CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214520Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214520
PDUFA Goal Date	February 26, 2021
OSE RCM #	2020-476 and 2020-2501
Reviewer Name	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	December 22, 2020
Subject	Evaluation of Need for a REMS
Established Name	Neutrolin (1.35% Taurolidine/5000 units heparin)
Trade Name	Defencath
Name of Applicant	CorMedix Inc.
Therapeutic Class	A catheter lock solution contains taurolidine (an anti-microbial) and heparin (an anti-coagulant).
Formulation(s)	A sterile catheter lock solution of 67.5 mg/5 ml taurolidine and 5,000 USP unit/5 ml heparin in a single-dose vial
Dosing Regimen	Install 3 ml to 5 ml into the catheter lumen at the conclusion of each hemodialysis session

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Defencath (taurolidine/heparin) is necessary to ensure the benefits outweigh its risks. CorMedix, Inc. submitted a New Drug Application (NDA) 214520 for Defencath with the proposed indication to reduce the incidence of catheter-related bloodstream infections (CRBSIs) in patients with end-stage renal disease (ESRD) receiving hemodialysis (HD) through a central venous catheter. This drug combination is indicated for use in a limited and specific population of patients. The concerned risks associated with Defencath include heparin-induced thrombocytopenia and hypersensitivity reactions. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Anti-Infectives (DAI) have determined that a REMS is not needed to ensure the benefits of Defencath outweigh its risks. There remains a clear need to develop a new therapy that is both effective and safe to reduce catheter-related bloodstream infections in patients receiving HD through a central venous catheter. The clinical trial demonstrated that patients treated with Defencath had a reduction of 71% in the risk of CRBSI compared to heparin . If approved, the risks of heparin-induced thrombocytopenia and hypersensitivity reactions will be communicated in the Section Warnings and Precautions in the labeling.

1. INTRODUCTION

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Defencath is necessary to ensure the benefits outweigh its risks. CorMedix, Inc. submitted a New Drug Application (NDA) 214520 for Defencath with the proposed indication to reduce the incidence of catheter-related bloodstream infections (CRBSIs) in patients with end-stage renal disease (ESRD) receiving hemodialysis (HD) through a central venous catheter (CVC). This application is under review in the Division of Anti-Infectives (DAI). The applicant did not submit a proposed REMS or risk management plan with this application.

2. BACKGROUND

2.1 PRODUCT INFORMATION

Defencath is a combination of a thiadiazinane antimicrobial (taurolidine) and an anti-coagulant (heparin). Defencath 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 as a sterile, non-pyrogenic, (b) (4), preservative-free, clear aqueous solution. Taurolidine, a new molecular entity, is an antimicrobial agent derived from the naturally

[a]Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

occurring amino acid, taurine [1]. Taurolidine, in aqueous solution, is in equilibrium with its toxic hydrolysis metabolites, formaldehyde and methylene glycol. Formaldehyde and methylene glycol contain active N-methylol groups that cross-link with the protein component of microbial cell walls, causing damage and inhibit adherence of microorganisms to biological surfaces. Due to the broad, non-targeted nature of taurolidine toxicity, microbial resistance has not been documented, and laboratory efforts to induce resistance have failed.[2]

Defencath is to be installed into the catheter lumen, at a volume of 3-5 ml depending on the catheter lumen volume, as a lock solution at the conclusion of each hemodialysis session. Prior to initiation of the next dialysis treatment, the product must be aspirated from the catheter. Defencath, under the brand name of Neutrolin, was initially approved by the European Medicines Agency in July 2013 for use in the prevention of CRBSIs and maintenance of catheter patency in HD patients using an CVC for vascular access. The indication was expanded in September 2014 to include oncology patients receiving chemotherapy, intravenous (IV) hydration and IV medications via CVCs, patients receiving medication and IV fluids via CVCs in intensive or critical care units, and for use in total parental nutrition.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214520 relevant to this review:

- 01/08/2015: Fast Track designation was granted.
- 01/16/2015: Qualified Infectious Disease Product (QIDP) designation was granted.
- 07/01/2020: received the last part of rolling submission.
- 08/31/2020: Priority review was granted.
- 10/14/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Defencath. The agency also informed the Applicant that an Advisory Committee (AC) meeting is scheduled on 01/14/2021 to discuss the primary efficacy analysis, specifically related to the many protocol revisions and some lack of clarify on the adjudication process.
- 11/16/2020: The Agency informed the Applicant that the AC meeting is cancelled because the Agency's ongoing review of this NDA, and the Applicant's responses to multiple information requests have addressed the concerns of the primacy efficacy analysis.

