CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216483Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 15, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216483
Product Name, Dosage Form, and Strength:	Pivya (pivmecillinam) tablet, 185 mg
Applicant Name:	UTILITY therapeutics, Ltd
FDA Received Date:	April 15, 2024
TTT ID #:	2023-6865-3
DMEPA 1 Safety Evaluator:	Kristine Needleman, RPh
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

UTILITY therapeutics, Ltd submitted revised 9-count and 50-count carton labeling for Pivya that were received on April 15, 2024. The Division of Anti-Infectives (DAI) requested that we review the revised carton labeling for Pivya (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[a,b,c]

2 CONCLUSION

UTILITY therapeutics, LTD implemented all of our recommendations and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Needleman, K. Label and Labeling Review for Pivya (NDA 216483). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Mar 5. TTT ID: 2023-6865.

[b]Needleman, K. Label and Labeling Review Memo for Pivya (NDA 216483). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Apr 5. TTT ID: 2023-6865-1.

[c]Needleman, K. Label and Labeling Review Memo for Pivya (NDA 216483). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Apr 12. TTT ID: 2023-6865-2.

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/s/

KRISTINE P NEEDLEMAN
04/15/2024 04:54:15 PM

VALERIE S VAUGHAN
04/15/2024 05:13:20 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 12, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216483
Product Name, Dosage Form, and Strength:	Pivya (pivmecillinam) tablet, 185 mg
Applicant Name:	UTILITY therapeutics, Ltd
FDA Received Date:	April 10, 2024
TTT ID #:	2023-6865-2
DMEPA 1 Safety Evaluator:	Kristine Needleman, RPh
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

UTILITY therapeutics, Ltd submitted revised 10-count blister sheet label and 50-count carton labeling as well as a new 9-count blister sheet label and 9-count carton labeling for Pivya that were received on April 10, 2024. The Division of Anti-Infectives (DAI) requested that we review the revised and new blister sheet labels and carton labeling for Pivya (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions and new labels are in response to recommendations that we made during previous label and labeling reviews.[a,b]

2 CONCLUSION

UTILITY therapeutics, LTD implemented all of our previous recommendations; however, we note they removed the linear barcode from the carton labeling. Additionally, we note a typographical error on the carton labeling. Thus, we provide our recommendation for UTILITY therapeutics, LTD in Section 2.1.

2.1 RECOMMENDATIONS FOR UTILITY THERAPEUTICS, LTD

Carton labeling

1. The 9-count and 50-count carton labeling are missing the linear barcode. The linear barcode is required per 21 CFR 201.25(c)(2). Add the product's linear barcode to each carton labeling in accordance with 21 CFR 201.25(c)(2).
2. We note that there is a typographical error on the rear panel of the carton labeling where the word "information" is misspelled as "informaiton." Revise the spelling to "information."

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Needleman, K. Label and Labeling Review for Pivya (NDA 216483). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Mar 5. TTT ID: 2023-6865.

[b] Needleman, K. Label and Labeling Review Memo for Pivya (NDA 216483). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Apr 5. TTT ID: 2023-6865-1.

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KRISTINE P NEEDLEMAN
04/12/2024 09:11:21 AM

VALERIE S VAUGHAN
04/12/2024 09:30:16 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 5, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216483
Product Name, Dosage Form, and Strength:	Pivya (pivmecillinam) tablet, 185 mg
Applicant Name:	UTILITY therapeutics, Ltd
FDA Received Date:	March 22, 2024
TTT ID #:	2023-6865-1
DMEPA 1 Safety Evaluator:	Kristine Needleman, RPh
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

UTILITY therapeutics, Ltd submitted revised blister sheet label and carton labeling received on March 22, 2024 for Pivya. The Division of Anti-Infectives (DAI) requested that we review the revised blister sheet label and carton labeling for Pivya (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The blister sheet label and carton labeling are unacceptable from a medication error perspective. The revised blister sheet label and carton labeling may be improved to promote safe use of this product from a medication error perspective. Below we provide recommendations to minimize the risk for medication errors.

3 RECOMMENDATIONS FOR UTILITY THERAPEUTICS, LTD

A. Blister Sheet Label

As designed, your proposed blister sheet label is unacceptable for the following reasons:

1. The proprietary name, established name, identifying lot, and name of manufacturer, packer, or distributor are part of the minimum information that is required to be on small labels and is important for product distinction and identification. However, the proposed blister sheet label is missing the following minimum information required for small labels per 21 CFR 201.10(i):
    - Name of manufacturer, packer, or distributor of the drug.

