CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214520Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	214520
Applicant Name	CorMedix Inc.
Drug Product Name	DEFENCATH (taurolidine and heparin) catheter lock solution
Dosage Form.	Solution
Proposed Strength(s)	13.5 mg/mL and 1,000 USP Units/mL (3 mL and 5 mL fill volumes/strengths)
Route of Administration	For central venous catheter instillation use
Maximum Daily Dose	N/A
Rx/OTC Dispensed	Rx
Proposed Indication	To reduce the incidence of catheter-related bloodstream infections (CRBSI) in adult patients with kidney failure receiving chronic hemodialysis (HD) through a central venous catheter (CVC).
Drug Product Description	DEFENCATH is a combination product of a thiadiazinane antimicrobial (taurolidine) and an anti-coagulant (heparin) indicated to reduce the incidence of catheter-related bloodstream infections (CRBSI) in patients with end-stage renal disease (ESRD) receiving hemodialysis through a central venous catheter. As described in the proposed labeling, this product is indicated for use in a limited and specific population of patients. DEFENCATH is intended for use with central venous catheter (CVC) only and is not intended for systemic administration. DEFENCATH catheter lock solution is provided as a sterile, preservative-free, clear, aqueous-based solution in a single-dose vial. Two fill volumes/strengths are proposed for commercial use via this NDA resubmission:

	3 mL solution containing taurolidine 40.5 mg/3 mL (13.5 mg/mL), and heparin 3,000 USP Units/3 mL (1,000 USP Units/mL) of heparin, and *5 mL solution containing 67.5 mg/5 mL (13.5 mg/mL) of taurolidine and 5,000 USP Units/5 mL (1,000 USP Units/mL) of heparin* DEFENCATH is to be instilled into the catheter lumen using 3 mL or 5 mL single-dose vial (depending on the volume of the catheter lumen), as a lock solution at the conclusion of each hemodialysis session. Prior to initiation of the next hemodialysis treatment, the DEFENCATH solution must be withdrawn from the catheter and discarded.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Controlled room temperature of 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Paresma Patel	Gaetan Ladouceur
	Drug Product/ Labeling	Akshata Nevrekar	Dorota Matecka
	Labeling	Akshata Nevrekar	David Claffey
	Manufacturing	Rose Xu	Vidya Pai
	Biopharmaceutics	N/A	N/A
	Microbiology	Ryan Blower	John Metcalfe
	Other (specify):	N/A	N/A
	RBPM	Anh-Thy Ly	
	ATL	Dorota Matecka	

Consults	N/A

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

36 months at a controlled room temperature of 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]

b. Additional Comments for Action
N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

This NDA, originally submitted on June 30, 2020, was recommended by the OPQ team for Complete Response (CR) in the first review cycle due to deficiencies related to the drug product manufacturing facility, ROVI Pharma Industrial Services S.A., and inadequate in-process controls for the (b) (4) in the drug product manufacturing process. In addition, a non-CR comment recommending the inclusion of the (b) (4) in the drug product manufacturing process was also issued (refer to the OPQ Reviews # 1 and # 2, dated December 21, 2020, and February 19, 2021, respectively, in DARRTS). The CR letter was issued on February 26, 2021, and the NDA was resubmitted on February 25, 2022. In the second review cycle the fill volume issue and the non-CR comments were addressed adequately; however, the status of the drug product manufacturing facility, was found again unacceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA). In addition, the proposed commercial manufacturer of heparin sodium ((b) (4)) was also found unacceptable. Therefore, the NDA was again recommended for CR from the Product Quality perspective (refer to the OPQ Review # 3 dated July 28, 2022) and another CR letter was issued on August 23, 2022.

The proposed changes in the current NDA resubmission (dated May 15, 2023, SDN#78) include an addition of an alternate heparin drug substance

supplier ([(b) (4)]) and inclusion of the 3 mL fill volume/strength as an additional commercial drug product packaging presentation. There are no proposed changes to the drug product formulation/composition, container closure or manufacturing process. Several testing sites associated with the proposed addition of [(b) (4)] as an additional heparin drug substance manufacturer have also been added via this NDA resubmission.

The CMC information for both drug substances submitted to support the proposed drug product and the NDA was found adequate in the first review cycle. The CMC information for taurolidine drug substance is referenced to DMF [(b) (4)] which was reviewed by Katherine Windsor on April 19, 2022 and remains adequate to support this NDA. The CMC information for heparin sodium drug substance is referenced to DMF [(b) (4)] (held by [(b) (4)]) and was reviewed by Paresma Patel on August 29, 2023, to support this NDA resubmission. The resubmission also references DMF [(b) (4)] for heparin sodium that was previously reviewed and found adequate by Paresma Patel to support this NDA. No additional drug substance information is submitted in this NDA resubmission (refer to the comments included under Task Number 359 in Panorama).

The overall CMC information provided in this NDA resubmission related to the drug product, manufacturing, and microbiological controls has been found acceptable. In addition, all manufacturing facilities currently listed in the NDA have been found acceptable, which includes Alcami, Rovi and [(b) (4)], proposed to be used as [(b) (4)], respectively (for details refer to the Manufacturing Integrated Assessment attached below). It should be noted that [(b) (4)], initially also proposed as the commercial heparin sodium manufacturer, and all other [(b) (4)] facilities were withdrawn from the NDA by the Applicant on September 29, 2023 (for details refer to the Manufacturing Integrated Assessment attached below). The overall manufacturing inspection recommendation (OMIR) for this NDA as "Approved" was entered in Panorama on October 20, 2023. Based on the assessment of the overall Product Quality information submitted in the NDA (including the current resubmission), this NDA is now recommended for approval by the OPQ review team.

Note:
This OPQ Review document includes updated Drug Product, Labeling, Manufacturing and Microbiology reviews. For previous reviews, including other discipline reviews refer to the OPQ Reviews # 1, #2, #3, dated

December 21, 2020, February 19, 2021, and *July 28, 2022, respectively, in DARRTS*.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substances	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The information submitted in the PI, carton label and vial label of the drug product (3.0 mL label claim and 5.0 mL label claim) are adequate.

Minor comments have been issued in the PI sent out to the applicant for revision.

Comments include:

1. **Revise the IUPAC name for the drug substance taurolidine in accordance with the IUPAC name submitted in section 3.2.S.1.1.**
2. **Revise the storage conditions for the drug product, to include temperature excursions, in the container and carton label to be in accordance with the storage conditions proposed in the PI.**

Note: In response to agency's request, the applicant in AM 07/19/2023 has submitted revised prescription information to combine the Prescribing Information for the Company's 3 mL and 5 mL fill single-dose vial product, DefenCath®, that was provided as separate documents to NDA 214520 submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME (Taurolidine and heparin) catheter lock solution	The proposed proprietary name for the drug product (label claim: 3.0 mL and 5.0 mL) is Defencath®. In the original submission, the proposed name was Neutrolin®. Please refer to DMEPA review for acceptance of the proprietary name of the drug product. (Label claim 3.0 mL and 5.0 mL)
Established name(s)	Taurolidine and heparin catheter lock solution	Adequate
Route(s) of administration	For instillation in central venous catheter.	Adequate

Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	TRADENAME is a sterile CLS available in a 3 mL single-dose vial and a 5 mL single-dose vial. The 3 mL single-dose vial consists of taurolidine 40.5 mg/3 mL (13.5 mg/mL), and heparin 3,000 USP Units/3 mL (1,000 USP Units/mL). The 5 mL single-dose vial consists of taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL).	Adequate. As per labelling review 002 by Shalini Ananad: (The Applicant proposed to use the abbreviated term for “Catheter lock solution” as CLS In the updated PI. The proposed changes were found acceptable by the labelling review team.)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	**3.0 mL label claim:** Single-dose vial **5.0 mL label claim:** Single-dose vial	Adequate Additional statement “Discard any unused portion of TRADENAME remaining in the vial” added to the label.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A **Note:** TRADENAME is for instillation into central venous catheters (CVCs) only. TRADENAME is not intended for systemic administration. Do not use TRADENAME as a catheter lock flush product	The drug product (label claim 3.0 mL and 5.0 mL) will not be diluted/ reconstituted prior to the administration.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Catheter lock solution (CLS)	Adequate As per labelling review 002: (The Applicant proposed to use the abbreviated term for "Catheter lock solution" as CLS In the updated PI. The proposed changes were found acceptable by the labelling review team.)
Strength(s) in metric system	3 mL of catheter lock solution in a 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 of catheter lock solution in a 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)	Adequate

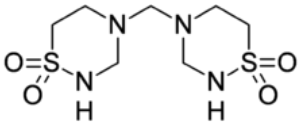
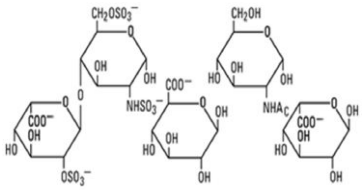
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate Taurolidine: Not a salt form Heparin: sodium salt As per labelling review 002: The active ingredients are heparin sodium and taurolidine. However, as per the feedback from heparin drug substance reviewer (Paresma Patel, Ph.D.) and OPPQ – the equivalency statement is not necessary for heparin because the strength is determined by a bioassay. So, the actual quantity can vary from batch to batch. There is no equivalency statement on Heparin sodium containing DPs that are not intended to be used systemically (email dated Oct. 15, 2020, and Dec. 01, 2020).
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	TRADENAME CLS is available as a sterile, preservative-free, clear, aqueous-based solution in the following strengths: 3 mL of catheter lock solution in a single-dose vial and 5 mL of catheter lock solution in a single-dose vial.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	**3.0 mL label claim:** Single-dose vial **5.0 mL label claim:** Single-dose vial	Adequate

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME (taurolidine and heparin) catheter lock solution	Adequate
Dosage form(s) and route(s) of administration	Catheter lock solution	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Adequate Taurolidine: Not a salt form Heparin: sodium salt -No equivalency statement is necessary for heparin for DPs that are not intended to be used systemically. (Refer the review of section 3 above for more information)
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Inactive ingredients: Citric acid, anhydrous, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Citric acid, anhydrous (26.1 mg/mL) (which is added to control pH and maintain the solubility of taurolidine) and hydrochloric acid and/or sodium hydroxide for pH adjustment.	Adequate as per information submitted in P.1 **3.0 mL label claim:** 78.3mg **5.0 mL label claim:** 130.5mg
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Sterile, non-pyrogenic, (b) (4), preservative-free, clear aqueous solution of taurolidine and heparin with a pH of 5.5-6.5	Adequate

Pharmacological/ therapeutic class	Heparin sodium as anti-coagulant and taurolidine as thiadiazinane antimicrobial.	Adequate
Chemical name, structural formula, molecular weight	**Taurolidine** **Chemical Name:** (b) (4) [redacted]. **Empirical formula:** $C_7H_{16}N_4O_4S_2$ **Molecular weight:** 284.36 g/mol. **structural formula:**  **Heparin Sodium** Heparin is an anticoagulant consisting of heterogeneous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans. It is composed of polymers of alternating derivatives of α-D-glucosamido (*N*-sulfated, *O*-sulfated, or *N*-acetylated) and *O*-sulfated uronic acid (α-L-iduronic acid or β-D-glucuronic acid). Heparin is derived from porcine intenstinal mucosa. Structure of heparin sodium (representative subunits) is: 	Adequate Upon discussion with drug substance reviewer Dr. Paresma Patel, Minor comment issued to applicant in PI to revise the IUPAC name for taurolidine in the PI as a part of the description section to be in accordance with the IUPAC name proposed in section 3.2.S.1.1. "4,4'-methylenebis(1,2,4-thiadiazinane)-1,1,1',1'-tetraoxide" The molecular weight of taurolidine was revised to be 284.36 for consistency with the NDA and DMF. The drug substance reviewer Dr. Paresma Patel agreed with the description of heparin provided by the applicant in the PI.

