Extracorporeal Antimicrobial Administration During Renal Replacement Therapy

C & M Coding Meeting

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DEFENCATH™ for the reduction of catheter related blood stream infection (CRBSI) in hemodialysis (HD) patients with central venous catheters (CVCs)

Upon approval, DEFENCATH is expected to be the first and only FDA-approved antimicrobial catheter lock solution in the US

- DEFENCATH is an investigational Catheter Lock Solution (CLS) demonstrating broad antimicrobial activity and no development of resistance in laboratory studies [6]
- DEFENCATH was studied in LOCK-IT-100, the most rigorous lock solution trial conducted in the US to date [4,7,8]
  - DEFENCATH achieved a 71% reduction in risk of CRBSIs vs control [6]
  - Compared to heparin, there was no statistically significant difference in either catheter removals for any reason or loss of catheter patency [6]
  - TESAEs were infrequent and similar between the DEFENCATH and control arms [6]

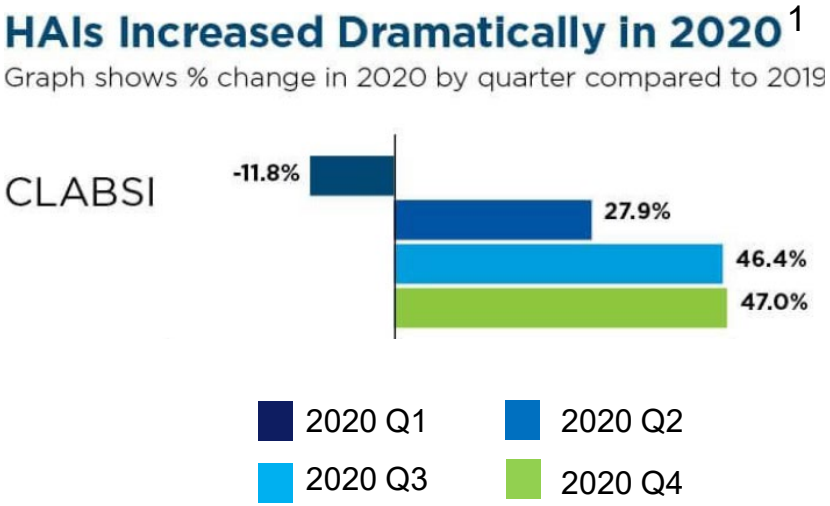
References: 1. Nguyen DB et al. *Clin J Am Soc Nephrol.* 2017;12(7):1139–1146. **2.** Silverstein DM et al. *Clin J Am Soc Nephrol.* 2018;13:1924–1932. **3.** Betjes MGH. *Nat Rev Nephrol.* 2011;7:257–265. **4.** Soi et al. *Int J Nephrol Renovasc Dis.* 2016;9:95–103. **5.** Dalrymple LS et al. *Clin J Am Soc Nephrol.* 2011;6:1708–1713. **6.** Data on file. CorMedix Inc. **7.** Labriola et al. *Nephrol Dial Transplant.* 2008;23:1666–1672. **8.** Lok CE, Mokrzycki MH. *Kidney Int.* 2011;79:587–598.

Hemodialysis patients are inherently at high risk for infections

- Infections, including CRBSI's are the second leading cause of death in Hemodialysis (HD) patients, largely related to central venous catheter (CVC) use [1-3]
- ~ 80% of HD patients initiate dialysis on a CVC and as many as 17.6% of prevalent patients [4]
- Compared to arteriovenous access patients, CVC patients have twice the risk of death at 18 months [4]
- 40% higher "…compared to 2019, 2020-Q3 and 2020-Q4 saw large and significant increases in the CLABSI"…[standard infection ratio] [5]