3 THERAPEUTIC CONTEXT AND TREATMENT OPTIONS

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Catheter-related bloodstream infection (CRBSI) is defined as the presence of bacteremia originating from an IV catheter. CRBSI is one of the most frequent complications in patients who have CVCs implanted and is associated with substantial morbidity and mortality.[b] In a study performed from 05/01/2000 to 04/40/2003[3], it is estimated that 2.04 % CVC developed CRBSI and CRBSI incidence density was 2.79 infections per 1,000 catheter days[c]. A meta-analytical study demonstrated that bloodstream infections were the third leading cause of hospital-acquired infections.[4] Currently, arteriovenous fistulas (AVF) are preferred access for HD patients; nevertheless, when AVFs are not available, a CVC has to be installed to start HD. Using a CVC for HD exposes patients to events such as infections and thrombosis. A common complication among patients who undergo HD through CVCs is CRBSI. CRBSI increases treatment cost and adversely affect patients' quality of life.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are currently no approved drugs for the prevention of CRBSIs in patients with ESRD receiving HD through a CVC. However, several antimicrobial drugs are used off-label as catheter lock solution at the discretion of the treating physician. Gentamicin, cefazolin, cefotaxime, vancomycin, linezolid, vancomycin plus gentamicin, cefazolin plus gentamicin, sulfamethoxazole/trimethoprim, and minocycline have been used to prevent CRBSIs.[5] Defencath is the first catheter lock solution seeking regulatory approval in the United States for the prevention of CRBSI in a limited population of ESRD patients on HD using CVC.

4 BENEFIT ASSESSMENT

The efficacy of Defencath catheter lock solution for the reduction of catheter-related CRBSIs in patients with ESRD receiving HD were evaluated in Trial 1 (NCT02651428), a randomized, double-blind, active-controlled, multicenter trial. There were 806 patients randomized in a 1:1 ratio to receive either Defencath or heparin (heparin sodium USP 1,000 units/ml, benzyl alcohol 9.45 mg/ml, and sodium chloride 9 mg/ml) as a catheter lock solution. Defencath or heparin was instilled into central venous HD catheters at the end of all HD sessions and was withdrawn prior to the initiation of the next HD session. The median age of the study population was 63 years (range 21-94 years), 57.8% were males and 63% were White. [1]

A clinical adjudication committee (CAC) assessed CRBSI. The CAC definition for CRBSI included one positive blood culture from a peripheral site or either the arterial or venous catheter hub or the arterial

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[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

or venous dialysis blood line and no other apparent source of bloodstream infection. Patients in the Defencath arm had 71% reduction in the risk of CRBSI, as shown in Table 1.

Table 1 Results of analysis of time to CAC-adjudicated CRBSI

	Defencath (n=397)	Heparin (n=398)
CAC-adjudicated CRBSI	9 (2.3%)	32 (8%)
Event rate per 1000 catheter-days (95% CI[1])	0.13 (0.07, 0.26)	0.46 (0.33, 0.66)
Hazard ratio (Defencath/heparin) (95% CI)	0.29 (0.14, 0.62)	
Log-rank test p-value	0.0006	
CAC-adjudicated CRBSI or death[2]	24 (6%)	44 (11%)
Event rate per 1000 catheter-days (95% CI)	0.35 (0.24, 0.53)	0.64 (0.48, 0.86)
Hazard ratio (Defencath/heparin) (95% CI)	0.57 (0.35, 0.94)	
Log-rank test p-value	0.0250	

