of Anti-Infective Products (DAIP)

From: Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, PharmD
Team Leader
OPDP

Subject: OPDP Labeling Comments for Defencath (taurolidine and heparin) catherter lock solution, for central venous catheter instillation use

NDA: 214520

In response to DAIP consult request dated September 14, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Defencath (taurolidine and heparin) catheter lock solution, for central venous catheter instillation use.

PI: OPDP has reviewed the attached proposed labeling received by electronic mail from DAIP (Kristine Park) on November 17, 2020, and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 30, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ZARNA PATEL
11/25/2020 01:37:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatric and Maternal Health Review

Date: 10/13/2020 **Date consulted:** 09/14/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Anti-Infectives (DAI)

Drug: Defencath (taurolidine/heparin/citrate)

NDA: 214520

Applicant: CorMedix Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Prevention of catheter-related bloodstream infections (CRBSIs) in patients with end-stage renal disease receiving hemodialysis through a central venous catheter

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214520
- DAI consult form for DPMH, DARRTS Reference ID 4670391
- DPMH review of Fosrenol (lanthanum carbonate) chewable tablets NDA 21468 on August 28, 2019 DARRTS Reference ID 4483987. This memo was reviewed for the background information of end-stage renal failure in pregnancy.

Consult Question:

DAI is seeking assistance from DPMH in developing Sections 8.1, 8.2 and 8.3 of the product's labeling.

INTRODUCTION AND BACKGROUND

On June 30, 2020, the applicant (CorMedix Inc.) submitted a new NDA for Defencath (taurolidine/heparin/citrate) for approval. The Division of Anti-Infectives (DAI) consulted the Division of Pediatric and Maternal Health (DPMH) on September 14, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Neutrolin, the brand name for taurolidine/heparin/citrate in Europe, was initially approved by the European Medicines Agency in July 2013 for use in the prevention of catheter-related bloodstream infections (CRBI) and maintenance of catheter patency in hemodialysis patients using a tunneled, cuffed central venous catheter for vascular access. This label was expanded on September 19, 2014 to include oncology patients receiving chemotherapy, intravenous (IV) hydration and IV medications via central venous catheters, patients receiving medication and IV fluids via central venous catheters in intensive or critical care units, and for use in total parenteral nutrition. It has not been previously approved for use in the U.S.
- On January 8, 2015, Fast Track Designation was granted.
- On January 16, 2015, Qualified Infectious Disease Product (QIDP) designation was granted.
- On June 30, 2020, the applicant submitted a new NDA under 505(b)1 pathway for Defencath, NDA 214520, indicated for the prevention of catheter-related bloodstream infections in patients with end-stage renal disease receiving hemodialysis through a central venous catheter. The applicant requested a priority review.
- On August 31, 2020, FDA granted a rolling review as well as priority review.

Drug Characteristics Based on Applicant's Proposed labeling

Defencath is a clear aqueous solution consisting of taurolidine 1.35%, citrate 3.5%, and heparin 5,000 units/5 mL (1,000 U/mL) with a pH of (b) (4) (5 mL fill in a 6 mL vial). Defencath is a catheter lock solution and not intended for systemic administration.

Taurolidine and heparin are both considered active ingredients. Taurolidine is a new molecular entity (NME). Heparin is a mixture of large polar molecules, with an average molecular weight of approximately (b) (4) Dalton. It has been previously approved in United States and used in other catheter lock solution, ranging 10-100 USP units/mL.[1]

Citric acid is an inactive ingredient in the solution. Although the lock solution is not intended for systemic use, in the event that the entire 5ml of lock solution were accidentally injected into the patient, the amount citric acid present (130.5mg) is less than the amount of citrate in one unit of

[1] https://www.drugs.com/pro/heparin-lock-flush-solution html Accessed 9/29/2020

Packed Red Blood Cell (1018mg-1268mg) and less than azithromycin for injection (ANDA 065506) ([(b) (4)] mg).[2] For these reasons, this review will not include a review for citrate.

Taurolidine Drug Characteristic from Proposed Product Labeling

Drug Class	Antimicrobial
Proposed Mechanism of action	[(b) (4)]
Proposed Dose and administration	
Molecular weight	284.36 g/mol
Metabolism	NA
Half-life	NA*
Protein Binding	NA
Bioavailability	NA
Serious Adverse Reactions	No serious adverse reactions.

Reviewer's table

* Under the applicant proposed labeling, subsection 13.1 states:

[(b) (4)]

Reviewer comment:
Defencath is not intended for systemic administration. The proposed labeling notes that Defencath is to be instilled into the catheter lumen as a lock solution at the conclusion of each dialysis session. Prior to initiation of the next dialysis treatment, the product must be aspirated from the catheter. Therefore, when used as directed, systemic exposure to the patient is not expected. This information was confirmed in discussion with the Clinical Pharmacology team of

[2] Campbell-Lee SA, et al. Chapter 18 Packed red blood cells and related products. Blood Banking and Transfusion Medicine Basic Principles and Practice (Second edition), Churchill Livingstone, 2007, pages 250-258. https://doi.org/10.1016/B978-0-443-06981-9.50023-5

DAI. If Defencath were to accidentally be injected into the patient, taurolidine would be cleared rapidly and exposure to the patient would be limited.

REVIEW

PREGNANCY

Catheter-related bloodstream infection in end stage renal disease and pregnancy[3]

There are no specifics in the published literature on Catheter-related bloodstream infections (CRBSI) in pregnant women with end stage renal disease (ESRD). CRBSI is defined as the presence of bacteremia originating from an intravenous catheter. Central venous catheters (CVCs) pose a greater risk of device-related infections than any other types of medical device and are major causes of morbidity and mortality.[4] According to Lorente et al., the incidence of CRBSI was 2.79 infections per 1000 catheter days, among which CVC were responsible for 2.09% of cases.[5] A meta-analytical study done at Johns Hopkins University showed that bloodstream infections (BSIs) were the third leading cause of hospital-acquired infections. These infections have an attributable mortality rate of 12% to 25%.[6] Patients with ESRD requiring dialysis are at risk for CRBSI.

Overall, pregnancies with ESRD are uncommon secondary due to infertility as the results of endocrine dysfunction secondary to chronic kidney disease. These pregnancies are associated with a high rate of complications including increased maternal mortality, hypertension, preeclampsia, anemia, intrauterine growth restriction, preterm delivery, major congenital malformations, and stillbirth.[7] Women with ESRD may also be counseled to delay pregnancy until successful kidney transplantation. With the introduction of intensive hemodialysis (daily after 16-20 weeks, at least 24-28 hours per week; some recommend >36 hours per week), the overall pregnancy outcomes have improved in the past three decades, , with increased fetal survival from 23% in 1980 to over 90% in the recent years.[7,8,9]

Nonclinical Experience

No animal reproduction study was done.

[3] DPMH review of Fosrenol (lanthanum carbonate) chewable tablets NDA 21468 on August 28, 2019. DARRTS Reference ID 4483987

[4] Gahlot R, et al. Catheter-releated bloodstream infections. Int J Crit Illn Inj Sci. 2014 Apr-Jun; 4(2): 162–167.

[5] Lorente L, Henry C, Martín MM, Jiménez A, Mora ML. Central venous catheter-related infection in a prospective and observational study of 2,595 catheters. Crit Care. 2005; 9(6):R631-5.

[6] Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc. 2006 Sep; 81(9):1159-71.