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	pH - 5.5-6.5	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Catheter lock solution	Adequate
Strength(s) in metric system	TRADENAME cathether lock solution is available in: 3 mL of catheter lock solution in a 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) (NDC 72990-0103-(b)(4)) 5 mL of catheter lock solution in a 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) (NDC 72990-0105-(b)(4))	Adequate
Available units (e.g., bottles of 100 tablets)	3 mL single-dose vial and 5 mL single-dose vial; Each carton contains 10 single-dose vials.	Adequate In original submission and as per review cycle 03: Carton containing (b)(4) vials was proposed.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	3 mL single-dose vial as well as a 5 mL single-dose vial supplied as Sterile, preservative-free, clear aqueous based solution.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	**single-dose vial (label claim 3 mL and 5 mL label claim).** (b) (4)	Adequate **single-dose vial**

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.)	Do not freeze. TRADENAME vials must be stored in the commercial carton, prior to the instillation in central venous catheters.	Adequate (The drug product is light sensitive if stored in the primary packaging i.e., vials only. The secondary packaging provides protection from light. The applicant included this statement as per the CMC Recommendation communicated in review cycle 02.)
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	TRADENAME vials must be stored at a controlled room temperature of 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. Excursions are	Adequate. The supporting stability data is provided in section 3.2. P.8. The storage conditions are same as submitted in section 3.2.P.8.1. As per 3.2.P.8.1: DefenCath® is intended to be stored at controlled room

	permitted from 15 ºC to 30 ºC Do not freeze.	temperature conditions—i.e., 20˚C to 25˚C (68˚F to 77˚F)—as defined by USP. Temperature excursions have been added to the storage conditions in the PI in accordance with USP <659>. Comment issued to the sponsor in PI to include temperature excursions to the storage conditions of the drug product as a part of the container and carton label to be in accordance with the PI for the drug product.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	N/A	The product will be used only in the clinical settings.

i. Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

ii. **Manufacturing Information After Section 17 (for drug products)**

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	CorMedix Inc. 300 Connell Drive, Suite 4200 Berkeley Heights, NJ 07922	Adequate

2.0 PATIENT LABELING

Note: In response to agency's request, the applicant in AM 07/19/2023 has submitted revised prescription information to combine the Prescribing Information for the Company's 3 mL and 5 mL fill single-dose vial product, DefenCath®, that was provided as separate documents to NDA 214520 submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

Minor comments have been issued in the PI sent out to the applicant for revision.

Comments include:

1. **Revise the IUPAC name for the drug substance taurolidine in accordance with the IUPAC name submitted in section 3.2.S.1.1.**
2. **Revise the storage conditions for the drug product, to include temperature excursions, in the container and carton label to be in accordance with the storage conditions proposed in the PI.**

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	TRADENAME™ Taurolidine and Heparin catheter lock solution Limited Population	Adequate
Dosage strength	**3 mL Fill:** 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 Fill:** Taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)	Adequate
Route of administration	For instillation in Central Venous Catheters- Not for systemic administration	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	Adequate No equivalency statement is necessary for heparin for DPs that are not intended to be used systemically. (Refer the review of section 3 of the PI for more information)
Net contents (e.g., tablet count)	3 mL Fill single dose vial 5 mL Fill single dose vial	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	3 mL Fill: NDC 72990-103 (b) (4) 5 mL Fill: NDC 72990-105	Adequate
Lot number and expiration date	Yes	Adequate

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F).	Adequate (3.0 mL single dose vial: and 5.0 mL single dose vial) Revision of the storage condition for the drug product (3.0 mL fill and 5.0 mL fill) to include permitted temperature excursions as a part of the container and carton label is requested in PI.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	3 mL Fill and 5 mL Fill: Single-Dose Vial - Discard Unused Portion	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	NA	The carton includes term “Limited Population” for 3.0 mL fill and 5.0 mL fill.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	CorMedix Inc. 300 Connell Drive, Suite 4200 Berkeley Heights, NJ 07922	Adequate
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available		

Assessment of Carton and Container Labeling: *{Adequate/Inadequate}*

CorMedix submitted the updated container and carton labels in amendment dated 09/14/2023 for drug product (label claim 5.0 mL and 3.0 mL).

The information on carton and container labels submitted in the current resubmission are acceptable from CMC perspective.

Inclusion of temperature excursions to the storage conditions for the drug product (5.0 mL and 3.0 mL) in the container and carton label has been requested the PI sent to the applicant for revision.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Assessment of inclusion of temperature excursions to the storage conditions for the drug product (5.0 mL and 3.0 mL) in the container and carton label.

Overall Assessment and Recommendation:

Adequate:
Refer to discussion above and recommendations in OND labeling.

Primary Labeling Assessor Name and Date:

Akshata Nevrekar, PhD, Branch 2, ONDP Division of New Drug Products I, OPQ, 09/29/2023.

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Akshata Nevrekar

Digitally signed by Akshata Nevrekar
Date: 9/29/2023 04:33:30PM
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David Claffey

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Date: 9/29/2023 04:34:53PM
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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the NDA IQA Guide

Product Information	
NDA Number	214520
Assessment Cycle Number	002
Drug Product Name/ Strength	DefenCath, 13.5 mg/mL
Route of Administration	Catheter Lock Solution
Applicant Name	CorMedix Inc
Therapeutic Classification/ OND Division	CDER/OND/OID/DAI
Manufacturing Site	ROVI Contract Manufacturing, S.L. Paseo de Europa No. 50, San Sebastian de los Reyes, Madrid 28703, Spain
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
eCTD Seq #0136	05/15/2023

Highlight Key Issues from Last Cycle and Their Resolution: This is a resubmission after a Complete Response Letter issued to the firm on August 4, 2022. The original marketing submission (dated Mar 11, 2020) was sent a Complete Response Letter due to issues from other disciplines, but the Microbiology review of the original submission (N214520MR01.docx, dated Oct 14, 2020) was found Adequate. However, the firm is proposing to add an additional 3 mL fill size. There is no change to the manufacturing process, equipment, formulation, analytical methods, or container closure system for the 3 mL fill size compared to the currently adequate 5 mL fill size.

Remarks: N/A

Concise Description of Outstanding Issues: None identified.

Supporting Documents:

- **N214520MR01.docx (10/14/2020, adequate) for sterility assurance review of 5 mL presentation.**

Summary Of Changes

In this resubmission, the firm is proposing to add an additional 3 mL fill size. The formulation, container closure system, manufacturing process, in-process controls, facility, equipment, release specifications, analytical methods, and stability protocol for the proposed 3 mL fill size remain unchanged from the currently adequate 5 mL fill size. The information provided to support the manufacturing of the proposed presentation is reviewed below.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section 3.2.P.1, pg. 1/2 in "3.2.P.1 Description and Composition of the Drug Product 2023-May"

The drug product is a sterile, single-(b) (4), aqueous Catheter Lock Solution (CLS). The approved formulation for the 5 mL fill format remains unchanged for the proposed 3 mL fill format. The proposed container closure system for the 3 mL fill format remains unchanged from the approved 5 mL fill formats and includes a 6 mL 13 mm USP Type (b) (4) glass vial, 13 mm (b) (4) grey stopper, and 13 mm flip-off aluminum seal.

Assessment: *Adequate*

The applicant provided an adequate description of the composition and container closure system for the proposed additional 3 mL fill format.

(b) (4)

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Ryan Blower

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John Metcalfe

Digitally signed by John Metcalfe
Date: 7/26/2023 09:45:57AM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOROTA M MATECKA
11/07/2023 07:18:13 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 214520
Assessment # 3

Drug Product Name	DEFENCATH* (taurolidine and heparin) catheter lock solution
Dosage Form	Solution
Strength	13.5 mg/mL and 1,000 USP Units/mL
Route of Administration	Central venous catheter lock solution
Rx/OTC Dispensed	Rx
Applicant	CorMedix Inc.
US agent, if applicable	N/A

**Proposed trade name*

Submission(s) Assessed	Document Date	Discipline(s) Affected
0120 (SDN067) ***NDA Resubmission***	February, 2022	All
0123	April 1, 2022	Drug Substance, Drug Product, Process, Facilities
0124	May 23, 2022	Drug Product, Process
0125	June 8, 2022	Process, Facilities
0126	June 9, 2022	Process, Facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance (Taurolidine)	Katherine Windsor	Katherine Windsor
Drug Substance (Heparin Sodium)	Paresma Patel	Paresma Patel
Drug Product	Shalini Anand	Dorota Matecka
Manufacturing	Rose Xu	Vidya Pai
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs*:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	June 29, 2022	Paresma Patel
	II			Adequate	April 19, 2022	Katherine Windsor

**Several Type III DMFs for the components of the proposed container/closure system are also listed in the NDA; overall information provided for the container/closure system was assessed and found acceptable in the first NDA review cycle*

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	113764	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, taurolidine and heparin catheter lock solution. Overall information provided for both drug substances (taurolidine and heparin sodium), and the drug product (taurolidine and heparin catheter lock solution) was found acceptable. However, the status of the drug product manufacturing facility, ROVI Pharma Industrial Services S.A., was found unacceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA). In addition, the proposed commercial manufacturer of heparin sodium ((b) (4) was also found unacceptable. The overall manufacturing inspection recommendation (OMIR) of "Withhold" was entered in Panorama for this NDA by OPMA on July 25, 2022. Therefore, this NDA is currently recommended for Complete Response (CR) by the Office of Pharmaceutical Quality (OPQ).

