CorMedix™

Leading Development of Novel Anti-Infective Products
in the Era of Increasing Bacterial Resistance

Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)

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COMPANY BACKGROUND

Founded in 2006

Mission Statement: *To harness our taurolidine technology for the prevention and treatment of infectious, inflammatory, and other serious diseases*

The Company's lead product Neutrolin® is a broad spectrum antimicrobial catheter-lock solution designed to prevent catheter-related bloodstream infections (CRBSIs) associated with the use of central venous catheters in hemodialysis patients

CE marked in the EU, where it is regulated as a medical device, and distributed in Europe and other territories

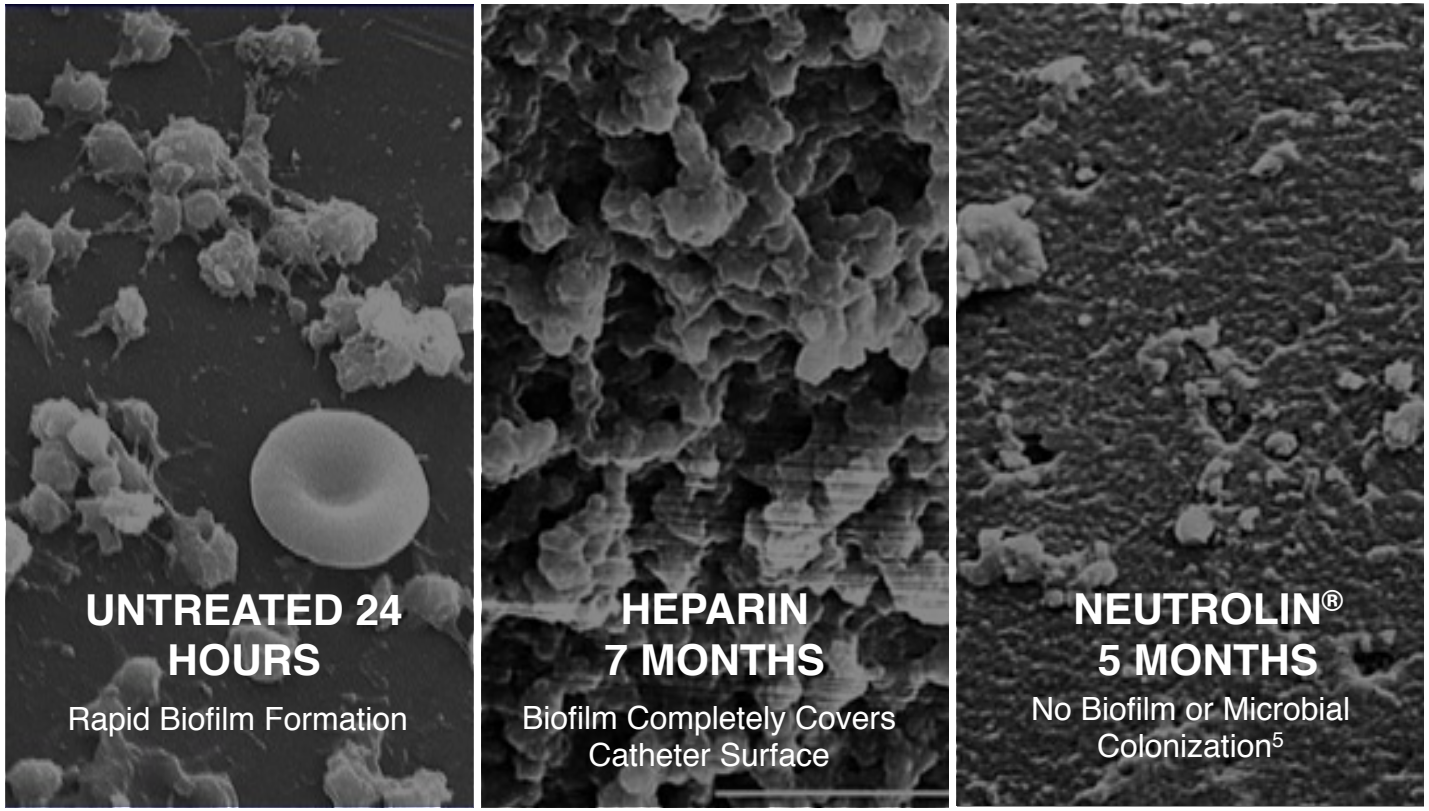
Neutrolin is regulated as an investigational new drug in the US and has received designation for Fast Track and Qualified Infectious Disease Product from FDA