[7] Manisco G, et al. Pregnancy in end-stage renal disease patients on dialysis: how to achieve a successful delivery. Clin Kidney J, 2015; 8:293-299

[8] Piccoli GB, Zakharova e, et al. Pregnancy in Chronic Kidney Disease: Need for Higher Awareness. A Pragmatic Review Focused on What Could Be Improved in the Different CKD Stages and Phases, J Clin Med, 2018; 7(11): E415

[9] Nadeau-Fredette AC, Hladunewich M, et al. End-stage renal disease and pregnancy, Adv in Chronic Kid Dis, 2013; 20(3): 246-252

Review of Clinical Trials

There were two reports of pregnancies in 806 subjects clinical trial LOCK-IT-100. Both were in the Neutrolin arm. One subject became pregnant and chose to carry to term and delivered a full-term healthy baby. One subject had a spontaneous abortion. The subject recovered and the study drug was withdrawn.

- CRMLOCKIT100-(b) (6) is a 38-year-old Native Hawaiian female with ESRD since (b) (6) who was treated with Neutrolin between (b) (6) to (b) (6). She had history of septic shock due to vancomycin resistant enterococcus in the urine, left internal carotid artery occlusion, right carotid artery total occlusion, acute cerebrovascular accident, diabetes type II with retinopathy, and hypertension. Co-medications included clonidine, gabapentin, hydralazine, aspirin, clopidogrel, and atorvastatin. Her HCG was positive at 8750 on (b) (6). Her last menstrual period (LMP) was (b) (6). She experienced vaginal bleeding on (b) (6) and had an ultrasound that showed a small intrauterine cystic focus around 0.5cm. Her HCG rose to 14,111 on (b) (6) and 18,000 on (b) (6). She had another ultrasound on (b) (6) which showed a 3.6 cm cystic structure in the uterus without yolk sac or fetal pole. Her last dose of Neutrolin was administered on (b) (6). She later experienced a spontaneous loss and withdrew from the drug treatment. Her last follow-up was on (b) (6).
- CRMLOCKIT100-(b) (6) is a 35-year-old Black female who was treated with Neutrolin from (b) (6) to (b) (6) who became pregnant during the trial. She was exposed in the first trimester and withdrew from the study. She delivered a live baby at term. There was no report of any congenital anomaly. No additional information was given.

Review of Pharmacovigilance Database

The product is regulated as a medical device in the European Union and marketed as Neutrolin. The applicant provided a cumulative review of cases of Neutrolin use in pregnancy from the company safety database. There are no reported case reports of Neutrolin use in pregnancy.

Review of Literature

DPMH's Review of Literature

DPMH conducted an updated published literature review using Embase, Pubmed, Micromedex,[10] ReproTox,[11] Shepard,[12] and TERIS.[13] Search terms used were "Neutrolin AND pregnancy," "Neutrolin AND pregnancy AND fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage."

- No relevant articles were found.

Neutrolin was not discussed in Micromedex.[10]

[10] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 9/18/2020

[11] ReproTox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 9/18/2020.

[12] 2020 Shepard's: A Catalog of Teratogenic Agents, compilations of scientific reviews on the teratogenic effects of over 2000 drugs chemicals, and other physical and biologic agents. Accessed 9/18/2020.

[13] Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 9/19/20

In similar manner, a literature search was performed on each of the active ingredients of Defencath.

Taurolidine

No relevant articles were found on the use of toluidine in pregnancy. Taurolidine was not found in Micromedex.[10]

Reviewer comment:
When used as directed, there is no systemic exposure of the lock solution to the patient. Therefore, maternal use is not expected to result in fetal exposure to the drug.

In general, in the event the lock solution is accidentally injected into a patient, the level of taurolidine present in the catheter lock solution (1.35% in 5 mL) is below the level at which toxicity would be expected. This was confirmed by discussions with the DAI Clinical Pharmacology team, Clinical team, and Pharmacology Toxicology team. In previous publications by Gong et al.[14] taurolidine was administed intravenously (2% in 250 mL) in 18 healthy male volunteers and no serious adverse effects reported. Taurolidine in catheter lock solution is considerably lower than those used in this study. However, there are no specific data on intravenous injection of taurolidine in pregnant women, including clinical trial, postmarket experience, and the published literature. It is not known if an accidental exposure would result in any adverse effect on pregnancy. *There were no cases of inadvertent/accidental injection of catheter lock solution in the Phase 3 clinical trial.*

Heparin

There are numerous publications including controlled studies and observational studies on the use of heparin in pregnancy. Heparin is a mixture of large polar molecules with large molecular size, which do not cross the placenta. Heparin is frequently used in pregnancy. Although early published studies with heparin use in pregnancy reported an increased incidence of miscarriage, stillbirth, and prematurity, these studies were confounded by disease process.[15,16,17] After excluding such pregnancies, the incidence of adverse fetal outcomes and congenital malformations with heparin therapy was similar to the incidence in an untreated population.[18,19] The reader is referred to Appendix A for a tabulated list of some of the important studies of heparin use in pregnancy.

[14] Gong L, et al. The pharmacokinetics of taurolidine metabolites in healthy volunteers. The Journal of clinical pharmacology 2013 https://doi.org/10.1177/0091270007299929|
[15] Lee P-K et al: Combined use of warfarin and adjusted subcutaneous heparin during pregnancy in patients with an artificial heart valve. J Am Coll Card 8:221-224, 1986.
[16] Hall JG et al: Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 68:122-40, 1980.
[17] Nageotte MP et al: Anticoagulation in pregnancy. Am J Obstet Gynecol 141:472, 1981.
[18] Ginsberg JS, Hirsh J: Anticoagulants during pregnancy. Annu Rev Med 40:79-86, 1989.
[19] Ginsberg JS, et al: Risks to fetus of anticoagulant therapy during pregnancy. Thromb Haemost 61:197-203, 1989.

The American College of Obstetricians and Gynecologists states neither low molecular weight heparins (LMWH) or unfractionated heparin (UFH) cross the placenta and both are considered safe in pregnancy.[20]

American College of Chest Physicians clinical guidelines recommend the use of LMWH and UFH in pregnancy for maternal thromboembolic diseases.[21]

Micromedex[10] gives Pregnancy Risk Rating: "Fetal risk cannot be ruled out."

> "Studies in which heparin has been given intravenously and subcutaneously have generally reported normal deliveries with no maternal or fetal bleeding and no other complications... Heparin induced thrombocytopenia is an immune, IgG mediated condition that occurs rarely in patients treated with unfractionated heparin, or less commonly, low molecular weight heparin. The incidence of thrombocytopenia in pregnant patients has been reported to be 4%, which compares to an estimated incidence of 3% in non-pregnant patients. Any such reports may be confounded by other conditions."

ReproTox[11] states the incidence of adverse fetal outcomes with and without heparin therapy are similar.