The following deficiency related to the drug substance and drug product facility status will be included in the CR letter:

During a recent inspection of the (b) (4) *and Rovi Pharma Industrial Services S.A (FEI 3016688535) manufacturing facilities for this application, our field investigators conveyed deficiencies to the representatives of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.*

Additionally, a non-CR comment related to facilities, was also provided by the OPMA team, and will be included in the CR letter (in the Additional Comments section):

There are facilities (e.g., release/stability testing sites) included in DMF (b) (4) *for* (b) (4) *that were not listed in your application (i.e., Form FDA 356h and/or in Section 3.2.S.2.1). Please note that the FDA cannot provide to you the status facilities not listed in your application. Please contact the DMF holder to identify and resolve any discrepancies and clarify which facilities listed in the DMF support your application. We recommend that the DMF related facilities supporting your application be added to your Form FDA 356h and in Section 3.2.S.2.1. If only a subset of the facilities listed in the DMF will be referenced in your application to support commercial manufacturing and/or testing, the letter of authorization (LOA) should specify those facilities. Absent this specificity, the FDA intends to assume that all facilities listed in a referenced DMF support your application.*

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

DEFENCATH is a combination product of a thiadiazinane antimicrobial (taurolidine) and an anti-coagulant (heparin) indicated to reduce the incidence of catheter-related bloodstream infections (CRBSI) in patients with end-stage renal disease (ESRD) receiving hemodialysis through a central venous catheter. As described in the proposed labeling, this product is indicated for use in a limited and specific population of patients.

DEFENCATH is intended for use with central venous catheter (CVC) only and is not intended for systemic administration.

DEFENCATH catheter lock solution is provided as a sterile, preservative-free, clear, aqueous-based solution 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 single-dose vial. DEFENCATH is to be instilled into the catheter lumen, (in the amount of 3 mL to 5 mL depending on the volume of the catheter lumen), as a lock solution at the conclusion of each hemodialysis session. Prior to initiation of the next hemodialysis treatment, the DEFENCATH solution must be withdrawn from the catheter and discarded.

Proposed Indication(s) including Intended Patient Population	To reduce the incidence of catheter-related bloodstream infections (CRBSI) in patients with end-stage renal disease (ESRD) receiving hemodialysis through a central venous catheter. This drug is indicated for use in a limited and specific population of patients
Duration of Treatment	DEFENCATH is to be instilled into the catheter lumen as a lock solution 3 mL to 5 mL at the conclusion of each hemodialysis session. Prior to initiation of the next hemodialysis treatment, the DEFENCATH solution must be aspirated from the catheter and discarded.
Maximum Daily Dose	N/A This product is intended for central venous catheter (CVC) lumen instillation. It is not intended for systemic administration.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance (Heparin Sodium): Adequate

The overall CMC information for heparin sodium drug substance to be used in the manufacture of the commercial drug product was found acceptable in the first NDA review cycle (refer to the OPQ Review # 1 dated December 21, 2020, in DARRTS). The CMC information for heparin sodium is provided by reference to DMF (b) (4) held by (b) (4) The DMF was reviewed in support of this NDA and was found adequate. In addition, information provided in the NDA, including responses to several Information Requests, was also found adequate.

For details, refer to the Drug Substance/Heparin Sodium Review, below.

Drug Substance (Taurolidine): Adequate

The overall CMC information for taurolidine drug substance to be used in the manufacture of the commercial drug product was found acceptable in the first NDA review cycle (refer to the OPQ Review # 1 dated December 21, 2020, in DARRTS). The CMC information for taurolidine is provided by reference to DMF (b) (4) held by CorMedix, Inc. The DMF was reviewed in support of this NDA and was found adequate. In addition, information provided in the NDA to support taurolidine drug substance (which included several updates originating from DMF (b) (4)) was also found adequate.

For details, refer to the Drug Substance/Taurolidine Review, below.

Drug Product: Adequate

The overall CMC information submitted for the drug product in the initial NDA and subsequent amendments was found adequate (refer to the OPQ Reviews # 1 and 2 dated December 21, 2020, and February 19, 2021, in DARRTS).

The Applicant resubmitted all drug product sections (3.2.P.1 – 3.2.P.8) in the NDA resubmission. In response to the FDA request, in subsequent amendments dated April 1, 2022, and May 23, 2022, the Applicant provided a tabulated list highlighting only the updates and new information included in the NDA resubmission. The Applicant has also confirmed that most of the updates are administrative updates; therefore, the current Drug Product Review covers only changes, which can impact the drug product quality.

These changes include a proposal to (b) (4) The proposed in-process

control limits have been found acceptable by the OPMA review team. The Applicant also revised the acceptance criterion for (b) (4) in drug product specifications.

In addition, the Applicant submitted 36-month long term stability and 36-month leachable data for three drug product registration batches (packaged in the to-be marketed container/closure system). All three registration batches met the proposed regulatory specifications at the 36-month time point. Therefore, the proposed drug product shelf life of 36 months along with the proposed storage conditions (20ºC to 25ºC) have been found acceptable by the Drug Product Reviewer.

The Applicant also proposed to replace the (b) (4) with (b) (4) in drug product stability specification. The Product Quality Microbiology Team (Dr. Yan Zheng) was notified about this change and found it acceptable (via email dated July 5, 2022).

The overall information submitted for the drug product was found adequate (*refer to the Drug Product Review, below*).

Labeling: Adequate

The review of the CMC sections of the labeling, including the container carton label and carton labeling, has been completed and recommendations conveyed to the Applicant in the first review cycle along with the comments from other disciplines. The Applicant has submitted the updated labeling documents in the NDA resubmission. The revised Prescribing Information, container label, and carton labeling were found acceptable from the Product Quality perspective (refer to the Labeling Review, below). Due to the anticipated Complete Response action for this NDA, no further labeling discussions or meetings were held in the current review cycle; the proposed labeling will need to be assessed again in the next NDA review cycle.

Manufacturing: Inadequate

This NDA was found inadequate by OPMA team in the first NDA review cycle due to the unacceptable status of the drug product manufacturer, Rovi Pharma Industrial Services S.A. In a previous cycle, due to travel restrictions related to the COVID-19 pandemic, a 704(a)(4) based review was conducted for this facility and a number of deficiencies were identified. Therefore, the overall recommendation of "Withhold" was entered in Panorama for this NDA on January 29, 2021. In addition, data to demonstrate that the proposed extractable volume of 5.0 mL can be extracted from the vial (b) (4) were not provided. These two issues were listed in the CR letter as deficiencies. In addition, a comment recommending an inclusion of the (b) (4)

in the drug product manufacturing process, was also included in the CR letter under Additional (non-CR) Comments. Refer to the OPQ Review # 2 dated February 19, 2022, in DARRTS, for details.

The issues related to the manufacturing process have been addressed adequately in the current NDA resubmission. In addition, additional comments and information requests regarding the drug product manufacturing process conveyed to the Applicant during the NDA resubmission review have also been addressed adequately.

Regarding facilities, the drug product manufacturer, Rovi Pharma Industrial Services S.A., has been inspected by FDA in the current review cycle and again found unacceptable. In addition, the heparin sodium drug substance manufacturing site was also found inadequate due to the currently unresolved OAI status following the FDA inspection in (b) (4) . Therefore, the overall recommendation of "Withhold" was entered in Panorama for this NDA on July 25, 2022, and the overall manufacturing information was found inadequate by the OPMA Reviewer (for further details, including the comments that should be included in the CR letter for this NDA, refer to the *Manufacturing Integrated Assessment, below*).

Biopharmaceutics: Adequate

Refer to the OPQ Review # 2 dated February 19, 2021 (in DARRTS)..

Microbiology (if applicable): Adequate

Refer to the OPQ Review # 1 dated December 21, 2020 (in DARRTS).

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, stability	Formulation Raw materials Process parameters Scale/equipment	Low	Adequate long-term stability data for three registration	Acceptable	

	Site		batches were provided		
Volume in Container/ Extractable Volume	Process parameters Scale/equipment Site	Low		Acceptable	
pH	Formulation Raw materials Process parameters Scale/equipment	Low	Adequate (b) (4) controls established	Acceptable	
Particulate Matter	Formulation Raw materials Process parameters Scale/equipment Site	Medium	Adequate procedure and data provided; test included in drug product specification	Acceptable	
Bacterial endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	High	Adequate microbiological controls	Acceptable	
Sterility	Formulation Raw materials Process parameters Scale/equipment Site	High	Adequate microbiological controls	Acceptable	
Extractable /leachable	Formulation Raw materials	Medium	The packaging includes a glass vial and a rubber stopper. The results of the one-time E&L study found acceptable.	Acceptable	
Facilities	Site	*N/A*	*The status of drug substance (heparin sodium) and drug product manufacturing facilities has been found unacceptable*	Not Acceptable	

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U.S. FOOD & DRUG ADMINISTRATION

Drug Product Labelling Review # 2

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

Note- The CMC recommendations were communicated to the Applicant in the last review cycle. CoMedix submitted the updated labelling documents in the current review cycle. Only an initial labelling planning meeting was held in the current review cycle to go the revised labelling documents. The revised Prescribing Information, container and carton labels were found acceptable by the labelling review team. No further labelling discussions/meetings were held in the current review cycle.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	DEFENCATH (taurolidine and heparin) catheter lock solution	Adequate.
Established name(s)	Taurolidine and heparin catheter lock solution	Adequate.
Route(s) of administration	For instillation in central venous catheter	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	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)	Adequate.
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose vial	Adequate (As per the recommendation communicated in the last review cycle, the Applicant revised the package type term to 'single-dose vial'.)

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	The drug product will not be diluted/ reconstituted prior to the administration.