[1]CI: confidence interval

[2]referred to death prior to removal of the first catheter

5 RISK ASSESSMENT & SAFE-USE CONDITIONS

The safety of Defencath was evaluated in Trial 1 that included 797 patients with 398 patients who received Defencath and 399 patients who received heparin. The mean duration of Defencath therapy in Trial 1 was 173 days. The mean patient age was 61 years old, 57.8% were male and 63% were White. There were 18 deaths (4.5%) in Defencath arm and 21 deaths (5.3%) in heparin arm, respectively.[2] The cause of death was investigator-determined and the investigators did not attribute any of the deaths to study drug. The most common cause of death was cardiac disorders with 5 patients in both the heparin arm and the Defencath arm. There were 4 deaths due to infections and infestations in the heparin arm and none in the Defencath arm. Other causes of death were infrequent, such as respiratory disorders, renal disorders, gastrointestinal disorders, and vascular disorders.

The followings are the risks[d] associated with the use of Defencath that will be included in warnings and precautions of the label.

5.1 HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Defencath therapy could be associated with the development of HIT since it contains heparin. In Trial 1, HIT was reported at a rate less than 1% in patients treated with heparin, a component of Defencath. Healthcare providers (HCPs) will be advised to discontinue Defencath and institute appropriate supportive measures if HIT occurs. [1]

5.2 HYPERSENSITIVITY REACTIONS

In Trial 1, hypersensitivity reactions, including anaphylaxis, were reported at a rate less than 1% in patients treated with heparin, a component of Defencath arm. HCPs will be advised that Defencath is contraindicated in patients with known hypersensitivity to taurolidine, heparin, or citrate (components of Defencath). If a hypersensitivity reaction occurs, Defencath should be discontinued and institute appropriate supportive measures.

6 EXPECTED POSTMARKET USE

If approved, Defencath will be used in both outpatient dialysis center and inpatient settings. The likely prescribers will be nephrologists, infectious disease physicians, and intensivists.

7 RISK MANAGEMENT ACTIVITIES PROPOSED BY THE APPLICANT

The Applicant did not propose any risk management activities for Defencath beyond routine pharmacovigilance and labeling.

8 DISCUSSION OF NEED FOR A REMS

The Clinical Reviewer recommends approval of Defencath based on the efficacy and safety information currently available. DRM and DAI agree that a REMS is not necessary to ensure the benefits of Defencath outweigh its risks. When evaluating factors of a REMS is necessary to ensure that the benefits outweigh the risks for Defencath, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and prescribing population.

CRBSI is one of the most frequent complications in patients who have CVCs implanted and is associated with substantial morbidity and mortality. Patients with ESRD requiring dialysis are at risk for CRBSI. In a study performed from 05/01/2000 to 04/40/2003, it is estimated that 2.04% CVC developed CRBSI.

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[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Infection is the second leading cause of death in dialysis patients and the leading cause of catheter removal and morbidity in patients with ESRD.[6]

The clinical trial, Trial1, demonstrated that patients treated with Defencath had a reduction of 71% in the risk of CRBSI compared to heparin therapy alone. The risks of HIT and hypersensitivity reactions will be communicated in the section of Warnings and Precautions in the labeling. There are currently no adverse events that rise to a Box Warning for this product. DRM and DAI agree that there are currently no risks identified that require a need for a REMS.

9 CONCLUSION & RECOMMENDATIONS

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Defencath to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 APPENDICES

10.1 REFERENCES

[1] Defencath draft prescribing information, accessed 11/17/2020

[2] Workneh M, Qi K, Defencath NDA 212819 mid-cycle slides presentation, 09/28/2020

[3] Lorente L, Henry C, et al Central venous catheter-related infection in a prospective and observational study of 2,595 catheters. Crit CaRE. 2005; 9(6):R631-5

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

[5] Arechabala M, et al Antimicrobial lock solutions for preventing catheter-related infections in HD, Cochrane Database syst rev. 2018 Apr; 2018 (4): CD010597

[6] Zhang J, Li RK, Chen KH, et al. Antimicrobial lock solutions for the prevention of catheter-related infection in patient undergoing hemodialysis: study protocol for network meta-analysis of randomized controlled trials. BMJ Open. 2016; 6:e010264

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