- "A 2010 report did not find evidence of [heparin use and aspirin] alone or their use in combination significantly improved live birth rates or reduced the risk of miscarriage in women with a history of unexplained recurrent miscarriage.[22]
- Long term use of heparin has been associated with osteopenia, which can become severe in pregnancy.[23,24,25,26,27]
- Epidural analgesic has been said to be contraindicated with all forms of heparin because the risk of trauma to a blood vessel could result in a compression lesion of the spinal cord.[28]"

[20] ACOG Practice Bulletin 196. Thromboembolism in pregnancy. Obstet Gynecol 2018;132(1): e1-e17.
[21] Bates SM, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141 (2): E291S-E736S.
[22] Kaandorp SP, Goddijn M, van der Post JA, Hutten BA, Verhoeve HR, Hamulyk K, Mol BW, Folkeringa N, Nahuis M, Papatsonis DN, Bller HR, van der Veen F, Middeldorp S. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med. 2010 Apr 29;362(17):1586-1596.
[23] Wise PH, Hall AJ: Heparin-induced osteopenia in pregnancy. Br Med J 281:110-111, 1980.
[24] De Swiet M et al: Prolonged heparin therapy in pregnancy causes bone demineralization. Br J Obstet Gynaecol 90:1129-1134, 1983.
[25] Dahlman TC: Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol 168:1265-70, 1993.
[26] Barbour LA, Kick SD, Steiner JF, LoVerde ME, Heddleston LN, Lear JL, Baron AE, Barton PL. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. Am J Obstet Gynecol 1994;170:862-9.
[27] Douketis JD, Ginsberg JS, Burrows RF et al: The effects of long-term heparin therapy during pregnancy on bone density. A prospective matched cohort study. Thromb-Haemost. 1996; 75: 254-7.
[28] Crawford JS: Principles and Practice of Obstetric Anaesthesia 5th ed. 2000 Blackwell Scientific Publications, Oxford, p. 229.

Shepard's[12] states multiple studies showed no increased risk of malformation, miscarriage, and adverse pregnancy outcomes.

TERIS[13] categorized the magnitude of teratogenic risk to child born after exposure to heparin during gestation as "unlikely" based on a "fair" amount of quality and quantity data on which risk estimates are based. In addition, TERIS states there is an increased risk of maternal postpartum hemorrhage associated with the use of heparin during pregnancy.[29]

Reviewer comment:
Overall, the applicant provided an adequate review of their clinical trial and pharmacovigilance cases regarding Neutrolin use in pregnant women. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION
Nonclinical Experience
No animal reproduction study was done.

Review of Clinical Trials
There were no lactating women in the clinical trial.

Review of Pharmacovigilance Database
There are no reported case reports of Neutrolin use in lactation.

Review of Literature
DPMH's Review of Literature
DPMH conducted a published literature review using Embase, Pubmed, Micromedex,[30] ReproTox,[31] LactMed[32], Hale[33], and Briggs.[34] Search terms used in Embase and Pubmed were "Neutrolin AND lactation," "Neutrolin AND breastfeeding."

- No relevant articles were found.

[29] Sirico, A.; Saccone, G.; Maruotti, G.M.; Grandone, E.; Sarno, L.; Berghella, V.; Zullo, F. and Martinelli, P.: Low molecular weight heparin use during pregnancy and risk of postpartum hemorrhage: a systematic review and meta-analysis. J. Matern. Fetal Neonatal Med. 2018 Jan 5
[30] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 9/18/2020.
[31] ReproTox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 9/18/2020.
[32] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The Lactmed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 9/18/2020.
[33] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.
[34] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 9/18/20

In similar manner, a literature search was performed on each of the active ingredients of Defencath.

Taurolidine

No relevant articles were found on the use of toluidine during lactation. Taurolidine was not found in Micromedex,[30] LactMed,[31] Hale,[32] and Briggs.[33]

Heparin

There are no published studies of heparin use during lactation.

Micromedex,[30] LactMed,[31] Hale,[32] and Briggs[33] all agree that based on high molecular weight, 3000 to 30,000 Daltons, heparin is not expected to be excreted into human breast milk. "Heparin is safe to administer during breastfeeding. Any heparin present in human milk would be rapidly destroyed by the gastric contents of the infant." Micromedex[30] gives heparin the Lactation Rating: "Infant risk is minimal." Hales rates heparin as "L1-No Data-Probably Compatible." Briggs[33] categorizes heparin as breastfeeding "Compatible." World Health Organization also considers heparin as compatible with breastfeeding.[35]

Reviewer comment:
When used as directed, there is no systemic exposure of the lock solution to the lactating patient. Therefore, maternal use is not expected to result in exposure of the breastfed infant to the catheter lock solution.

In the event that the lock solution is accidentally administered, there are no data on the presence of taurolidine in human milk, the effects on the breastfed infant, or the effects on milk production. Based on the physical characteristic of taurolidine, low molecular weight and short half-life, taurolidine is likely to be present in breastmilk but unlikely to accumulate. A previous pharmacokinetic study[14] has shown that taurolidine is rapidly cleared after intravenous infusion of taurolidine (2% in 250 mL). Taurolidine exists in equilibrium with taurultam and is subsequently transformed to taurinamide. The plasma taurolidine concentrations could not be measured directly and instead were calculated from plasma levels of taurultam and taurinamide. The terminal half-life of the taurultam is calculated to be 1.5 hours. Based its molecular weight, heparin is not expected to be present in human breast milk.

Overall, the applicant provided an adequate review of the clinical trial and pharmacovigilance database on the use of Neutrolin during lactation. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Please refer to the Pharmacology/Toxicology review by Amy Ellis, Ph.D. and Terry Miller, Ph.D.

[35] Micromedex. Accessed 9/18/2020.

Review of Clinical Trials
There were no cases of infertility detected in the clinical trials.

Review of Pharmacovigilance Database
There are no reported case reports of Neutrolin use adversely affecting fertility in females and males of reproductive potential.

Review of Literature
DPMH's review of literature
DPMH conducted a review of published literature using Embase, Pubmed, Micromedex,[36] ReproTox,[37] and TERIS.[38] Search terms used were "Neutrolin AND reproduction," "Neutrolin AND infertility," and "Neutrolin AND contraception."

- There are no articles regarding Neutrolin use adversely affecting human fertility.

In similar manner, a literature search was performed on each of the active ingredients of Defencath.

Taurolidine
No relevant articles were found on the use of toluidine during lactation. Taurolidine was not found in Reprotox.[37]

Heparin
There are no articles that indicate heparin adversely affects fertility. LMWH has been used to improve birth rate after recurrent implantation failures.

- A meta-analysis in 2013[39] included one randomized controlled trial and one quasi-randomized trial that showed improvement in the live birth rate and a reduction in miscarriage rate with LMWH compared with controls in women with recurrent implantation failures.
- A 2014 prospective controlled study included 334 cycles of women with unexplained infertility with failed one or two intracytoplasmic sperm injection (ICSI) attempts. Women were randomly assigned to received prednisolone (20mg/day) starting on the first day of ovarian stimulation and LMWH 1mg/kg/day starting one day after oocyte retrieval or standard treatment. Compared with standard treatment, prednisolone and LMWH resulted in more clinical pregnancies (40.7% versus 27.5%) and implantation rate (23.9 versus 14.7%).[40]

[36] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 9/18/2020
[37] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 9/18/2020.
[38] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 9/18/20
[39] Potdar N, et al. Adjunct low-molecular-weight heparin to improve live birth rate after recurrent implantation failure: a systematic review and meta-analysis. Hum Reprod Update 2013;19(6): 674-84.
[40] Fawzy M, El-Refaeey AA. 2014. Does combined prednisolone and low molecular weight heparin have a role in unexplained implantation failure? Arch Gynecol Obstet 289(3): 677-680.

- A randomized controlled trial (RCT) of 241women undergoing 271 IVF cycles randomized to either parnaparin or routine hormonal therapy only showed miscarriage rate to be 10.3% and 22.9%, p=0.319 in treatment and control group, respectively. Live birth rate was similar.[41]

ReproTox[37] notes that administration of heparin to female rats at 144 or 400 UI/kg/day subcutaneously did not alter fertility.