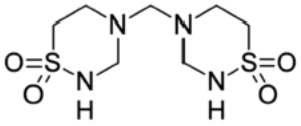
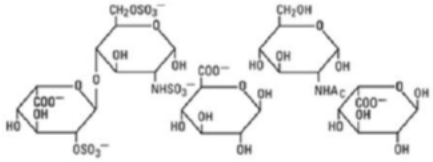
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Catheter lock solution (CLS)	Adequate. (The Applicant proposed to use the abbreviated term for "Catheter lock solution" as CLS In the updated PI. The proposed changes were found acceptable by the labelling review team.)
Strength(s) in metric system	Taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate The active ingredients are heparin sodium and Taurolidine. However, as per the feedback from heparin drug substance reviewer (Parmesan Patel, Ph.D.) and OPPQ - the equivalency statement is not necessary for heparin because the strength is determined by a bioassay. So, the actual quantity can vary from batch to batch. There is no equivalency statement on Heparin sodium containing DPs that are not intended to be used systemically (email dated Oct. 15, 2020 and Dec. 01, 2020).
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Sterile, preservative-free, clear, aqueous-based solution	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose vial	Adequate

1.2.3 Section 11 Description

Item	Information Provided in the NDA	Assessor's Comments
Proprietary and established name(s)	DEFENCATH (taurolidine and heparin) catheter lock solution	Adequate
Dosage form(s) and route(s) of administration	Catheter lock solution	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	As per the feedback from heparin drug substance reviewer (Parmesan Patel, Ph.D.) and OPPQ - No equivalency statement is necessary for heparin for DPs that are not intended to be used systemically. (Refer the review of section 3 above for more information)
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Inactive ingredients: Citric acid, anhydrous, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	The inactive ingredients are 130.5 mg of citric acid, anhydrous (which is added to control pH and maintain the solubility of taurolidine), and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Sterile, non-pyrogenic, (b) (4) , preservative-free, clear aqueous solution of taurolidine and heparin with a pH of 5.5-6.5	Adequate
Pharmacological/ therapeutic class	Heparin as anti-coagulant and Taurolidine as thiadiazinane antimicrobial.	Adequate.

Chemical name, structural formula, molecular weight	The chemical name of Taurolidine is (b) (4) [redacted]. The empirical formula is $C_7H_{16}N_4O_4S_2$ and the molecular weight 284.35g/mol. It has the following structural formula:  Heparin Sodium Heparin is an anticoagulant consisting of heterogeneous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans. It is composed of polymers of alternating derivatives of α-D-glucosamido (N-sulfated, O-sulfated, or N-acetylated) and O-sulfated uronic acid (α-L-iduronic acid or β-D-glucuronic acid). Heparin is derived from porcine intenstinal mucosa. The structure of heparin sodium (representative subunits) is: 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	pH - 5.5-6.5	-

1.2.4 Section 16 HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Catheter lock solution	Adequate.
Strength(s) in metric system	Contains 67.5 mg/5 mL (13.5 mg/mL) of taurolidine, and 5,000 USP Units/5 mL (1,000 USP Units/mL) of heparin	Adequate.

Available units (e.g., bottles of 100 tablets)	Carton containing (b) (4) vials	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Sterile, preservative-free, clear aqueous-based solution	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose vial	Adequate
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Defencath vials must be stored in the commercial carton, prior to the instillation in central venous catheters.	Adequate (The drug product is light sensitive if stored in the primary packaging i.e., vials only. The secondary packaging provides the protection from light. The Applicant included this statement as per the CMC recommendation communicated in the last review cycle.)
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	DEFENCATH vials must be stored at a controlled room temperature of 20°C to 25°C (68°F to 77°F). Do not freeze.	Adequate. The supporting stability data is provided in section 3.2. P.8.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	

Include information about child-resistant packaging	No	The product will be used only in the clinical settings.

1.2.3 Other Sections of Labeling

1.2.4 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	CorMedix Inc. 300 Connell Drive, Suite 4200 Berkeley Heights, NJ 07922	Adequate

Reviewer's Assessment of Package Insert: Adequate

The CMC recommendations were communicated to the Applicant in the last review cycle. CoMedrix submitted the updated Prescribing Information (PI) in the current review cycle. The updated PI is acceptable from CMC perspective.

2.0 CARTON AND CONTAINER LABELING

IMAGES OF LABEL AND LABELING RECEIVED ON December 30-2020

3.1 Container Label

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Item	Information provided in the container label(s)	Information provided in the carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	DEFENCATH (taurolidine and heparin) catheter lock solution	DEFENCATH (taurolidine and heparin) catheter lock solution
Dosage strength	Taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)	Taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)
Route of administration	For instillation in Central Venous Catheters- Not for systemic use	For instillation in Central Venous Catheters- Not for systemic use
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	As per the feedback from heparin drug substance reviewer (Parmesan Patel, Ph.D.) and OPPQ - No equivalency statement is necessary for heparin for DPs that are not intended to be used systemically. (Refer the review of section 3 of the PI for more information)	As per the feedback from heparin drug substance reviewer (Parmesan Patel, Ph.D.) and OPPQ - No equivalency statement is necessary for heparin for DPs that are not intended to be used systemically. (Refer the review of section 3 of the PI for more information)
Net contents (e.g. tablet count)	5 mL Fill	5 mL Fill
"Rx only" displayed on the principal display	Yes	Yes
NDC number	NDC 72990- (b) (4)	NDC 72990- (b) (4)
Lot number and expiration date	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	DEFENCATH vials must be stored at a controlled room temperature of 20°C to 25°C (68°F to 77°F). Do not freeze.	DEFENCATH vials must be stored at a controlled room temperature of 20°C to 25°C (68°F to 77°F). Do not freeze.
Bar code	Yes	Yes

Item	Information provided in the container label(s)	Information provided in the carton label(s)
Name of manufacturer/distributor	CorMedix Inc. 300 Connell Drive, Suite 4200 Berkeley Heights, NJ 07922	CorMedix Inc. 300 Connell Drive, Suite 4200 Berkeley Heights, NJ 07922
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Yes
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	Discard unused portion.	Discard unused portion

Assessment of Carton and Container Labeling: Adequate

DMEPA and CMC recommendations/comments for the container carton labels were communicated to the Applicant in the last review cycle. CoMedix submitted the updated container and carton labels in this review cycle. The updated carton and container labels are acceptable from CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, PhD, Branch 2, ONDP Division of New Drug Products I, OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Dorota Matecka, Ph.D., Branch 2, ONDP Division of New Drug Products I, OPQ

Shalini Anand

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Dorota Matecka

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 214520
Assessment # 2

Drug Product Name	DEFENCATH (taurolidine and heparin) catheter lock solution
Dosage Form	Solution
Strength	13.5 mg/mL and 1,000 USP Units/mL
Route of Administration	Central venous catheter lock solution
Rx/OTC Dispensed	Rx
Applicant	CorMedix Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Pre-submission	March 11, 2020	All
0051	June 1, 2020	Drug Product
0052	June 2, 2020	Microbiology
0055	June 15, 2020	Drug Substances, Drug Product, Process, Facilities, Device
0056 (complete NDA submission)	June 30, 2020	Labeling, Drug Product
0057	July 10, 2020	Drug Substance, Drug Product, Microbiology
0059	July 17, 2020	Process, Facilities
0063	August 13, 2020	EA
0067	August 26, 2020	Microbiology
0069	August 28, 2020	Device
0070	September 9, 2020	Drug Substance, Drug Product, Microbiology
0075	September 29, 2020	Facilities
0077	September 30, 2020	Drug Substance, Microbiology, Process, Facilities, EA
0082	October 9, 2020	Microbiology
0083	October 15, 2020	Drug Substance
0085	October 27, 2020	Process, Facilities
0088	October 29, 2020	Drug Substance

0090	November 10, 2020	Drug Product
0093	November 18, 2020	Process
0094	November 24, 2020	Process, Device
0095	December 4, 2020	Drug Substance, Drug Product
0099	December 16, 2020	Drug Product, Process
0100	December 16, 2020	Device
0102	December 23, 2020	Drug Product
0109*	February 5, 2021	Drug Product

**Refer to the Drug Product section of the Executive Summary regarding this amendment*

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance (Taurolidine)	Katherine Windsor	Ali Al Hakim
Drug Substance (Heparin Sodium)	Paresma Patel	Ali Al Hakim
Drug Product	Shalini Anand	Thomas Oliver
Manufacturing	Rose Xu	Vidya Pai
Microbiology	Yan Zheng	Jesse Wells
CDRH	Ramesh Panguluri	Cynthia Chang
Biopharmaceutics	Elsbeth Chikhale	N/A
Environmental Analysis	*Refer to the Drug Product Review*	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs*:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	April 17, 2019 (chemistry) May 1, 2020 (microbiology)	Paresma Patel Yan Zhang
	II			Adequate	November 20, 2020	Katherine Windsor
	III			Adequate	February 1, 2021	Shalini Anand

**Several other Type III DMFs are listed in the NDA; overall information provided for the container/closure system was found acceptable*

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	113764	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, DEFENCATH (taurolidine and heparin) catheter lock solution. Overall information provided for both drug substances (taurolidine and heparin sodium), the drug product, and information related to the microbiological quality aspects of the drug product was found acceptable. However, the status of the drug product manufacturing facility, ROVI Pharma Industrial Services S.A., was found unacceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA), and the overall recommendation of "Withhold" was entered in Panorama for this NDA on January 29, 2021. In addition, there are several issues regarding the drug product manufacturing process that will need to be addressed in the next review cycle. Therefore, this NDA is currently recommended for Complete Response (CR) by the Office of Pharmaceutical Quality (OPQ).

The following deficiency related to the drug product facility status should be included in the CR letter:

> *"During a review of records requested under Federal Food, Drug, and Cosmetic Act section 704(a)(4) provided by Rovi Pharma Industrial Services S.A. (FEI 3016688535) manufacturing facility the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved. If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.*
>
> *For more information, please see the FDA guidances related to COVID-19 (https://www.fda.gov/emergency-preparedness-and-/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders)."*

Other comments to be included in the CR letter are listed in Section D of the Executive Summary, below.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

DEFENCATH is a combination product of a thiadiazinane antimicrobial (taurolidine) and an anti-coagulant (heparin) indicated to reduce the incidence of catheter-related bloodstream infections (CRBSI) in patients with end-stage renal disease (ESRD) receiving hemodialysis through a central venous catheter. As described in the proposed labeling, this product is indicated for use in a limited and specific population of patients.

DEFENCATH is intended for use with central venous catheter (CVC) only and is not intended for systemic administration.

DEFENCATH catheter lock solution is provided as a sterile, preservative-free, clear, aqueous-based solution 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 single-dose vial. DEFENCATH is to be instilled into the catheter lumen, (in the amount of 3 mL to 5 mL depending on the volume of the catheter lumen), as a lock solution at the conclusion of each hemodialysis session. Prior to initiation of the next hemodialysis treatment, the DEFENCATH solution must be withdrawn from the catheter and discarded.