PREVENTING CRBSIs = UNMET MEDICAL NEED FOR LIMITED POPULATION [1]

Despite improvements and initiatives to control infection, CRBSIs develop from repeated vascular access through central venous catheters and lead to life-threatening disease

Hemodialysis Patients at Risk for Infections

1. 420,000 patients with End-Stage Renal Disease in the US receive hemodialysis
2. CRBSIs are associated with substantial morbidity, mortality, and excess healthcare costs
3. CRBSIs can lead to hospitalization, catheter dysfunction and replacement, and risk of death
4. CDC reports methicillin-resistant *S. aureus*, cephalosporin-resistant *E. coli*, vancomycin-resistant *Enterococcus* and carbapenems-resistant *Enterobacter* in hemodialysis patients



FDA's LPAD Guidance
Important for Industry and Public Health

CorMedix respectfully requests that FDA:

- Strengthens the LPAD Guidance to focus on the Agency's current thinking on how to apply and implement Congressional intent from the 21st Century Cures Act
- Retains inclusion of products to prevent life-threatening infections
- Makes a determination for eligibility for LPAD earlier in product development for predictability and to maximize resources for Sponsor and FDA
- Removes exclusionary criterion of not being appropriate if criteria for non-LPAD approval are met
- Provides clarity on review of promotional material
- Clarifies the "streamlined clinical development program" anticipated

FDA's LPAD Guidance

- 21st Century Cures Act required guidance "describing criteria, processes, and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial and antifungal drugs"
  - Helpful for sponsors to understand more specifically the Agency's current thinking on how "limited population" will be interpreted

"clinically relevant to health care providers"

Explicitly address any numbers limitation

"a health care provider would be able to identify the patients in the clinical setting"

Identify what is required beyond usual prescribing information, which is apparent in the indication for use and label (

Physician education program required? (

- Strengthen the LPAD Guidance to focus on the Agency's current thinking on how to apply LPAD

FDA's LPAD GUIDANCE RECOGNIZES THE IMPORTANCE OF (**PREVENTION** OF LIFE-THREATENING INFECTIONS (

- "FDA intends to consider a drug to *treat a serious or life-threatening infection* if (the drug diagnoses, **prevents**, or treats such an infection." (emphasis added) (
  - CDC reports that in 2016, infectious and parasitic diseases accounted for 3.7 million emergency department visits of which 280,000 led to hospital admission[6]
  - Prevention of these diseases could dramatically reduce the number of hospital visits and admissions for the populations targeted by preventative therapies
  - For fragile populations, such as those with chronic illnesses and suppressed immune systems, an infection can be deadly. Prevention could be life saving for these populations
  - Preventing disease can help combat resistance. If the infection never occurs, multiple treatments with antimicrobials, a selective force in the development of resistance, is avoided
- Valuable to include prevention in definition

COMMENTS ON FDA'S **LPAD GUIDANCE** '

- "The Agency intends to make the determination of whether a drug meets the criteria for the LPAD pathway at the time of the drug's approval."
  - This strategy defeats the purpose of the LPAD pathway, which is to provide a more streamlined road to approval with the potential for a single trial and/or smaller clinical studies
  - By deferring the discussion of the applicability until approval, Sponsors may encounter significant delay in Phase 3 development, which is counter to the goal of facilitating antimicrobial drugs under LPAD
- We request the addition to the LPAD Guidance of a determination of ***eligibility*** to be made earlier in product development, with meeting criteria of LPAD retained as an approval decision

COMMENTS ON LPAD GUIDANCE (

❖ LPAD guidance states that the ***"Agency does not consider the LPAD pathway to be appropriate for products that could instead meet the criteria for non-LPAD pathway approval"***

FDA's proposed consideration for approval of drugs under the LPAD pathway is **not** in, and may be **in conflict with**, statutory language

- Section 506(h)(4) of the FD&C Act explicitly states that sponsors seeking approval under the LPAD pathway **are not precluded** from seeking designation **or approval** under **any other applicable provision in the FD&C Act or PHS Act**
- Congress intended this program to be available; therefore, use should not be unreasonably limited

➢ FDA's LPAD program should not limit a Sponsor's or FDA's flexibility in having the program available depending on circumstances, as intended by Congress

COMMENTS ON LPAD GUIDANCE (

- ❖ Copies of all promotional materials related to the product must be submitted at least 30 calendar days before dissemination

  More information on the process and timeline for FDA response should be provided

  - Will sponsor receive FDA's assessment in 30 days after submission?
  - Is the review of the promotional materials under the LPAD pathway similar or different to the requirements under the accelerated review pathway (see section 506(c) of the FD&C Act, 21 CFR 314 (subpart H), and 21 CFR 601 (subpart E))?