Reviewer comment:
When use as directed, the systemic exposure of the lock solution to the patient is not expected. Therefore, use in females and males of reproductive potential is not expected to affect fertility.

In the event of accidental injection, there are no data on the effect of taurolidine on fertility. Experience with heparin does not show that heparin adversely affects fertility.

Overall, the applicant provided an adequate review of clinical trial and published literature regarding Neutrolin use in females and males of reproductive potential. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Defencath is not intended for systemic administration and is intended for use in a dialysis catheter for prevention of infection. The product is intended to be removed prior to use of the catheter. Therefore, use in pregnant patients is not expected to result in fetal exposure to the drug. There are no cases of accidental injection of Neutrolin in the clinical trials and postmarketing experience. No animal reproduction study was conducted due to lack of systemic administration of this drug. Since Defencath is not systemically administered, DPMH does not recommend a postmarking pregnancy safety study.

Available data in the clinical trials and postmarketing experience on the use of taurolidine in pregnant women did not contain any cases of accidental injection in pregnancy and therefore are insufficient to inform a drug-associated risk of major birth defects, miscarriage, and adverse maternal and fetal outcomes if it was administered intravenously. Prolonged experience with heparin in pregnant women over several decades, based on published literature, controlled trials and observational studies, have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Lactation

Defencath is not intended for systemic administration and is intended for use in a dialysis catheter for prevention of infection. The product is intended to be removed prior to use of the

[41] Lodigiani C, et al. The effect of parnaparin sodium on in vitro fertilization outcome: A prospective randomized controlled trial. Thrombisis Research 2017;159: 116-121.

catheter. Therefore, use in pregnant lactating patients is not expected to result in infant exposure to the drug. Therefore, DPMH does not recommend a postmarketing clinical lactation study.

Available data in the clinical trials and postmarketing experience on the use of taurolidine in lactation did not contain any cases of accidental injection and therefore insufficient to inform on the presence of taurolidine in human milk, the effects on the breastfed infant, or the effects on milk production in case of accidental intravenous administration. Based on its molecular weight, heparin is not expected to be excreted into human breast milk.

Females and Males of Reproductive Potential

Defencath is intended to be used external to the body and therefore Defencath use is not expected to result in any effects on fertility or interaction with hormonal contraception. DPMH recommends omitting subsection 8.3.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH recommendations are below and reflect the discussions with Division of Anti-Infectives. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

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APPENDIX A. Major Published Studies of Heparin Use in Pregnancy.

Publication; author/date/Country	Type of study	Population/control/n/disease	Medication/ N	Exposure time	Outcomes	Comments (Strength/Limits)
Li J, et al. (2020) China	Meta-analysis	8 RCT with 994 women were taking heparin (H) and ASA (N=493) or ASA alone (n=501).	H (UFH and LMWH) ASA 994 (493 exposed)	not specified	-Live births were higher in the treatment group (P=0.003). -Among women who had a live birth, gestational age at delivery tended to be older in ASA alone group (P=0.054). -No differences in birthweight or intrauterine growth restriction were observed. Adverse effects were sporadically reported.	L: heterogenous studies
Hamulyák EN, et al.[42] (2020) Netherland	Cochrane Systematic review	Systematic review of clinical trials with women with recurrent pregnancy loss and antiphospholipid syndrome in comparison of ASA versus placebo H +ASA versus ASA	H (UFH and LMWH) ASA 11 trials 1672 women	variable (usually entire pregnancy)	-H (UFH or LMWH) + ASA increase number of live births (RR 1.27, 95% CI 1.09 to 1.49, 5 studies, 1295 women, low certainty evidence) -UFH +ASA v ASA increase number of live births (RR 1.74, 95% CI 1.28 to 1.35) -No women in the study had heparin induced thrombocytopenia, allergic reaction or venous or arterial thromboembolism. -There were no infants with congenital malformations. -H (UFH or LMWH) plus ASA may reduce risk of pregnancy loss (RR0.48, 95% CI 0.32 to 0.71, 5 studies, 1295 women, low certainty evidence)	
Tong L, et al.[43] (2016) China	Meta-analysis	A meta-analysis including 6 RCT, 907 pregnant women with unexplained recurrent miscarriage, evaluating treatment with H and ASA (n=367) versus placebo (N=540).	H (LMWH and UFH) ASA 907 (367 exposed)	not specified	-live birth rate was RR = 1.18, 95% CI (1.00–1.39), P=0.04, treatment group versus control -no significant differences found between the two groups in the incidence of preterm delivery [RR=1.22, 95% CI (0.54–2.76), P=0.64], preeclampsia [RR=0.52, 95% CI (0.25–1.07), P=0.08], intrauterine growth restriction [RR=1.19, 95% CI (0.56–2.52), P=0.45] and thrombocytopenia [RR=1.17, 95% CI (0.09–14.42), P=0.90].	L: heterogenous studies

[42] Hamulyák EN, et al. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. Cochrane Database of Systematic Reviews 2020 2020:5

[43] Tong L, Wei XJ. Meta-analysis of aspirin-heparin therapy for un-explained recurrent miscarriage. Chinese Medical Sciences Journal 2016 31:4 (239-246)

Maged AM,[44] et al. (2016) Egypt	Prospective case controlled	180 pregnant women with history of recurrent unexplained pregnancy loss randomized to treatment group or no treatment group.	UFH (5000IU sc q12h) ASA (81mg) 180 (90 exposed)	starting 5-7 weeks	-There were statistically significantly more patients who completed 1st trimester in the treatment group (66 versus 39) (p values 0.018). -Complications of the use of aspirin heparin occurred in 60% of the patients. The most common complication was bruising at injection site occurring in 60% of the patients followed by bleeding gums (14.4%), gastrointestinal troubles (12.2%), epistaxis (10%) and transient thrombocytopenia in only 2.22% of the patients.	L: small sample size, end point was end of first trimester and not delivery
Hanania G, et al.[45] (1994) France	Retrospective cohort	155 pregnancies in 103 pregnant women with prosthetic heart values under anticoagulation therapy	Warfarin Heparin 155 pregnancies 57 received heparin	Various	-1 malformation: phocomelia (with warfarin) 5 still births (1 had multiple malformations exposed heparin 2nd and 3rd trimester) -20 miscarriages (13%), 4% without anticoagulant and 17% with anticoagulant, although women miscarried more frequently with vitamin K antagonist (7/27) than heparin (7/57) when treated in the first trimester. 4-maternal deaths (due to thrombosis of mechanical valve and acute pulmonary edema) -5 still births	L: small sample size, retrospective, no control, some received both warfarin and heparin.
Xu Z, et al.[46] (2016) China	Meta-analysis	All published studies before 2015 with anticoagulation in pregnant women with MHV; 4 regiments were present: 1) VKA 2) H/VKA (UFH or LMWH during 6-12 weeks gestation then switch to VKA) 3) LMWH (adjusted dose) 4) UFH (adjusted dose)	Warfarin LMWH UFH 51 studies 2113 pregnancies	various	-There are no congenital fetal anomalies present in LMWH (0/99) and UFH (0/105) group. Although there were 3/404 present in the H/VKA group and 20/938 in the VKA group. -The rate of fetal wastage was 37/69 in UFH group, 12/98 in LMWH group, 77/340 in the H/VKA group, and 325/999 in the VKA group.	L: compilation of heterogenous observational studies

[44] Maged AM, et al. The role of prophylactic use of low dose aspirin and calheparin in patients with unexplained recurrent abortion. Gynecological Endocrinology 2016 32:12 (970-972)

[45] Hanania, G.; Thomas, D.; Michel, P.L.; Garbarz, E.; Ages, C.; Millaire, A. and Acar, J.: Pregnancy and prosthetic heart valves: a French cooperative retrospective study of 155 cases. Eur. Heart J. 15:1651-1658, 1994.