Proposed Indication(s) including Intended Patient Population	To reduce the incidence of catheter-related bloodstream infections (CRBSI) in patients with end-stage renal disease (ESRD) receiving hemodialysis through a central venous catheter. This drug is indicated for use in a limited and specific population of patients
Duration of Treatment	DEFENCATH is to be instilled into the catheter lumen as a lock solution 3 mL to 5 mL at the conclusion of each hemodialysis session. Prior to initiation of the next hemodialysis treatment, the DEFENCATH solution must be aspirated from the catheter and discarded.
Maximum Daily Dose	N/A This product is intended for central venous catheter (CVC) lumen instillation. It is not intended for systemic administration.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance (Heparin Sodium): Adequate

Refer to the OPQ Review # 1 dated December 21, 2020 (in DARRTS).

Drug Substance (Taurolidine): Adequate

Refer to the OPQ Review # 1 dated December 21, 2020 (in DARRTS).

Drug Product: Adequate

Refer to the OPQ Review # 1 dated December 21, 2020 (in DARRTS), which found most of the drug product information adequate with several outstanding issues pending. These issues have been addressed adequately by the Applicant.

The DMF information for the [redacted] (b) (4) to be used in the commercial drug product container closure system has been provided to the NDA. This DMF was reviewed by Dr. Shalini Anand in support of this NDA and was found to be adequate.

The [redacted] (b) (4), which is an issue related to the in-process controls for the [redacted] (b) (4) in the drug product manufacturing process, has been addressed in detail in the OPMA/Manufacturing Integrated Assessment, below.

In-use stability data, which were provided in the initial NDA for two types of catheters, indicated a loss of the DEFENCATH extractable volume from the catheters and an increase in the heparin and taurolidine assay results during the tested in-use period. To assess the risk for taurolidine precipitation in the catheters, additional information regarding the taurolidine solubility in the drug product solution was requested by the OPQ. The data provided in response to this request, demonstrate that taurolidine would remain in solution at the higher concentration during the catheter in-use period.

The photostability data for the drug product in the proposed commercial container closure system was submitted in the amendment dated December 23, 2020. The drug product packaged in the primary container closure (vials) failed to meet the regulatory specification; however, the drug product packaged in commercial packaging configuration (vials plus carton) met the proposed regulatory specification. Therefore, the Applicant was recommended to include a statement in the labeling that the vials should be stored in the original secondary packaging (box) to mitigate the risk of exposure to light.

The Applicant also updated the proposed storage conditions for the finished drug product in section 3.2.P.8.1 and in the labeling, per OPQ recommendations. The overall stability information provided in the initial NDA indicate that the proposed drug product formulation in the proposed container closure system is stable through 24 months of storage at room temperature. It should be noted that the Applicant has recently submitted an amendment (dated February 5, 2021), which includes previously submitted (and reviewed, as described above) photostability study, which has been now added to section 3.2.P.8 of the NDA. In addition, the amendment dated February 5, 2021 also includes a 30-month time point stability update for the three drug product registration batches. Although the updated stability results appear adequate, the detailed review of this stability update will be captured in the next OPQ Review (Drug Product Chapter) in the next review cycle.

The overall information submitted for the drug product in the initial NDA and subsequent amendments was found adequate (*refer to the Drug Product Review for details*).

Labeling: Choose an item.

The review of the CMC sections of the labeling, including the container/carton labels, has been completed and recommendations conveyed to the Applicant, along with the comments from other disciplines. The labeling negotiations and review are currently pending.

Manufacturing: Inadequate

Refer to the OPQ Review # 1 dated December 21, 2020 (in DARRTS), which included an interim assessment of the process and facilities.

Most of the comments and information requests regarding the drug product manufacturing process conveyed to the Applicant during the NDA review have been addressed adequately. However, several issues, including the issue of the in-process (b) (4), remain outstanding. The (b) (4) was set without supporting study data. Therefore, the OPQ review team requested data to demonstrate that the proposed extractable volume of 5.0 mL can be extracted from the vial (b) (4) or, alternatively, a revision to the in-process (b) (4) was recommended. However, the requested information was not provided, and the Applicant proposed to retain the originally proposed in-process (b) (4), which is not adequate. In addition, the (b) (4) has not been included as part of the in-process controls for the (b) (4) in the drug product manufacturing process.

Most of the facilities listed in the NDA have been found adequate. However, the drug product manufacturer, Rovi Pharma Industrial Services

S.A., has been found unacceptable. This facility, which has never been inspected by the FDA, was inspected by [redacted] (b) (4) ; however, the inspection did not cover the quality system items such as PQR, complaints, rework, returns, and stability. Due to travel restrictions related to the COVID-19 pandemic, a 704(a)(4) based review was conducted for this facility and a number of deficiencies were identified. Therefore, the overall recommendation of "Withhold" was entered in Panorama for this NDA on January 29, 2021.

The comments regarding the drug product facility and manufacturing process will be included in the CR letter for this NDA. For further details refer to the *Manufacturing Integrated Assessment, below*.

Biopharmaceutics: Adequate

The drug product is a clear solution; therefore, there is no need for drug release or dissolution testing. In addition, the proposed commercial drug product has the same formulation as the drug product used in the pivotal clinical trial. Therefore, there is no need for bridging between the clinical drug product and the commercial to-be-marketed formulation. A biowaiver is not requested, nor required.
For additional details refer to the *Biopharmaceutics Review, below*.

Microbiology (if applicable): Adequate

Refer to the OPQ Review # 1 dated December 21, 2020 (in DARRTS).

Device/catheters: Choose an item.

The assessment of the information provided in the NDA regarding the catheter integrity issues has been transferred to another CDRH team (OPEQ/DHT3). Their assessment has been included in the unireview of this NDA (NDA Multidisciplinary Review and Evaluation), which is currently pending (*and will be entered in DARRTS when finalized*).

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**

		H, M, or L		Acceptable or Not Acceptable	
Assay, stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	Adequate long-term stability data for three registration batches were provided	Acceptable	
Volume in Container/ Extractable Volume	Process parameters Scale/equipment Site	Low		Not Acceptable	*Data were not provided to justify the proposed fill range*
pH	Formulation Raw materials Process parameters Scale/equipment	Low	Adequate (b) (4) controls established	Acceptable	
Particulate Matter	Formulation Raw materials Process parameters Scale/equipment Site	Medium	Adequate procedure and data provided; test included in drug product specification	Acceptable	
Bacterial endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	High	Adequate microbiological controls	Acceptable	
Sterility	Formulation Raw materials Process parameters Scale/equipment Site	High	Adequate microbiological controls	Acceptable	
Extractable /leachable	Formulation Raw materials	Medium	The packaging includes a glass vial and a rubber stopper. The results of the one-time E&L study found acceptable.	Acceptable	

Facilities	Site	*N/A*		Not Acceptable	*Deficiencies identified based on the 704 review*

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

N/A

5. Manufacturing Deficiencies

The following deficiencies and comments are listed in the OPMA/Manufacturing Integrated Assessment (below):

Facility:

1. During a review of records requested under Federal Food, Drug, and Cosmetic Act section 704(a)(4) provided by Rovi Pharma Industrial Services S.A. (FEI 3016688535) manufacturing facility the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved. If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID-19 (https://www.fda.gov/emergency-preparedness-and-/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders).

Process:

(b) (4)

3. We acknowledge you updated Section 3.2.P.3.4 with the revised IPC and (b) (4)*. However, we could not locate the* (b) (4) *. Please include the* (b) (4) *as part of the IPC for* (b) (4) *with acceptance criteria. Submit the testing method. Also, update Section 3.2.P.3.4 and proposed MBR, accordingly.*

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

N/A

Dorota Matecka

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

Note- The CMC recommendations captured in this review document were communicated to the Applicant as information requests on 02/05/2021. The response from the Applicant has not been received yet (02/08/2021). The pending CMC labelling issues will be addressed in the next review cycle.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	DEFENCATH (taurolidine and heparin) catheter lock solution	Adequate.
Established name(s)	Taurolidine and heparin catheter lock solution	Adequate.
Route(s) of administration	For instillation in central venous catheter	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	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)	Adequate.
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	(b) (4)	As per the feedback from OPPQ, the Applicant will be recommended to revise the package type term to "Single-Dose". Refer the reviewer's assessment section below for additional details.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

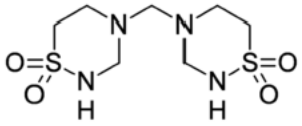
Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	The drug product will not be diluted/ reconstituted prior to the administration.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Catheter lock solution	Adequate.
Strength(s) in metric system	Taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	The active ingredients are heparin sodium and Taurolidine. However, as per the feedback from heparin drug substance reviewer (Parmesan Patel, Ph.D.) and OPPQ - the equivalency statement is not necessary for heparin because the strength is determined by a bioassay. So, the actual quantity can vary from batch to batch. There is no equivalency statement on Heparin sodium containing DPs that are not intended to be used systemically (email dated Oct. 15, 2020 and Dec. 01, 2020).
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Sterile, preservative-free, clear, aqueous-based solution	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	(b) (4)	As captured in Highlights of Prescribing Information, the Applicant will be asked to revise the package type term to "Single-Dose", in all DP labelling sections.

1.2.3 Section 11 Description

Item	Information Provided in the NDA	Assessor's Comments
Proprietary and established name(s)	DEFENCATH (taurolidine and heparin) catheter lock solution	Adequate
Dosage form(s) and route(s) of administration	Catheter lock solution	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	As per the feedback from heparin drug substance reviewer (Parmesan Patel, Ph.D.) and OPPQ - No equivalency statement is necessary for heparin for DPs that are not intended to be used systemically. (Refer the review of section 3 above for more information)
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Inactive ingredients: Citric acid, anhydrous, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	The inactive ingredients are 130.5 mg of citric acid, anhydrous (which is added to control pH and maintain the solubility of taurolidine), and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Sterile, non-pyrogenic, (b) (4) , preservative-free, clear aqueous solution of taurolidine and heparin with a pH of 5.5-6.5	Adequate
Pharmacological/ therapeutic class	Heparin as anti-coagulant and Taurolidine as thiadiazinane antimicrobial.	Adequate.