1. Kliger et al. *Clin J Am Soc Nephrol*. (2017) **2.** USRDS End Stage Renal Disease 2016 Annual Data Report; Chapter 5; *Mortality* **3.** Wetmore et al. *AJKD*. (2018) **4.** USRDS End Stage Renal Disease 2020 Annual Data Report; Chapter 3; *Vascular Access*. 5.Weiner-Lastinger, et al; Infection Control and Hospital Epidemiology (2021). 1-14

COVID 19 fuels hospital acquired infections (HAIs) such as inpatient central line associated blood stream infections (CLABSI)



"The unfortunately reality is that in one year we lost nearly a decade of progress against HAI's like central line-associated bloodstream infections…" [2]

1. Weiner-Lastinger LM, et al. (2021). The impact of coronavirus disease2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infection Control & Hospital Epidemiology, https://doi.org/10.1017/ice.2021.362
2. Statement from APIC President, Ann Marie Pettis, BSN, RN,CIC

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There is no Catheter Lock Solution currently approved for the reduction of CRBSI in the US

A safe intraluminal approach to CRBSI prevention in HD patients is urgently needed

- Attributes of an effective CLS [1,2]:
  - Broad-spectrum antimicrobial activity
  - Addresses CRBSI risk
  - Addresses mortality
  - Low potential for antimicrobial resistance
  - Low risk of systemic toxicity
- An effective solution will be critical **to reducing dialysis-related hospitalizations and decreasing the financial burden** to the system

References: 1. Golestaneh L, Mokryzycki MH. *Hemodial Int.* 2018;22(S2):22:S75–S82. **2.** Girand HL, McNeil JC. Lock therapy for intravascular non-hemodialysis catheter-related infection. UpToDate. https://www.uptodate.com/contents/lock-therapy-for-intravascular-non-hemodialysis-catheter-related-infection. Accessed October 6, 2020.

Introducing DEFENCATH™ for CRBSI reduction

An investigational antibacterial and antifungal Catheter Lock Solution designed to prevent life-threatening CRBSIs in chronic hemodialysis patients with CVCs

- Broad antimicrobial activity in vitro, including:
  - Gram-positive and Gram-negative bacteria
  - Multi-drug resistant bacteria
- Activity against clinically relevant fungi:
  - *Candida albicans*
  - *Candida glabrata*
- Utilizes taurolidine, a new chemical entity that denatures surface proteins, chemically alters membrane lipids, and directly attacks cell wall integrity
    - Proprietary Formulation
      - Taurolidine – 1.35% (anti-infective; new chemical entity)
      - Heparin* – 1000 USP U/ml (anti-coagulant)

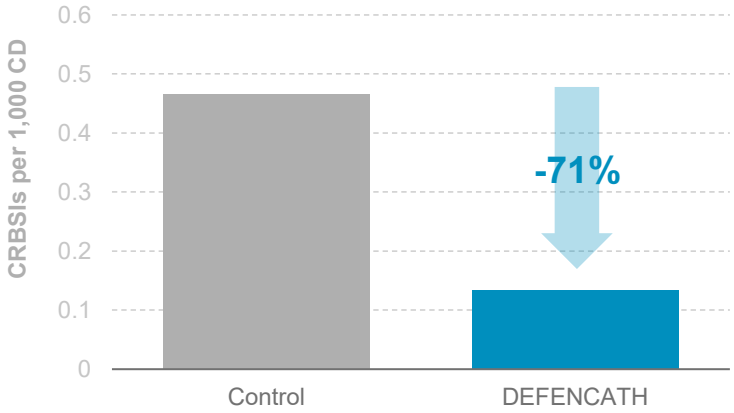
*Heparin used in DEFENCATH is subject to rigorous evaluation and must comply with USP standards requiring extensive testing for source and impurities.

Reference: Data on file. CorMedix Inc.