[46] Xu, Z.; Fan, J.; Luo, X.; Zhang, W.B.; Ma, J.; Lin, Y.B.; Ma, S.H.; Chen, X.; Wang, Z.P.; Ou, J.S. and Zhang, X.: Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a systematic review and meta-analysis. Can. J. Cardiol. 32(10):1248.e1-1248.e9, 2016.

Chan WS, et al.[47] (2000) Canada	Systematic review	systematic review of the medical literature to evaluate the fetal risks associated with maternal use of oral anticoagulants during pregnancy for thromboembolic prophylaxis. Pooled estimates of maternal and fetal risks associated with the 3 approaches: 1) OA 2) H/OA (H during 6-12 weeks gestation then switch to OA) 3) H	OA H 28 articles 1234 pregnancies of 976 women	various	-Congenital anomalies was 4/141 (2.8%) in liveborn infants whose mothers had used heparin during the first trimester of pregnancy. Warfarin was used beyond six weeks of pregnancy in these four affected cases. -Overall risk for "fetal wastage" (SAB, stillbirths and neonatal deaths) dropped from 33.6% (266/792) to 16.3% (21/129) when maternal treatment was switched from warfarin to heparin prior to six weeks of pregnancy.	
Sbarouni E, et al.[48] (1994) UK	Retrospective cohort	214 pregnancies in 182 women with prosthetic heart valve (151 mechanical valves and 63 bio-protheses) were included, 161 were treated with various anticoagulation in pregnancy H n=37 Warfarin n=56 H + Warfarin (H to Warfarin switch after 1st trimester) n=68	Warfarin H 214 pregnancies	variable depend on group	-Bio prosthesis (n=63): 6 SAB; 2 stillbirths; 3 TAB (2 related to valve complications and 1 had heart failure); 48 term deliveries; 4 PTD -Mechanical valve (n=141): 17 SAB; 75 term deliveries; 30 PTD; 9 stillbirths (4 warfarin, 1 H + Warfarin, 4 H-related to valve failure); 3 neonatal death (2 due to prematurity and 1 due to cerebral hemorrhage; 2 warfarin, 1 was H + Warfarin); 3 TAB (due to heart failure); 1 mental retardation; 2 maternal death; 1 ectopic -no congenital malformation -There is no difference in pregnancy outcomes when comparing patients taking no anticoagulant and those taking Heparin in the first trimester followed by W. Women on heparin followed by warfarin had lower stillbirth rate than the other 2 groups. (13%) rates. Thirty-five percent of the valves had functional deterioration during pregnancy. Heparin treatment was associated with more thromboembolic complications and more bleeding than in the oral anticoagulant group	L: some women with SAB were excluded in the analysis at their request (10 additional SABs in mechanical valve group).

[47] Chan, W.S.; Anand, S. and Ginsberg, J.S.: Anticoagulation of pregnant women with mechanical heart valves. A systematic review of the literature. Arch. Intern. Med. 160(2):191-196, 2000.

[48] Sbarouni E, Oakley CM, Outcome of pregnancy in women with valve prostheses. Br Heart J 1994;71: 196-201.

Ginsberg JS, et al.[49] (1989) Ginsberg JS, et al.[50] (1989) Canada	Review	Review of literature with 186 studies and 1325 pregnancies with AC, including retrospective series and case reports. They are categorized to 1) H 2) OA 3) H/OA	AC H 1325 pregnancies	All	-Adverse pregnancy outcomes are 77/355 (21.7%), 161/578 (27.9%), 76/394 (19.4%) in H, OA, H/OA groups, respectively. -After excluding pregnancies with maternal comorbid conditions, adverse outcomes are 29/278(10.4%), 150/567(26.5%), and 70/383 (18.3%) in H, OA, H/OA groups, respectively. -After excluding pregnancies with maternal comorbid conditions and prematurity with normal outcomes, adverse outcomes are 10/278(3.6%), 148/567(26.1%), and 70/383 (18.3%) in H, OA, H/OA groups, respectively. -Deaths including abortions, stillbirth, and neonatal deaths after excluding pregnancies with maternal comorbidities are 7/278 (2.5%), 95/567 (16.8%), and 44/383 (11.5%) in H, OA, H/OA groups, respectively.	S: took comorbidities and preterm deliveries into consideration.
Dahlman TC,[51] (1993) Sweden	Prospective cohort	Long-term (mean 25 weeks) subcutaneous prophylaxis with heparin twice daily in pregnancy was prescribed for 184 women. 1) High dose group (started at conception due to mechanical heart valve, or recurrent thromboembolism with or without coagulation disorder; adjusted to 0.1-0.2 IU/ml of plasma or 10 sec prolongation of aPTT): n=48; 2) Low dose group (Xa adjusted to 0.08-0.15 IU/ml of plasma)	UFH 184 women	All	-Symptomatic osteoporotic fractures of the spine occurred PP in 4 women (2.2%), for whom the mean dosage of heparin ranged from 15,000 to 30,000 IU per 24 hours (mean 24,500 IU per 24 hours), and the duration of treatment ranged from 7 to 27 weeks (mean 17 weeks) -Thromboembolic complications occurred in five women. (Either due to coagulation disorder diagnosed later or none satisfactory concentration of heparin). -2 women had major bleeding complications, both were given heparin by continuous intravenous infusion in connection with elective C-section. One had subcutaneous hematoma, and another had a second laparotomy due to intraabdominal bleeding.	

[49] Ginsberg JS, et al: Risks to fetus of anticoagulant therapy during pregnancy. Thromb Haemost 61:197-203, 1989.
[50] Ginsberg JS, Hirsh J: Anticoagulants during pregnancy. Annu Rev Med 40:79-86, 1989.
[51] Dahlman TC: Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol 168:1265-70, 1993.

De Swiet M et al.[52] (1983) UK	Prospective cohort	20 pregnant women with history of thromboembolism in the past had been treated with oral anticoagulants for ≥ 6 weeks were included to be treated with heparin sc either for 6 weeks prior to delivery or from entry to trial (between 6-26 weeks) to delivery.	H 20 pregnant women	some all through pregnancy and some third trimester	The phalangeal cortical area ratio was significantly less after longer term therapy (>25 weeks) compared with that after short term therapy (<7 weeks). The same trend was found in the metacarpal area ratio, although it was not statistically significant.	L: small sample size, no control
Wise PH, et al.[53] (1980) UK	case report	38-year-old with history of DVT of left leg became pregnant 7 years later and was initiated on prophylaxis UFH during pregnancy. She developed severe pain and tenderness over L2 postpartum without history of trauma or other medical disorder.	1	All	Osteoporosis of thoracolumbar spine with compression fracture of T11, T12, L2, and prominent "codfish" changes in the other vertebra.	
Barbour LA,[54] et al. (1994) USA	Prospective controlled	14 pregnant women requiring heparin therapy and 14 pregnant controls matched for age, race, and smoking status was identified by 20 weeks', bone density was measured at baseline, immediately postpartum and 6 months postpartum.	UFH 28 women (14 exposed)	All	5/14 (36%) had a ≥ 10% decrease from the baseline proximal femur measurements to immediate postpartum values, and 0/14 matched controls had loss (p = 0.04). Mean proximal femur bone density measurements also decreased in the cases (p = 0.01); this difference continued to be statistically significant 6 months post-partum (p = 0.03). No dose-response relationship could be demonstrated.	L: small sample size, not randomized
Douketis JD, et al.[55] (1996) Canada	Prospective controlled	25 women who received UFH during pregnancy were matched with 25 women who did not underwent dual photon absorptiometry of the lumbar spine in the post-partum period.	UFH 50 women (25 exposed to heparin 1 month or longer)	anytime	None developed fractures. Heparin-treated patients had a 0.082 g/cm2 lower bone density compared to untreated controls, which is clinically and statistically significant (p = 0.0077). There were 6 matched pairs in which only the heparin-treated patient had a bone density below 1.0 g/cm2, compared to only one pair	L: only long-term corticosteroid use > 6 month were excluded; small sample size.