Chemical name, structural formula, molecular weight	The chemical name of Taurolidine is (b) (4) [redacted]. The empirical formula is $C_7H_{16}N_4O_4S_2$ and the molecular weight 284.35g/mol. It has the following structural formula:  Heparin- The Applicant was asked to add information about heparin in Description section (Information request).	The Applicant is asked to add information about heparin in Description section (Information request).
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	pH - 5.5-6.5	-

1.2.4 Section 16 HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Catheter lock solution	Adequate.
Strength(s) in metric system	Contains 67.5 mg/5 mL (13.5 mg/mL) of taurolidine, and 5,000 USP Units/5 mL (1,000 USP Units/mL) of heparin	Adequate.
Available units (e.g., bottles of 100 tablets)	Carton containing (b) (4) vials	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Sterile, preservative-free, clear aqueous-based solution	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	(b) (4)	As captured in Highlights of Prescribing Information, the Applicant will be asked to revise the package type term to “Single-Dose”.
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	None	The Applicant is recommended to include a statement that ‘Defencath vials must be stored in the commercial carton, prior to the instillation in central venous catheters’ (The details are captured in reviewer’s assessment section below.)
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	DEFENCATH vials must be stored at a controlled room temperature of 20°C to 25°C (68°F to 77°F). Do not freeze.	Adequate. The supporting stability data is provided in section 3.2. P.8.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	No	The product will be used only in the clinical settings.

1.2.3 Other Sections of Labeling

1.2.4 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	CorMedix Inc. 300 Connell Drive, Suite 4200 Berkeley Heights, NJ 07922	Adequate.

Reviewer's Assessment of Package Insert: Ina*dequate*

1. ***Package- type term-*** In the labelling comments issued on 12/14/2020, the Applicant was asked to revise the package type term to 'single dose' (describe a container designed for use with a single patient as a single injection/ infusion, i.e., instillation), to be consistent with the injectable product's package-type guidance (https://www.fda.gov/media/117883/download, as per the feedback from OPPQ, DMEPA and clinical team.

However, in the IR response (dated 12/30/2020), the Applicant justified that the typical hemodialysis CVC (central venous catheter) consists of two lumens (arterial/venous), which must be separately filled with catheter lock solution in accordance with current clinical practice guidelines. (b) (4)

The package-type term was further discussed with OPPQ, and as per the feedback (email dated 1/15/2021, from Jibril Abdus-Samad, Ph.D.), although the recommended dose is administered into two separate lumens of central venous catheter, this is a one treatment dose. Furthermore, the labeling does not indicate that 'the health care professionals should administer the recommended dose in each catheter lumen, store the remaining portion under a specific temperature range, and then reuse the same vial to administer to the patient at the next recommended dose interval (i.e. next dialysis treatment)'.Instead, section 2 (dosage and administration section) of the PI states that 'Discard any unused portion of DEFENCATH remaining in the vial.' So, the applicant will be asked to revise the package-type term to single-dose' throughout all the labels and labeling. The following IR was issued-

We acknowledge your rationale proposing the appropriate package type as "(b) (4) " since the Defencath vial will be used for the same patient multiple times. Your response notes that the Health Care Provider (HCP) will fill and lock each lumen (arterial and venous). Please note that although the recommended dose is administered into two separate lumens, we consider this as one treatment dose. The labeling does not indicate that the HCP should administer the recommended dose in each catheter lumen, store the remaining portion under a specific temperature range, and then

reuse the same vial to administer to the patient at the next recommended dose interval (i.e. next dialysis treatment). Rather the labeling states to, withdraw the dose, and then discard any unused portion of DEFENCATH remaining in the vial. These instructions support labeling the product as a single-dose vial. Therefore, we recommend that the package term should be revised to single-dose throughout all the labels and labeling.

2. ***Heparin Information (Section 11, Description Section of the PI)-*** The Applicant was previously asked to include the heparin sodium drug substance related information in section 11. But the revised PI received on 12/30/2020, didn't include the relevant information. So, the similar comment was issued again to update the description section.

3. ***Discard statement (Section 16- How supplied/Storage and Handling) –*** The Applicant proposed the following statement in section 16- '(b) (4) '.

   Per the internal discussion with OND team, since heparin is not a (b) (4), the Applicant was asked to remove the following text - '(b) (4) .

   In the revised PI received on 12/23/2020, the Applicant proposed to retain this statement with the justification that (b) (4) .

   (b) (4) As per the feedback from OPPQ, health care professionals (b) (4) after administering the drug product. This is not a unique practice reserved for the proposed product. Therefore, this statement should not appear in the proposed labeling. So, the Applicant was asked to revise the (b) (4) statement in section 16.

4. The drug product packaged in the primary container closure system (i.e. vials) failed to meet the (b) (4) and (b) (4) acceptance criteria, for the photostability study (quality submission dated 12/23/2020, section 3.2.P.8). However, drug product packaged in the intended commercial package (i.e. vial + carton met all the regulatory specifications. So, the Applicant was recommended to include the following statement in section 16 of the PI and also on the carton label, i.e., 'Defencath

vials must be stored in the commercial carton, prior to the instillation in central venous catheters'

2.0 CARTON AND CONTAINER LABELING

IMAGES OF LABEL AND LABELING RECEIVED ON December 30-2020

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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Item	Information provided in the container label(s)	Information provided in the carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	DEFENCATH (taurolidine and heparin) catheter lock solution	DEFENCATH (taurolidine and heparin) catheter lock solution
Dosage strength	Taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)	Taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)
Route of administration	For instillation in Central Venous Catheters- Not for systemic use	For instillation in Central Venous Catheters- Not for systemic use
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	As per the feedback from heparin drug substance reviewer (Parmesan Patel, Ph.D.) and OPPQ - No equivalency statement is necessary for heparin for DPs that are not intended to be used systemically. (Refer the review of section 3 of the PI for more information)	As per the feedback from heparin drug substance reviewer (Parmesan Patel, Ph.D.) and OPPQ - No equivalency statement is necessary for heparin for DPs that are not intended to be used systemically. (Refer the review of section 3 of the PI for more information)
Net contents (e.g. tablet count)	DMEPA issued a comment to include the net content on the container label	DMEPA issued a comment to include the net content on the container label
"Rx only" displayed on the principal display	Yes	Yes
NDC number	NDC xxxxx-xxx-xx	NDC xxxxx-xxx-xx
Lot number and expiration date	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	DEFENCATH vials must be stored at a controlled room temperature of 20°C to 25°C (68°F to 77°F). Do not freeze.	DEFENCATH vials must be stored at a controlled room temperature of 20°C to 25°C (68°F to 77°F). Do not freeze.
Bar code	Yes	Yes

Item	Information provided in the container label(s)	Information provided in the carton label(s)
Name of manufacturer/distributor	CorMedix Inc. 300 Connell Drive, Suite 4200 Berkeley Heights, NJ 07922	CorMedix Inc. 300 Connell Drive, Suite 4200 Berkeley Heights, NJ 07922
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Yes
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	The Applicant has been asked to include a discard statement on the container label - Discard the unused portion.	The Applicant has been asked to include a discard statement on the carton label

Assessment of Carton and Container Labeling:

Package type term- As discussed in the review of PI, the applicant will be asked to update the package type term to single-dose in all the drug product labelling sections.

Inactive ingredients – To be in-line with the PI, the Applicant will be asked to update the inactive ingredient section of the container and carton labels to read: Each vial contains citric acid, anhydrous, 130.5 mg (as pH adjuster and solubilizer), and may contain hydrochloric acid and/or sodium hydroxide (for pH adjustment).

The following comments (from DMEPA and OPQ) were sent on 02/05/2021-

1. 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.
2. 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.
3. Per the information provided in section 3.2.P.1, the proposed Defencath catheter lock solution contains citric acid, anhydrous (130.5 mg/5 mL) and it may also contain sodium hydroxide and/or hydrochloric acid for pH adjustment. Therefore, consistent with Section 11 of the prescribing information (PI), we recommend you update the inactive ingredient section of the container and carton labels to read: Each vial

contains citric acid, anhydrous, 130.5 mg (as pH adjuster and solubilizer), and may contain hydrochloric acid and/or sodium hydroxide (for pH adjustment).

4. Refer to the Agency's comment regarding the package-type term in the PI. Although, the recommended dose of Defencath catheter lock solution is administered into two separate lumens of the catheter, the Agency considers this as one treatment dose. Update the package type term to 'single-dose' on the container and carton labels. Also, include a discard statement on the container and carton labels (i.e., revise the statement [redacted] (b) (4)" to read "Single-Dose Vial – Discard Unused Portion").
5. Refer to the Agency's comment regarding storage in the commercial carton in the PI. We recommend you include the following statement on the carton label, i.e., 'Defencath vials must be stored in the commercial carton, prior to the instillation in central venous catheters'

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, PhD, Branch 1; ONDP Division of New Drug Products I; OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Thomas Oliver, PhD, Division Director; ONDP Division of New Drug Products I; OPQ

Shalini Anand

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Thomas Oliver

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CHAPTER VI: BIOPHARMACEUTICS

NDA: 214520-ORIG-1 [505(b)(1)]

Drug Product Name / Strength: Neutrolin Catheter Lock Solution (CLS) 5 mL per vial/ taurolidine 13.5 mg/mL and heparin sodium 1000 USP U/mL

Route of Administration: For Catheter Insillation use only (between hemodialysis; external to the body; not for systemic administration)

Applicant Name: CorMedix Inc.

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

Background:

Taurolidine-containing catheter lock solutions have been marketed in the European Union for more than a decade. Some of these catheter lock solutions also contain heparin and citrate. The proposed Neutrolin® Catheter Lock Solution (CLS), 5.0 mL/vial contains two drug substances: taurolidine (antimicrobial drug) and heparin sodium (anti-coagulant); and the following excipients: citric acid anhydrous (to increase the solubility of taurolidine), sodium hydroxide (for pH adjustment), and water for injection.

Table 1: Qualitative composition of the proposed drug product:

Ingredient	Concentration	Quantity per mL	Function
Taurolidine	1.35% wt/vol	13.5 mg	Antimicrobial
Heparin Sodium USP	1000 U/mL	1000 units	Anticoagulant
Anhydrous Citric Acid	2.61% wt/vol	26.1 mg	Buffer
Sodium Hydroxide (b) (4)	Not Applicable	QS to pH (b) (4)	pH Adjustment, (b) (4)
Water for Injection	Not Applicable	(b) (4)	

The formulation of Neutrolin has not changed since 2009.

Dissolution/drug release testing:

Both drug substances (taurolidine and heparin sodium) are fully dissolved in the drug product. The drug product is a clear solution. Therefore, a quality control in vitro drug release method is not applicable for the proposed dosage form, hence, there is no need for drug release or dissolution testing.

Bridging:

The key clinical study supporting this NDA is a single Phase 3 clinical trial: 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"

The proposed commercial drug product has the same formulation as the drug product used in the clinical trial (LOCK-IT-100). Therefore, there is no need for bridging between the clinical drug product and the commercial to-be-marketed formulation. A biowaiver is not requested, nor required.

Recommendation:

From a Biopharmaceutics perspective, NDA 214520 for Neutrolin Catheter Lock Solution (CLS) 5 mL per vial/ taurolidine 13.5 mg/mL and heparin sodium 1000 IU/mL is recommended for **APPROVAL**.

