CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214520Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 113764

MEETING PRELIMINARY COMMENTS

CorMedix, Inc.
Attention: Phoebe Mounts, PhD, Esq.
Executive Vice President and General Counsel
5825 Bellanca Drive
Elkridge, MD 21075

Dear Dr. Mounts:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Neutrolin (1.35% taurolidine, 3.5% citrate and 1,000 u/mL heparin) catheter lock solution.

We also refer to your September 27, 2019, correspondence, received September 27, 2019, requesting a Pre-NDA meeting.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Kristine Park, PhD, RAC, Regulatory Project Manager, at (301) 796-0471.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker, MS
Chief, Regulatory Project Management Staff
Anti-Infectives 2 Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 12, 2019, 3 – 4 PM (Eastern Time)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: IND 113764
Product Name: Neutrolin (1.35% taurolidine, 3.5% citrate and 1,000 u/mL heparin) catheter lock solution

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

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 12, 2019, 3 – 4 PM (Eastern Time) between CorMedix, Inc. and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1. BACKGROUND

On September 27, 2019, the Sponsor submitted a request to the Division for a Type B, Pre-NDA meeting for Neutrolin catheter lock solution. The Division granted the November 12, 2019, meeting on October 15, 2019.

2. DISCUSSION

Question 1: Does the FDA agree that Neutrolin is eligible for priority review?

FDA Response: The Division agrees that Neutrolin is eligible for priority review. This application received qualified infectious disease product (QIDP) designation for the indication of prevention of catheter-related bloodstream infections (CRBSI) in patients with end stage renal disease receiving hemodialysis through a central venous catheter on January 16, 2015. A drug that receives a QIDP designation is eligible under the statute for priority review provided that you are requesting approval for the indication for which the designation was granted. However, we recommend that you include a request for priority review designation with the original NDA. You will be notified within 60 calendar days of our receipt of the NDA if priority review is granted for your application.

Question 2: Does FDA agree that CorMedix can submit the NDA for Neutrolin using a rolling submission with the proposed sequence and timing of modules?

FDA Response: The investigation of Neutrolin catheter lock solution has been designated as a Fast Track development program for the prevention of CRBSI in patients with end stage renal disease receiving hemodialysis through a central venous catheter, on January 8, 2015, and is therefore eligible for submission under rolling review. While the proposal you have submitted in Appendix C of the meeting package seems reasonable, the request for rolling review should be submitted to the IND.

Clarify what you mean by “tabular data” as we will require tabulation and analysis datasets to support the findings of the LOCK-IT-100 study and any additional studies that might be used to support the safety and efficacy of Neutrolin. In your description of the datasets that you intend to use to support your NDA, please include the names and types of datasets plus whether those datasets are in legacy, study data tabulation model (SDTM) and/or analysis data model (ADaM) format. We request that you submit your datasets in SDTM/ADaM format as this will facilitate our review of the data. Please also clarify which specific datasets will be used to support safety and efficacy so that we can replicate your analyses during the NDA review. In particular, include an algorithm which clearly explains how findings from all primary and secondary analyses were produced (e.g., dataset, variable names and programming steps used). This would minimize potential discrepancies between Reviewer and Sponsor analyses.

Note that the CDER electronic submission system is able to handle terabyte submissions so there are no issues with handling data submissions of a large size.

Please confirm that you will be submitting the following:

- Study data reviewer guides for all key datasets
- A MedDRA coding dictionary so that we may understand how verbatim adverse event terms were mapped to MedDRA terms

- Information related to the CAC including procedures followed and decisions made during adjudication meetings
- A specific dataset with the following blood culture data: for each blood culture, please include the source (arterial line, peripheral line, etc.), timing of the blood culture specimen and timing of initiation of antibacterial treatment.

As the information requested above is crucial to allow an adequate review of your NDA, we are willing to review and provide feedback on any proposed draft/mock-up datasets prior to your NDA submission.

Question 3: Does the FDA anticipate requiring CorMedix to resubmit portions of the paper-based IND documents to the NDA as eCTD documents?

FDA Response: At this point in time, we do not see the need for you to resubmit portions of the paper-based IND documents to the NDA as eCTD documents. However, we may request additional information during the review of your NDA.

Question 4: Does FDA agree that the LPAD pathway is still applicable to Neutrolin and will be available to facilitate approval of the NDA, if applicable?

FDA Response: To be approved under the LPAD pathway an antibacterial or antifungal drug must treat a serious or life-threatening infection in a limited population of patients with unmet needs.

At this time, FDA agrees it would be appropriate to submit a written request for approval of Neutrolin under the LPAD pathway. Written requests for approval under the LPAD pathway should contain the following information:

- Identification of the submission in the cover letter as "REQUEST FOR LPAD APPROVAL"
- The specific serious or life-threatening infection that the drug is intended to treat
- The limited population of patients with unmet needs for whom the drug is intended, and
- A concise summary of how the conditions of approval under the LPAD pathway affect the benefit-risk assessment of the drug.