[52] De Swiet M et al: Prolonged heparin therapy in pregnancy causes bone demineralization. Br J Obstet Gynaecol 90:1129-1134, 1983.
[53] Wise PH, Hall AJ: Heparin-induced osteopenia in pregnancy. Br Med J 281:110-111, 1980.
[54] Barbour LA, Kick SD, Steiner JF, LoVerde ME, Heddleston LN, Lear JL, Baron AE, Barton PL. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. Am J Obstet Gynecol 1994;170:862-9.
[55] Douketis JD, Ginsberg JS, Burrows RF et al: The effects of long-term heparin therapy during pregnancy on bone density. A prospective matched cohort study. Thromb-Haemost. 1996; 75: 254-7.

					in which only the control patient had a bone density below this level (p = 0.089).	
von Mandach U, et al.[56] (2002) Switzerland	Prospective case-control	10 pregnant women on bedrest received UFH 10,000 IU per day for 7-46 days pre-study and 28 days per-study compared to 6 pregnant control with similar gestation and 10 nonpregnant control.	UFH 26 (10 pregnant exposure)	2nd and 3rd trimester	Short-term low-dose heparin plus bedrest suppresses 1,25-dihydroxyvitamin D and osteocalcin levels in pregnancy. Pregnancy outcome was not followed.	L: small sample size

VKA: vitamin K antagonist; H: heparin, UFH: unfractionated heparin, LMWH: low molecular weight heparin; MHV: mechanical heart valves; OA: oral anticoagulation; PPH: postpartum hemorrhage; PP: postpartum; DVT: deep vein thrombosis; aPTT: activated partial thromboplastin time; TAB: therapeutic abortion; SAB: spontaneous abortion; PTD: preterm deliver

[56] von Mandach U, Aebersold F, Huch R, Huch A: Short-term low-dose heparin plus bedrest impairs bone metabolism in pregnant women. Eur J Obstet Gynecol Reprod Biol 2003;106:25-30.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 6, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214520
Product Name and Strength:	Defencath (taurolidine and heparin) catheter lock solution,[a] 1.35%/1,000 units/mL[b]
Total Product Strength:	1.35%/5,000 units per 5 mL vial
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CorMedix Inc. (CorMedix)
FDA Received Date:	June 30, 2020 and September 21, 2020
OSE RCM #:	2020-477
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

[a] Applicant provided the dosage form as "catheter lock solution." The Office of Pharmaceutical Quality will make a final determination of the dosage form during the NDA review.

[b] Applicant provided the strength presentation as "taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 units/mL)." The Office of Pharmaceutical Quality will make a final determination of the strength presentation during the NDA review.

1 REASON FOR REVIEW

As part of the approval process for Defencath (taurolidine and heparin) catheter lock solution, the Division of Anti-Infectives (DAI) requested that we review the proposed Defencath prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container label, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, the package type term "(b) (4) " is included	The currently presented package term "(b) (4) " may not be the appropriate	We defer to the Office of Pharmaceutical Quality (OPQ) to determine if "(b) (4) " is an

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	throughout the Prescribing Information, as well as on the container label and carton labeling.	package type term[c] for the proposed product. This package type term is intended to describe a package that contains (b) (4) If " (b) (4) " is included as the package type term, (b) (4) resulting in use of deteriorated drug product medication errors. A more appropriate package type term may be "single-dose" which is intended to describe a container designed for use with a single patient as a single injection/ infusion (i.e., installation).	appropriate package type term for the proposed product. If OPQ determines that the package type term "single-dose" is the appropriate package type term, "single-dose" should also be included for the container label and carton labeling. In addition, if OPQ determines that it is appropriate to recommend a change to "Single-Dose Vial" we recommend including a discard statement on the container label and carton labeling. For example, revise the statement " (b) (4) " to read "Single-Dose Vial – Discard Unused Portion" on the container label and carton labeling.
2.	As currently presented, " (b) (4) " is included as part of the established name and within the product strength statement throughout	According to the "Description and Composition" document for the drug product[d], " (b) (4) " functions as a (b) (4) and	We defer to OPQ to determine in the inclusion of " (b) (4) " is appropriate as part of the established name and within the product strength

[c] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/media/117883/download.

[d] Description and Composition [Neutrolin® Catheter Lock Solution (CLS), Rovi Contract Manufacturing Services, S.L.] NDA 214520. Berkeley Heights (NJ): CorMedix Inc. 2020 MAR 11. Available from: \\CDSESUB1\evsprod\nda214520\0047\m3\32-body-data\32p-drug-prod\neutrolin-catheterlo\32p1-desc-comp\32p1-description-and-compo.pdf.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the proposed product labeling.	therefore should not be included in the established name or product strength statement.	statement throughout the product labeling.
3.	As currently presented, the dosage form "catheter lock solution" is included throughout the proposed product labeling.	The currently proposed "catheter lock solution" is not included as a dosage form in the USP general practices for pharmaceutical dosage forms.[e]	We defer to OPQ to determine the appropriate dosage form to be used throughout the product labeling.
4.	As currently presented, the strength statement "taurolidine 1.35% and heparin 1,000 units/mL" is included throughout the proposed product labeling.	The currently proposed "taurolidine 1.35% and heparin 1,000 units/mL" may not be the appropriate strength statement. As stated above, we defer to OPQ to determine the appropriate dosage form for the proposed product. However, we note according to the United States Pharmacopeia (USP)[f], for injectable products, the strength should be expressed as the quantity per total volume followed by the quantity per milliliter enclosed in parentheses. Therefore, expressing the taurolidine component in terms of percentage vs. quantity per total volume may not be appropriate.	We defer to OPQ to determine the appropriate strength statement to be used throughout the product labeling.