Biopharmaceutics Team Lead Name and Date: Elsbeth Chikhale, Ph.D., 01/22/2021

Elsbeth Chikhale

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/s/

DOROTA M MATECKA
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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 214520
Assessment # 1

Drug Product Name	DEFENCATH (taurolidine and heparin) catheter lock solution
Dosage Form	Solution
Strength	13.5 mg/mL and 1,000 USP Units/mL
Route of Administration	Central venous catheter lock solution
Rx/OTC Dispensed	Rx
Applicant	CorMedix Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Pre-submission	March 11, 2020	All
0051	June 1, 2020	Drug Product
0052	June 2, 2020	Microbiology
0055	June 15, 2020	Drug Substances, Drug Product, Process, Facilities, CDRH
0056 (complete NDA submission)	June 30, 2020	Labeling, Drug Product
0057	July 10, 2020	Drug Substance, Drug Product, Microbiology
0059	July 17, 2020	Process, Facilities
0063	August 13, 2020	EA
0067	August 26, 2020	Microbiology
0069	August 28, 2020	CDRH
0070	September 9, 2020	Drug Substance, Drug Product, Microbiology
0075	September 29, 2020	Facilities
0077	September 30, 2020	Drug Substance, Microbiology, Process, Facilities, EA
0082	October 9, 2020	Microbiology
0083	October 15, 2020	Drug Substance
0085	October 27, 2020	Process, Facilities
0088	October 29, 2020	Drug Substance

0090	November 10, 2020	Drug Product
0093	November 18, 2020	Process
0094	November 24, 2020	Drug Substance, Drug Product
0094	December 4, 2020	Process

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance (Taurolidine)	Katherine Windsor	Ali Al Hakim
Drug Substance (Heparin Sodium)	Paresma Patel	Ali Al Hakim
Drug Product	Shalini Anand	Thomas Oliver
Manufacturing	Rose Xu	Vidya Pai
Microbiology	Yan Zheng	Jesse Wells
CDRH	Ramesh Panguluri	Cynthia Chang
Biopharmaceutics	Elsbeth Chikhale	N/A
Environmental Analysis	*Refer to the Drug Product Review*	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

FDA U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	April 17, 2019 (chemistry) May 1, 2020 (microbiology)	Paresma Patel Yan Zhang
	II			Adequate	November 20, 2020	Katherine Windsor
	III					
	III					
	III					
	III					

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	113764	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	*Pending*			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The chemistry, manufacturing and controls (CMC) information provided for both drug substances (taurolidine and heparin sodium) and information related to the microbiological quality of the proposed product quality was found acceptable. However, there are several other drug product quality related issues that have not been yet resolved, which includes issues related to the compatibility of the proposed drug product solution with catheters and catheter integrity (under review by CDRH). Also, several information requests and issues regarding the drug product and manufacturing process, and the product labeling are pending. In addition, the facility assessment by the Office of Pharmaceutical Manufacturing Assessment (OPMA) is currently undergoing, and the overall facility recommendation has not been yet made for this NDA in Panorama.

Therefore, this NDA is currently recommended for Complete Response from the Product Quality perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

DEFENCATH is a combination product of a thiadiazinane antimicrobial (taurolidine) and an anti-coagulant (heparin) indicated to reduce the incidence of catheter-related bloodstream infections (CRBSI) in patients with end-stage renal disease (ESRD) receiving hemodialysis through a central venous catheter. As described in the proposed labeling, this product is indicated for use in a limited and specific population of patients.

DEFENCATH is intended for use with central venous catheter (CVC) only and is not intended for systemic administration.

DEFENCATH catheter lock solution is provided as a sterile, preservative-free, clear, aqueous-based solution 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 single-dose vial. DEFENCATH is to be instilled into the catheter lumen, (in the amount of 3 mL to 5 mL depending on the volume of the catheter lumen), as a lock solution at the conclusion of each hemodialysis session. Prior to initiation of the next hemodialysis treatment, the DEFENCATH solution must be withdrawn from the catheter and discarded.

Proposed Indication(s) including Intended Patient Population	To reduce the incidence of catheter-related bloodstream infections (CRBSI) in patients with end-stage renal disease (ESRD) receiving hemodialysis through a central venous catheter. This drug is indicated for use in a limited and specific population of patients
Duration of Treatment	DEFENCATH is to be instilled into the catheter lumen as a lock solution 3 mL to 5 mL at the conclusion of each hemodialysis session. Prior to initiation of the next hemodialysis treatment, the DEFENCATH solution must be aspirated from the catheter and discarded.
Maximum Daily Dose	N/A This product is intended for central venous catheter (CVC) lumen instillation. It is not intended for systemic administration.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance (Heparin Sodium): Adequate

Heparin sodium, serving as an anti-coagulant in the proposed drug product (catheter lock solution) formulation, is a heterogenous polymer of glycosaminoglycans composed of alternating derivatives of α-D-glucosamido (N-sulfated, O-sulfated or Nacetylated) and O-sulfated uronic acid (α-L-iduronic acid or β-D-glucuronic acid) derived from porcine intestinal mucosa.

The CMC information for heparin sodium drug substance to be used in the manufacture of the commercial drug product is provided by reference to DMF (b) (4) held by (b) (4). This DMF was reviewed in support of this NDA and was found adequate. In addition, data provided in the NDA to demonstrate that heparin sodium drug substance used in the pivotal clinical studies (sourced from (b) (4) and (b) (4)) is comparable to the proposed commercial source ((b) (4)) was also found adequate. The Applicant initially intended to use all three sources of heparin sodium as the commercial suppliers of this drug substance for their proposed drug product. However, due to the lack of complete sets of data for the drug product batches manufactured using heparin sodium from (b) (4) and (b) (4), these two manufacturers were withdrawn from the NDA (via amendment dated September 28, 2020) (b) (4) .

The overall information submitted in the NDA for the heparin sodium drug substance was found adequate (*refer to the Drug Substance/Heparin Sodium Review for details*).

Drug Substance (Taurolidine): Adequate

Taurolidine is an antimicrobial agent derived from the naturally occurring amino acid taurine, used as an antimicrobial component in the proposed drug product, a catheter lock solution. The drug substance may be isolated as one of two crystalline polymorphs, [redacted] (b) (4)

The CMC information for taurolidine drug substance is provided by reference to DMF [redacted] (b) (4) held by Cormedix. In addition, since the NDA Applicant is also the DMF holder, the quality information provided in the taurolidine DMF was also included in Module 3 of this NDA. The CMC information submitted in the DMF for this drug substance, including the proposed impurity controls, was found adequate. Stability data support the proposed retest period of [redacted] (b) (4) months for taurolidine drug substance stored at [redacted] (b) (4) in the proposed container closure system.

The overall information submitted in the NDA for the taurolidine drug substance was found adequate (*refer to the Drug Substance/Taurolidine Review for details*).

Drug Product: Inadequate

The proposed drug product is a sterile, preservative-free, clear, aqueous-based solution 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 single-dose vial solution to be used as a catheter lock solution. The formulation also contains citric acid (to increase the solubility of taurolidine), sodium hydroxide and/or hydrochloric acid (for pH adjustment), and water for injection. The manufacturing process includes [redacted] (b) (4). The primary container closure system consists of a 6-mL USP type [redacted] (b) (4) clear glass vial with a latex-free, [redacted] (b) (4) stopper, and aluminum/plastic flip-top13-mm cap. The drug product is filled in a 6-mL glass vial, with 5.0-mL fill volume. The extractable and leachable studies to support the proposed container closure system have been provided in the NDA and found adequate. The proposed in the NDA drug product specification was also found adequate. The stability data provided in the NDA indicate that the proposed drug product formulation is stable through 24 months of storage at room temperature. However, a response to the FDA request for photostability data is currently pending.

In-use stability data for two types of catheters was also provided in the NDA as part of the compatibility studies of the drug product with catheters. These data demonstrate a significant loss of the DEFENCATH extractable volume from the catheters and increase in the heparin and taurolidine assay results during the tested in-use period (up to 7 days). Additional information regarding these results was requested from the Applicant and is currently under review. In addition, other information submitted in the NDA in support of the compatibility of the proposed drug product with catheters is currently under review by CDRH.

The following issues/information requests related to the quality of the proposed drug product are pending and will be addressed in the OPQ Assessment # 2:

- In-catheter drug product stability
- Photostability study
- In-process (b) (4) for vials (*an issue under discussion with the OPMA reviewer*)
- Formulation composition of the vial stopper
- Drug product storage conditions statement

Labeling:

Review is pending.

Manufacturing:

The review of process and facilities is pending. Numerous comments and information requests regarding the drug product manufacturing process were conveyed to the Applicant during the NDA review and several of those issues are still pending.

A number of manufacturing facilities are listed in the NDA. Most of the facilities have been found adequate. However, the drug product manufacturer, Rovi Pharma Industrial Services S.A., has never been inspected by the FDA. This site was inspected by (b) (4) ; however, the inspection did not cover the quality system items such as PQR, complaints, rework, returns, and stability. Due to travel restrictions related to the COVID pandemic, a 704(a)(4) review of this facility is being conducted and is currently pending.

Due to the currently pending 704(a)(4) review, only an interim assessment of the process and facilities is included in the current OPQ Assessment # 1. The finalized process and facility assessment (Manufacturing Assessment # 2) will be included in the OPQ Assessment # 2.

Biopharmaceutics: Adequate

N/A

Microbiology (if applicable): Adequate

The drug product manufacturing process includes [redacted] (b) (4) [redacted]. No deficiencies for the proposed drug product were identified from the product quality microbiology perspective. During the NDA review several comments were forwarded to the Applicant and additional information was provided in areas such as container closure integrity testing, antimicrobial effectiveness testing for the drug product solution in catheters, environmental monitoring, [redacted] (b) (4), vial depyrogenation, sterilization validation/requalification study, [redacted] (b) (4) [redacted], and proposed microbiological controls in the drug product specification. The overall product quality microbiology information provided for the drug product in the NDA and the subsequent amendment was found acceptable adequate (*refer to the Microbiology Review for details*).

CDRH:

The review conducted by the CDRH/OPEQ/DHT4 reviewers (covering mainly the drug product in-use catheter studies), is attached to this review. Additional CDRH assessment (conducted by OPEQ/DHT3) of the catheter integrity information is currently pending and will be included in the OPQ Assessment # 2.