FDA will make a determination of whether a drug meets the criteria for the LPAD pathway at the time of the drug's approval. For more information, please see FDA's draft guidance Limited Population Pathway for Antibacterial and Antifungal Drugs.

Question 5: Does FDA agree that Neutrolin should be considered for a pediatric waiver?

FDA Response: Please refer to the PREA requirements below as you will need to submit an Initial Pediatric Study Plan (iPSP) as soon as possible for review by the

Division and FDA's Pediatric Review Committee (PeRC). Based on the advice provided for other similar development programs, it is likely that you will need to study Neutrolin in pediatric patients. Provide justification and supporting documentation for any planned waiver request for the Agency's review.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an iPSP within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

Additional Comments:

1) As previously communicated to you (most recently in preliminary comments ahead of our January 30, 2019 face-to-face meeting), two adequate and well-controlled trials are usually required to provide substantial evidence for the effectiveness of a product. In cases where a single trial, along with supportive evidence is to be used to support approval, the trial will need to demonstrate a highly reliable and persuasive clinical benefit. Please refer to the clinical effectiveness guidance that

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

discusses the type of information that can be used to support a single adequate and well-controlled trial. (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072008.pdf).

Based on the information provided thus far, we continue to have the following concerns:

- There have been significant revisions/amendments to the protocol, including revision of the definition of the primary endpoint, after the trial enrolled significant numbers of participants.
- The signal of increased thrombogenesis associated with Neutrolin as evidenced by the higher numbers of patients in the Neutrolin arm with loss of patency, including those subjects requiring use of tissue plasminogen activating factor.
- Issues of catheter malfunction and/or loss of patency are a safety concern given that maintaining vascular access is critical in the targeted patient population and will factor in our risk-benefit assessment.

Until we perform a thorough review of the data, we cannot agree that this single trial will be adequate to support an indication. You had previously mentioned two studies (Murray et al. 2014 and Solomon et al. 2012) as supportive evidence for demonstration of efficacy of taurolidine-citrate-heparin lock solution. At our January 30, 2019 meeting, you had noted that you had not attempted to obtain patient level data from Solomon et al. 2012, and that you had presumed that patient level data were not available from Murray et al. 2014. We continue to encourage you to try to obtain patient level data from these two studies or any additional studies that evaluated the use of taurolidine-citrate-heparin lock solution for the prevention of CRBSI.

2) In your NDA submission, please include the CRFs for the 59 cases reviewed by the CAC in PDF format with text recognition already enabled so that we may search on key words as well as the source document provided to the CAC for review of these cases (also in PDF format with text recognition enabled).

3) Please also include the meeting minutes of all CAC discussions with a summary of any conclusions reached by the committee, as well the meeting minutes from meetings of the DSMB.

4) Additionally, we request that you submit a 10% sample of CRFs from the Phase 3 trial with the NDA. When available, please submit the dataset in SAS transport (.xpt) format containing patient IDs and treatment codes that contain one row per patient. We will then generate a 10% random sample and send the listing to you. You may submit these datasets whenever they are available, but with enough time so the requested CRFs can be submitted with the initial NDA submission.

5) In the current submission, you reported the results of the primary efficacy endpoint as the percent of subjects who developed a CRBSI. While these data are informative, in your NDA submission, provide the primary efficacy endpoint results as the number of infections/catheter days.

6) The data for the secondary effectiveness endpoint (catheter patency) shows that there was greater usage of tPA in the Neutrolin group versus the Heparin group (Neutrolin, event rate of 0.72/1000 catheter days versus Heparin, event rate of 0.51/1000 catheter days). In addition, there was a greater overall loss of catheter patency (odds ratio 1.24, or 24% increased loss of catheter patency) in the Neutrolin group. It is possible that there was overlap between these two observations. In other words, if the majority of catheters lost in the Neutrolin group required tPA prior to catheter removal, tPA use and catheter loss may be, to some extent, indicating the same event. However, if greater tPA use in Neutrolin subjects saved many catheters, it is possible that the 24% lower rate of catheter patency in the Neutrolin group would have been far greater if not for the more frequent use of tPA. To further assess the difference in catheter patency between the Neutrolin and Heparin subjects, please provide the following data:
    a) A list of subjects (with ID number) in the Neutrolin and Heparin groups that required tPA
    b) A list of subjects (with ID number) in the Neutrolin and Heparin groups that had loss of catheter patency

7) Please include case narratives written by a physician for any discontinuations for any reason regardless of causality, any SAEs regardless of causality, and any deaths in either arm of treatment.

3. ADDITIONAL APPLICATION INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 15, 2019 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

[3] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial

period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

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[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

[8] https://www.fda.gov/media/85061/download

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/

MAUREEN P DILLON PARKER
11/07/2019 01:58:17 PM