DEFENCATH™ reduced CRBSI occurrence by 71% at full analysis (41 cases)

Primary endpoint

	Control (n=398)	DEFENCATH (n=397)
No. of cases (CRBSI/1000 CD)	32 (0.465)	9 (0.133)
Total catheter-days follow-up	68,890	67,593
Hazard ratio (95% CI)*	0.29 (0.14, 0.62)	
***P* value**†	**0.0006**	



*Cox Proportional Hazards Mode
†Log-Rank Test
Reference: Data on file. CorMedix Inc.

LOCK-IT-100 patient demographics

Demographics (randomized population)	Control n=403	DEFENCATH™ n=403
Mean age (years) (SD)	60.9 (14.39)	60.8 (14.22)
<65 years (%)	58.6	59.3
65–74 years (%)	23.6	24.6
≥75 years (%)	17.9	16.1
Female (%)	38.2	45.7
White (%)	65.0	61.5
Black or African American (%)	27.8	31.3
Hispanic or Latino ethnicity (%)	46.9	43.9
Asian (%)	4.5	3.7

SD=standard deviation.

Reference: Data on file. CorMedix Inc.

Treatment-emergent serious adverse events were comparable between treatment arms*

Death occurred in 5.3% of patients in the control arm vs 4.5% of patients in the DEFENCATHTM arm

TESAE	Control (n=399) %	DEFENCATH™ (n=398) %
Fluid overload	3.0	3.5
Pneumonia	5.3	3.0
Cardiac failure, congestive	1.8	3.0
Hyperkalemia	2.0	2.5
Sepsis	3.5	2.3
Respiratory failure	2.3	1.8
Device-related infection	2.0	1.5
Acute myocardial infarction	3.3	1.3
Hypertension	2.5	1.0

*Incidence ≥2% in either treatment arm (safety population).
Note: the table is a summary of the TESAEs, not an exhaustive list.
Reference: Data on file. CorMedix Inc.

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Patient Population may be inpatient or outpatient

- Assuming Limited Population for Antibacterial and Antifungal Drugs (LPAD) pathway is used for approval, DEFENCATH would be indicated for a limited population of patients with kidney failure receiving chronic* hemodialysis (HD) through a central venous catheter

- **Target Inpatient Population: Kidney failure patients receiving dialysis through a central venous catheter**
  - Acute Kidney Injury (AKI) patients
  - End Stage Renal Disease patients
  - Post-Transplant Patients

- **Target Outpatient Population: Kidney failure patients receiving dialysis through a central venous catheter**
  - Chronic hemodialysis patients receiving dialysis in a clinic

*Chronic definition: receiving or expected to require HD for >7-10 days

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DEFENCATH™ administration is consistent with current catheter locking procedures

- Instilled to the fill the entire volume printed on the catheter hubs of the arterial and venous lumens following each dialysis session
  - Instillation is consistent with heparin CLS, but with an added anti-infective agent
- Aspirated—not flushed—before initiation of the next HD session
- There is no intended systemic administration
- In the inpatient setting, DEFENCATH would likely be documented in the patients' medical record under the Medical Administration Record (MAR) or eMAR (electronic)

Reference: Data on file. CorMedix Inc.

DEFENCATH™ for CRBSI Reduction

- Investigational Catheter Lock Solution (CLS) demonstrating broad antimicrobial activity and no development of resistance in laboratory studies
- Achieved a 71% reduction in risk of Catheter Related Blood Stream Infections (CRBSIs) vs control in LOCK-IT 100, the most rigorous lock solution trial conducted in the US to date
- Received FDA Fast Track status and is designated as a Qualified Infectious Disease Product (QIDP).
- Initial FDA approval is being sought through the Limited Population for Antibacterial and Antifungal Drugs (LPAD) pathway recognizing its potential to address the unmet needs of a limited population of patients with serious or life-threatening infections.
- May be used in the inpatient or outpatient setting for a limited population of patients with kidney failure receiving chronic hemodialysis (HD) through a central venous catheter (CVC)
- In the inpatient setting, DEFENCATH would likely be documented in the patient's medical record under the Medical Administration Record (MAR) or eMAR (electronic)