C. Risk Assessment (*due to pending review of several Product Quality issues, Risk Assessment will be addressed in the OPQ Assessment # 2***)**

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

The assessment of facilities, including a 704(a)(4) review of the drug product facility, is pending. In addition, several drug product issues, including compatibility of the proposed drug product with catheters, and issues related to the drug product and manufacturing process have been identified and are currently under review.

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

Several issues regarding the quality of the drug product, including its in-catheter stability, are pending.

4. Labeling Deficiencies

Review is pending.

5. Manufacturing Deficiencies

Review of the drug product facility is pending. In additional several information requests regarding the manufacturing process are also pending.

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

CDRH consult review of the compatibility of the drug product with catheters is pending.

Application Technical Lead Name and Date:

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214520
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Neutrolin, 13.5 mg/mL
Route of Administration	Catheter Lock Solution
Applicant Name	CorMedix Inc
Therapeutic Classification/ OND Division	CDER/OND/OID/DAI
Manufacturing Site	ROVI Contract Manufacturing, S.L. Paseo de Europa No. 50, San Sebastian de los Reyes, Madrid 28703, Spain
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original Submission	03/11/2020
Response to IR	06/02/2020
Amendment	06/30/2020
Response to IR	07/10/2020
Amendment	08/26/2020
Amendment	08/28/2020
Response to IR	09/09/2020
Response to IR	09/30/2020
Response to IR	10/09/2020

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is a rolling submission. Submission dated 06/02/2020 is provided in response to the Agency's information request dated 05/08/2020. Submission dated 07/10/2020 is provided in response to the Agency's information request dated 06/30/2020. Amendment 06/30/2020 contains labeling information. Amendment 08/26/2020 and 08/28/2020 contains results and final report for AET study performed using product incubated in the catheter. Submission dated 09/09/2020 is provided in response to the Agency's information request dated 09/02/2020. Submission dated 09/30/2020

is provided in response to the Agency's information request dated 09/21/2020. Submission dated 10/09/2020 is provided in response to the Agency's information request dated 10/06/2020.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None.

Supporting Documents:
(b) (4) requalification study performed in Oct 2018 for (b) (4) stopper family was reviewed and found adequate in D(b) (4)M12R01 on 03/12/2019.
The (b) (4) studies for heparin from (b) (4) were reviewed and found adequate in D(b) (4) _2007_05_10_A1 dated 01/27/2011.
The (b) (4) studies for heparin from (b) (4) were reviewed and found adequate in DMF (b) (4)R1 dated 03/27/2014.
The (b) (4) studies for heparin from (b) (4) were reviewed and found adequate in D(b) (4)M01R01 dated 04/30/2020.

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Product description:

The subject drug product is a sterile, single-(b) (4), aqueous Catheter Lock Solution (CLS). It is not intended for direct injection into the body, but rather in the lumen reservoir of the central venous catheters between hemodialysis sessions to

prevent catheter-related bloodstream infections. It is packaged as 5.0 mL fill in 6 mL glass vials with 13 mm stoppers and aluminum caps.

Composition:

Table 3.2.P.1-1. Components of Neutrolin

Component	Function	Quality Reference	Quantitative Composition (per mL)
Taurolidine	Antimicrobial	In-house	13.5 mg
Heparin sodium	Anticoagulant	USP	1000 IU
Citric acid, anhydrous	pH adjuster/solubilizer	USP/Ph Eur	26.1 mg
Sodium hydroxide (b) (4)	pH adjuster	USP-NF/Ph Eur	*qs*
Hydrochloric acid (b) (4)	pH adjuster	USP-NF	*qs*
Water for injection	(b) (4)	USP/Ph Eur	(b) (4)
(b) (4)			

IU = international units; NF = National Formulary; Ph Eur = European Pharmacopoeia; *qs* = quantity sufficient; USP = United States Pharmacopeia.

(Table reproduced from the submission, 3.2.P.1, pg. 1)

Container closure system:

Component	Description	Item code	Manufacturer
Vial	Injection vial 6-mL USP Type (b) (4) glass 13 mm	(b) (4)	
Stopper	(b) (4) Grey 13 mm		
Cap	Cap, aluminum seal 13 mm, flip-off		

Assessment: Adequate

The product description is acceptable.

(b) (4)

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Jesse Wells

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Yan Zheng

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Date: 10/14/2020 10:28:19AM
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Submission Number: NDA 21450 (IND 113764)
Sponsor: CorMedix, Inc
Trade Name: Neutrolin Catheter Lock Solution (now changed to "Defencath")
Consult Type: Inter Center consult
Requestor: Shalini Anand, PhD, Chemist, CDER/OPQ/ONDP/DNDPI/NDPB2
Consultant: Kapil Panguluri, PhD, Microbiologist, CDRH/OPEQ/DHT4/DHT4B/THT4B2
Gatekeeper: Elizabeth Claverie, MS, Assistant Director, CDRH/OPEQ/DHT4/DHT4B/THT4B2

Scope: CDRH was asked by CDER to provide In-Use solvent loss from the catheters. Following is the CDRH evaluation and recommendation.

Device Description and Intended Use:

Defencath™ (formerly referred to as Neutrolin®) is a catheter lock solution being developed by CorMedix for the prevention of catheter-related blood stream infections in hemodialysis patients using a central venous catheter. The product consists of a sterile aqueous solution contained in a USP type (b) (4) glass vial equipped with a (b) (4) stopper and aluminum cap. Each mL of Neutrolin contains 13.5 mg of the antimicrobial Taurolidine and 1000 units of Heparin, an anticoagulant. Neutrolin contains 26.1 mg of Citric acid to maintain a buffered pH between 5.5 and 6.5. Defencath is intended to be instilled inside the lumen of intravenous catheters between hemodialysis sessions and to be removed from the catheter before commencing dialysis.

Stability and Solvent loss Testing:

The typical in-catheter residence time is 3 days and the study was designed to assess the stability of the Defencath after 1 hour, 72 hours (3 days), and 168 hours (7 days) of residence inside two commercially available hemodialysis catheter: MedComp and Merit. The MedComp catheters are made of silicone and Merit Catheters made of polyurethane. The firm performed four tests as part of the stability analysis: pH, Taurolidine assay, Heparin anti-Factor IIa, and Antimicrobial effectiveness. These tests were performed on solutions of Defencath combined from catheters incubated in a stability chamber at 37ºC and 65-75% relative humidity. Since Heparin solutions are the current standard of care catheter lock, a Heparin 1000 IU/mL control batch was also tested in order to compare changes in the activity of Heparin against Defencath.

The firm states that after the catheters were filled and allowed to dwell for 1 hour to 168 hours (7 days) there was an increased analyte concentration due to absorption of the solvent by the catheters. The reduction of volume was more prominent in the MedCom (silicone) catheter (initial lumen fill volume is 2.6 mL and the extracted volume after 168 hours (7 days) incubation was 0.8 mL) compared to Merit (polyurethane) catheter (initial lumen fill volume was 3.8 mL and reduced to 1.9 mL after 168 hours (7 days incubation). The following Table also summarizes the volume loss in both MedComp and Merit Catheters compared to Heparin control. The firm states that the inspection of catheters showed no evidence of leakage and the reduction of the extractable volume and increase in concentration of the active ingredients, could be attributed to water absorption from the solution into the catheter.

MedComp Catheters

Catheter Initial Fill Volume (mL)	Extracted Volume (mL) In-Catheter Stability Incubation Interval (days)		
	1	72	168
2.6	(S1) 2.1 (S2) 2.1 **AVG 2.1**	S1) 1.5 (S2) 1.5 **AVG 1.5**	S1) 0.7 (S2) 0.9 **AVG 0.8**

Merit Catheters

Catheter Initial Fill Volume (mL)	Extracted Volume (mL) In-Catheter Stability Incubation Interval (days)		
	1	72	168
2.6	(S1) 2.1 (S2) 2.1 **AVG 2.1**	S1) 1.5 (S2) 1.5 **AVG 1.5**	S1) 0.7 (S2) 0.9 **AVG 0.8**

Heparin filled Merit Centros FLO HD Catheters (Control)

Catheter Initial Fill Volume (mL)	Extracted Volume (mL) In-Catheter Stability Incubation Interval (days)		
	1	72	168
3.8	(S1) 2.5 (S2) 2.3 **AVG 2.4**	S1) 2.1 (S2) 2.1 **AVG 2.1**	S1) 1.9 (S2) 1.9 **AVG 1.9**

Reviewer Recommendation:

In-use stability studies of the drug should be evaluated by CDER as these are part of drug specifications (pH, Taurolidine assay, Heparin anti-Factor IIa, and Antimicrobial effectiveness). With regards to solvent loss, it is of CDRH review opinion that the original drug specifications (pH, Taurolidine assay, Heparin anti-Factor IIa, and Antimicrobial effectiveness) should be maintained through-out the patient use life (3 days) of the Defancath in the catheters within the ranges of tolerable loss of solvent from the catheters. The firm should provide in the labeling, the following:

1. How much amount of acceptable solvent loss is tolerable (based on validated testing) within the claimed 3 days of in-use life of the Defancath in the catheters. The testing should support that the original drug specifications (e.g., pH, Taurolidine assay, Heparin anti-Factor IIa, and Antimicrobial effectiveness) are maintained throughout the 3-day patient use-life within the catheter.
2. It is understandable that there will be solvent loss when using containment systems, however, the drug stability and specifications should be maintained throughout the in-use life of the Defancath solution within the catheters during the claimed dwell time and CDER should be able to review the acceptable range of volume loss.
3. There are two types of hemodialysis catheters that the firm proposes to be used with Neutrolin and they tested using MedComp and Merit catheters. MedComp is silicone based and Merit is polyurethane based. We know that silicone can imbibe solvents more than polyurethane. The firm should label the acceptable range of solvent absorbance of each specific catheter based on their

validations as described in comment 1 above (this should be reviewed by CDER because this is linked to CDER's drug specification during in-use conditions and acceptability).

4. The labeling should be limited to use withthe specific catheters that were tested: MedComp and Merit (with 510(k) cleared numbers). These catheters should identified in the labeling with an explanation that other catheter materials that were not tested may not be suitable for use with the drug.
5. Although, extractability and leachability studies were provided, however, you should clarify whether the MedComp and Merit catheters still meets their 510(k) cleared physical, mechanical and dimensional specifications and continue to be in conformance to the performance standards and acceptance critera after the 3 day dwell time with the drug Neutronil. Please provide validated performance testing with the dwelling of the subject 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 justificaction that the catheters are in conformance with the original OEM specifications as cleared in the 510(k), during in-use conditions.

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Director	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOROTA M MATECKA
12/21/2020 09:42:13 AM