- ➢ LPAD Guidance should clarify the process and timeline for review and approval of draft promotional materials

COMMENTS ON LPAD GUIDANCE

- "A streamlined clinical development program for a limited population may involve smaller, shorter, or fewer clinical trials"

  Clarify with specificity the "streamlined clinical development program"

  - Does "smaller" reflect more than a "limited population"?
  - Does a "streamlined clinical development program" include the use of Real World Evidence?
  - How similar to or different will the "streamlined clinical development program" for LPAD be to the streamlined approaches described in the Unmet Medical Needs Guidance?
  - How will this advantage be realized with LPAD applicability decided at product approval?
  - Are post-marketing registries or data collection an option?

- Provide more specificity on Agency's current thinking on potential options for streamlining clinical development

APPLICABILITY OF POST APPROVAL AUTHORITY (

- Dr. Janet Woodcock in her 2016 statement to the Energy & Commerce Committee on the LPAD pathway indicated:

  [B]ecause LPAD drugs would be approved based on streamlined development programs, there would be more uncertainty about potential risks posed by the product...

- Please clarify why any concern identified in "substantial evidence of safety and effectiveness" cannot be easily addressed using FDA's existing post-approval authority to monitor and identify risks available for any new drug approval, including:
  - Risk Evaluation and Mitigation Strategies (REMS)
  - Post-marketing reporting of adverse drug experiences
  - Post-marketing studies

APPLICABILITY OF LABELING REQUIREMENTS AND FDA'S EXISTING AUTHORITY FOR OFF-LABEL USE (

- Dr. Janet Woodcock in her 2016 statement to the Energy & Commerce Committee on the LPAD pathway suggested that the LPAD pathway could put a burden on the clinical community to avoid using treatments beyond their indication, or "off-label" for fear of breeding resistance to these therapies
  - (The LPAD program requires premarket review of labeling to ensure that clinicians will be aware of the limited applicability of the treatments
  - (Labeling clearly states that the treatment is only indicated in certain populations and for certain diseases
  - (Use of Untitled Letters and Warning Letters
- FDA should clarify why its authority under advertising and promotion regulations is inadequate to prevent Sponsors from marketing a drug for a condition beyond that for which it is approved

LPAD Program Should Facilitate Antimicrobial Development (

- Dr. Edward Cox in his 2018 statement during Biopharma Congress IV commented that “LPAD will play a specific role in limited circumstances”

  “The drugs are coming along and they’re actually doing better than expected. The degree of uncertainty is really not so large, even though it is a small clinical trial, because the drug is quite effective.”

  - Congressional intent from the 21st Century Cures Act was to provide an additional program to address the need to expeditiously develop new antimicrobial agents in the face of increasing drug resistance
  - LPAD should not be inappropriately limited and should be made available to assist antimicrobial drug development as needed (

- FDA’s LPAD policies should be designed to facilitate approval of safe and effective antimicrobial drugs, using “streamlined clinical development” (

FDA's LPAD Guidance

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FDA's LPAD Program (

Additional requests:

- Clarify applicability of post-approval authority to LPAD approvals
- Clarify inadequacies of existing authority to address off-label use
- Clarify why use of LPAD will only play a specific role in limited circumstances

CONCLUSION: LPAD should be designed to facilitate antimicrobial development and to be one of many important programs that are needed to address the ongoing development of microbial resistance, which is not reasonably anticipated to abate anytime soon

Citations

1. United States Renal Data System: USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States, 2015. National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Disease, Bethesda, MD.
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3. Wasse H., 2008. Catheter-Related Mortality among ERSD Patients. Seminars in Dialysis 21(6):547-549.
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5. Quarello F. and Forneris G., 2002. Prevention of Hemodialysis Catheter-Related Bloodstream Infection using an Antimicrobial Lock. Blood Purification 20(1):87-92.
6. CDC, National Center for Health Statistics. Available at: https://www.cdc.gov/nchs/fastats/infectious-disease.htm. Accessed July 6, 2019.

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