[e] United States Pharmacopoeia (USP) General Chapter <1151> Pharmaceutical Dosage Forms

[f] United States Pharmacopoeia (USP) General Chapter <7> Labeling

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	As currently presented in Section 11, "*Description*", the product is described as "([(b) (4)])."	Inclusion of [(b) (4)] may be misinterpreted as the volume of the drug product.	We defer to OPQ to determine if the inclusion of this description is required per regulation or standard. However, to minimize the potential for misinterpretation, we recommend the removal of the text "([(b) (4)])."
Highlights of Prescribing Information			
1.	As currently presented under the "*Dosage and Administration"* header, the dosage (volume to be instilled) is stated as "3-5 mL."	The lower dosage (volume to be instilled) may be overlooked because it does not include the appropriate unit of measure (mL). In addition, when a hyphen is included in a range instead of the word "to", the hyphen can be overlooked. For example, "3-5" could be misinterpreted as "35".	To provide clarity and minimize the risk of misinterpretation, add the unit of measure, "mL" after the first Arabic numeral in the dosage (volume to be instilled) range (i.e., "3"). We also recommend replacing the hyphen with its intended meaning "to." For example, "3 mL to 5 mL."
2.	As currently presented under the "*Dosage Forms and Strengths*" header, the abbreviation "U" is included in the strength statement "(1,000 U/mL)."	The abbreviation "U" is an error prone abbreviation that has been mistaken as the number zero, resulting in a ten-fold misinterpretation (e.g., 10000/mL) and has been involved in harmful medication errors.[g]	Eliminate the occurrences of the abbreviation "U" by replacing with its intended meaning "units." For example, "(1,000 units/mL)."

[g] ISMPs List of Error-Prone Abbreviations, Symbols and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2020 JUL 16] Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	As currently presented under the "*Dosage Forms and Strengths*" header, the product is described as "((b) (4))."	Inclusion of (b) (4)) may be misinterpreted as the volume of the drug product.	To minimize the potential for misinterpretation, remove the text "((b) (4))."
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented, the dosage (volume to be instilled) is stated as "3-5 mL."	The lower dosage (volume to be instilled) may be overlooked because it does not include the appropriate unit of measure (mL). In addition, when a hyphen is included in a range instead of the word "to", the hyphen can be overlooked. For example, "3-5" could be misinterpreted as "35".	To provide clarity and minimize the risk of misinterpretation, add the unit of measure, "mL" after the first Arabic numeral in the dosage (volume to be instilled) range (i.e., "3"). We also recommend replacing the hyphen with its intended meaning "to." For example, "3 mL to 5 mL."
2.	As currently presented, the (b) (4)) is buried within the text.	This important product information may be overlooked or missed.	To provide clarity and improve readability, relocate the (b) (4) following " (b) (4) ". Additionally, replace the current word " (b) (4) " with the appropriate container type "vial." For example, (b) (4) ial..."
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the abbreviation "U" is included in the strength	The abbreviation "U" is an error prone abbreviation that has been mistaken as	Eliminate the occurrences of the abbreviation "U" by

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	statement "(1,000 U/mL)."	the number zero, resulting in a ten-fold misinterpretation (e.g., 10000/mL) and been involved in harmful medication errors.	replacing with its intended meaning "units." For example, "(1,000 units/mL)."
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			
1.	As currently presented, the terminology "(b) (4)" in used in the sentence "(b) (4)"	The terminology "(b) (4)" is inconsistent with the Section 16 title "*How Supplied/Storage and Handling*."	To provide consistency, replace the terminology "(b) (4)" with the terminology "supplied." For example, "DEFENCATH is supplied…"
2.	As currently presented, the storage statement is, "…stored at a controlled room temperature of (b) (4) to 25°C ((b) (4) to 77°F)."	The degree symbol (°) and units of temperature measurement (Centigrade and Fahrenheit) following the first numbers in the temperature ranges (e.g., the degree and Centigrade symbols (°C) following the (b) (4) and the degree and Fahrenheit symbols (°F) following the (b) (4)) are missing. The lower temperatures in the ranges may be overlooked.	Add the degree and Centigrade symbols (°C) following the (b) (4) and degree and Fahrenheit symbols (°F) following the (b) (4) within the storage information to provide clarity. For example, "…stored at a controlled room temperature of (b) (4)°C to 25°C ((b) (4)°F to 77°F)."
3.	As currently presented, the package type is not included.	If an appropriate package type term is not included, (b) (4) resulting in use of deteriorated drug product medication errors.	We defer to OPQ to determine if it is appropriate to include the package type term, "single-dose" to be used in the PI labeling. If OPQ determines that the package type term "single-dose" is correct and recommends its use in the PI labeling, this recommendation to use the package type term,

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			"single-dose" should be included prior the word "vial." For example, (b) (4) "
4.	As currently presented, the product strength is not included.	The "strength or potency of the dosage form in metric system" is required by 21 CFR 201.57(c)(17)(i).	Add the proposed product strength (taurolidine 1.35%, and heparin 5,000 units/5 mL (1,000 units/mL)). Also, see General Issues recommendation related to strength presentation.
5.	As currently presented, the package configuration (cartons containing (b) (4) vials) is not included.	The "units in which the dosage form is ordinarily available for prescribing by practitioners" is required by 21 CFR 201.57(c)(17)(ii).	Add the proposed package configuration (cartons containing (b) (4) vials). For example, "…solution for instillation in central venous catheters packaged in cartons of (b) (4) vials…"
6.	As currently presented, the appropriate information to facilitate identification of the proposed "catheter lock solution" dosage form is not included.	A description of identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	We recommend that the description of identifying characteristics to facilitate identification of the proposed "catheter lock solution" dosage form, such as color (e.g., clear aqueous solution) or other identifying characteristics, be added. For example, for the proposed "catheter lock solution" dosage form, include description information that aligns with the description information currently included in Section 3, *Dosage Forms and Strengths*; "clear aqueous solution."

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
7.	As currently presented, the National Drug Code (NDC) is included.	To facilitate identification of the dosage form, the NDC is required per 21 CFR 201.57(c)(17)(iii).	We have provided a recommendation to the Applicant to revise their current NDC placeholders (i.e., XXXXX-XXXX-XX) on their container label and carton labeling. Additionally, in accordance with 21 CFR 201.57(c)(17)(iii), they will need to be add the NDC to the How Supplied section.
8.	As currently presented, the statement "…(b) (4) " contains a trailing.	The use of trailing zeros can result in a ten-fold misinterpretation (e.g., 50 mL) resulting in confusion. This presentation is also inconsistent with the use of 5 mL (without trailing zero) elsewhere in the labeling.	To avoid a ten-fold misinterpretation, we recommend the removal of the trailing zero in the statement "(b) (4) For example, "(b) (4)
9.	As currently presented, the (b) (4) is included (i.e., "(b) (4) ").	Inclusion of (b) (4) (i.e., "(b) (4) ") may be misinterpreted as the volume of the drug product.	To minimize the potential for misinterpretation, remove the text "(b) (4) " within the how supplied statement.

Table 3. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero

Table 3. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	As currently presented, the abbreviation "U" is included in the strength statement "(1,000 U/mL)."	The abbreviation "U" is an error prone abbreviation that has been mistaken as the number zero, resulting in a ten-fold misinterpretation (e.g., 10000/mL) and been involved in harmful medication errors.[h]	Eliminate the occurrences of the abbreviation "U" by replacing with its intended meaning "units."
3.	As currently presented, the National Drug Code (NDC) is denoted by a	We are unable to review the intended NDCs from a medication error	Once assigned, replace the current placeholders (NDC XXXXX-XXX-XX) with the

[h] ISMPs List of Error-Prone Abbreviations, Symbols and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2020 JUL 16] Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 3. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	placeholder (NDC XXXXX-XXX-XX) on both the proposed container label and carton labeling.	perspective. The NDC assigned to a carton containing more than one unit should have a different package code (last 2 digits) than that of the containers within the carton.	intended NDCs on the container labels and carton labeling and submit for our review. To provide differentiation between the individual vials within the carton of (b) (4) vials, and the carton of (b) (4) vials, the package code numbers (last 2 digits) for the individual vials and carton containing (b) (4) vials should be different and non-sequential. Additionally, in accordance with 21 CFR 201.57(c)(17)(iii), you will need to be add your intended NDC to Section 16, *How Supplied /Storage and Handling* of the Prescribing Information.
4.	As currently presented, the "Usual Dose" statement is not included.	Per 21 CFR 201.55, "…labels for prescription drugs bear a statement of the recommended or usual dosage."	Add the "Usual Dose" statement on the container label (if space permits) and carton labeling of the package. For example; "Recommended Dosage: See Prescribing Information."
5.	As currently presented, the statements "Not for systemic administration." and Discard unused portion." are included within a red box.	Negative statements such as "Not for systemic administration." have the potential to result in the opposite of its intended effect, as the word "not' can be overlooked and inadvertently encourage the unintended action (e.g., administered systemically) resulting in wrong route of	To provide clarity, we recommend: • Delete the statement "Discard unused portion." from inside the current red box. • Relocate the statement of the intended action (i.e., "(b) (4) ")

Table 3. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		administration medication errors. However, using an affirmative statement will help ensure that end users understand the intended route of administration, even if they do not read every word. We have received post-marketing reports that negative statements (e.g., do not) may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpret the warning as an affirmative action.[i]	to inside the current red box to provide this intended action prominence. (i.e., boxed). To further increase the prominence of this intended action, consider changing the color of the font to red, bolding the font, and/or increasing the font size of this statement. • We acknowledge your intent to include the clarification statement "Not for systemic administration." If you decide to keep this statement, we recommend that this statement be placed immediately following the intended action (i.e., "(b) (4) ") in a less prominent font (i.e., color (black like the remainder of the labeling text), not bolded, smaller size). For example, (b) (4)

[i] Institute for Safe Medication Practices. Affirmative w warnings (do not do that). ISMP Med Saf Alert Acute C

Table 3. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
6.	As currently presented, the container label and carton labeling lack a storage statement.	Not including a statement that the product requires refrigeration could result in improper storage and deteriorated drug medication errors.	Add the storage statement to the container label and carton labeling.
Container Label			
1.	As currently presented, the net quantity statement is missing.	The net quantity statement should appear on the principal display panel (PDP), but should be separated from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).[j]	Add the net quantity statement to the PDP. For additional information, see 21 CFR 201.51.
2.	As currently presented, the (b) (4) clutters the principal display panel (PDP) and takes the readers' attention away from important product information on the PDP.		We recommend you decrease the prominence, font size (height) of the letters within your (b) (4) or consider moving the (b) (4) to the side panel.
3.	As currently presented, there is no linear	The drug barcode is often used as an additional verification before drug	Add the product's linear barcode to each individual container label as required per

[j] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 461-463). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 3. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	barcode included on the container label.	administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	21CFR 201.25(c)(2). We recommend that the container label linear barcode be oriented in a vertical position to improve scannability of the barcode, as barcodes placed in a horizontal position may not scan due to the curvature of the container. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i). We note you plan to include a "2D Code"; however, inclusion of a data matrix barcode does not replace the requirement for a linear barcode on the container label. For more information see the draft guidance for industry, "Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers".[k]
Carton Labeling			
1.	As currently proposed, human-readable and machine-readable (2D	The drug package label must include the product identifier information (i.e.,	We recommend you include the NDC in your proposed product identifier.

[k] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Table 3. Identified Issues and Recommendations for CorMedix Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	data matrix barcode) product identifier on the smallest saleable unit (usually the carton) does not include the NDC.	the NDC, serial number, lot number, and expiration date) in both the human-readable form and machine-readable, 2D data matrix barcode format.	

4 CONCLUSION

Our evaluation of the proposed Defencath prescribing information (PI), container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to CorMedix Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Defencath that CorMedix Inc. submitted on June 30, 2020.

Table 4. Relevant Product Information for Defencath	
Initial Approval Date	N/A
Active Ingredient	taurolidine and heparin
Indication	For the prevention of catheter-related bloodstream infections in patients with end-stage renal disease receiving hemodialysis through a central venous catheter. Limitations of Use (b) (4)
Route of Administration	instilled into the catheter lumen
Dosage Form	catheter lock solution for intravenous treatment
Strength	1.35%/1,000 units/mL (1.35%/5,000 units per 5 mL vial)
Dose and Frequency	(b) (4)
How Supplied	5 mL vial; packaged in cartons containing (b) (4) vials
Storage	Vials must be stored at a controlled room temperature of (b) (4) to 25°C ((b) (4) to 77°F). Do not freeze.
Container Closure	Type (b) (4) glass vial with a (b) (4) stopper. The stopper (b) (4) the drug product and the rubber component. The sealing cap is to (b) (4) The cap has no drug product contact.

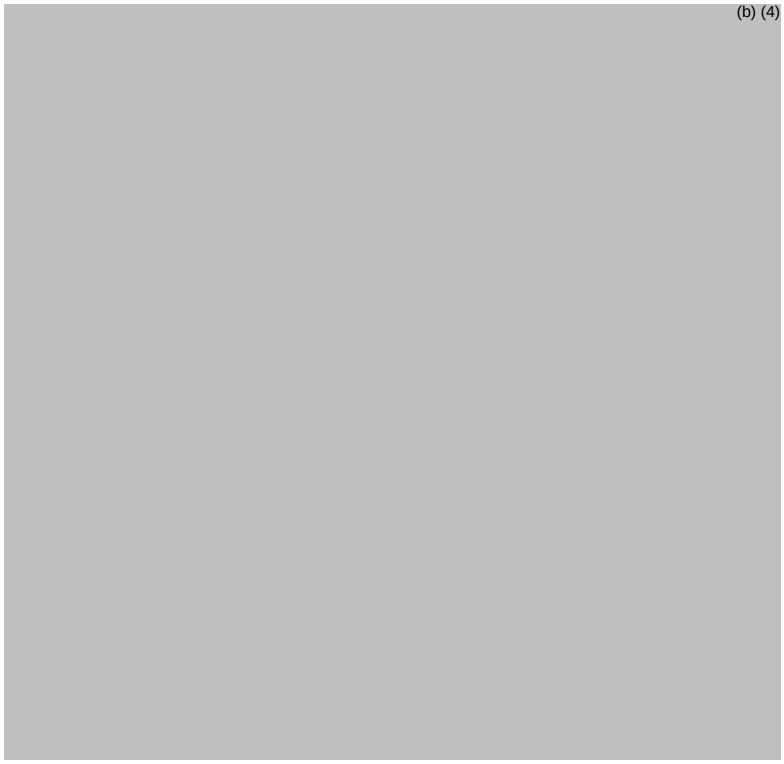
APPENDIX F. LABEL AND LABELING

F.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[l] along with postmarket medication error data, we reviewed the following Defencath labels and labeling submitted by CorMedix Inc.

- Container label received on June 30, 2020
- Carton labeling received on June 30, 2020
- Prescribing Information (PI) received on September 21, 2020
    - Track changes PI available at: \\CDSESUB1\evsprod\nda214520\0072\m1\us\14lbl\1dl\3dlt\3e2d1b0fa5.docx
    - Proposed (Draft) PI available at: \\CDSESUB1\evsprod\nda214520\0072\m1\us\14lbl\1dl\3dlt\pm-11413-defencath-prescri.docx

F.2 Label and Labeling Images



[l] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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