    Add the manufacturer, packer, or distributor information to the blister sheet.
2. The proposed blister sheet label cells do not contain a linear barcode for product identification. Per 21 CFR 201.25(c)(2), the barcode must appear on the drug's label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act. Replace the 2-D matrix barcode with a linear barcode in alignment with 21 CFR 201.25.
3. The format of the expiration date does not include a hyphen or forward slash between the year and month. We recommend adding a hyphen or forward slash to separate the portions of the expiration date to improve readability.
4. For products where each blister cell has a label, the barcode and other required or critical information (e.g., proprietary and established name, dosage form, strength, lot number, expiration date, manufacturer) should appear over each blister cell so that this important information remains available to the end user up to the point at which the last dose is removed. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). We recommend revising each blister label so that the proprietary and

[a] Needleman, K. Label and Labeling Review for Pivya (NDA 216483). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Mar 5. TTT ID: 2023-6865.

established name, dosage form, strength, lot number, expiration date, and manufacturer information appear on each blister cell label.

B. Carton Labeling
   1. Consider use of a different font color, boxing, or other means to further distinguish the strength statement from the proprietary name.
   2. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder in both the human-readable form and machine-readable 2D data matrix barcode to the carton labeling.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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04/05/2024 01:30:35 PM

VALERIE S VAUGHAN
04/05/2024 01:35:40 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urology, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatrics and Maternal Health PLLR Labeling Memorandum

Date: 3/13/24 **Date consulted:** 11/13/23

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
DPMH

Lynne P. Yao, MD, OND, Division Director
DPMH

To: Division of Anti-Infectives (DAI)

Drug: Pivmecillinam oral tablet

NDA: 216483

IND: 118650

Applicant: UTILITY Therapeutics, Ltd.

Subject: Pregnancy and Lactation Labeling (PLLR) and Pregnancy and Lactation Related Postmarketing Requirements (PMRs)

Proposed Indication: Treatment of adults with uncomplicated urinary tract infections (uUTI).

Consult Question: "DAI requests DPMH review of proposed PLLR labeling"

Materials Reviewed:

- Applicants NDA submission dated 10/24/23 including Systematic Literature Review

- Applicant's response to FDA Information Request (IR), submitted 1/8/24 and 2/22/24
- Division of Epidemiology (DEPI) II memo for Pivmecillinam NDA 216483 by Ikponmwosa Osaghae, MD, PhD dated February 2024.

INTRODUCTION

On October 24, 2023, the applicant, UTILITY Therapeutics, Ltd., submitted a new drug application (NDA 214483) a new molecular entity (NME) pivmecillinam tablets. On November 13, 2023, the Division of Anti-Infectives (DAI) consulted the Division of Pediatrics and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- The proposed indication for Pivmecillinam oral tablet (NDA 216483) is treatment of adults with uncomplicated urinary tract infection (uUTI).
- Pivmecillinam received its first marketing authorization in the United Kingdom in 1977. The product is marketed outside of the US by Karo Pharma AB under the proprietary name Selexid. Selexid is approved as 200 mg tablet in 10 European countries and 3 countries outside of Europe. The 400 mg tablet is approved in 13 European countries and 2 countries outside of Europe.
- On December 6, 2023, the Agency sent the applicant an information request (IR) to provide a cumulative review and summary of relevant global pharmacovigilance cases regarding pivmecillinam use during pregnancy, lactation, and any effects on male or female fertility.
- On January 8, 2024, the applicant submitted the requested information.
- On February 15, 2024, the Agency sent the applicant an IR to provide lactation data to support proposed labeling in subsection 8.2 Lactation.
- On February 22, 2024 the applicant submitted the requested information.

Drug Characteristics and proposed labeling[1]

- *Mechanism of action*: a beta-lactam antibiotic. It is active against gram-negative bacteria and works by interfering with the biosynthesis of the bacterial cell wall. Pivmecillinam is the pro-drug rapidly converted to mecillinam (the active antibacterial moiety).
- *Dosage and administration:* 200 mg (3 times a day for a duration of 3-7 days).
- *Molecular weight:* 439.57 g/mol
- *Protein-binding:* 5-10%
- *Half-life:* 1 hour
- *Contraindications:*
    - Patients who have experienced a serious hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to pivmecillinam or to other beta-lactam antibiotics (e.g., penicillins and cephalosporins).

[1] Pivmecillinam (NDA 216483) proposed package insert.

    - Patients with genetic metabolism anomalies known to result in severe carnitine deficiency, such as carnitine transporter defect, methylmalonic aciduria, or propionic acidemia.
    - Patients suffering from porphyria.
- *Warnings and Precautions*: serious hypersensitivity; carnitine depletion; porphyria; *Clostridioides difficile*-associated bacteria (CDAD); interference with neonatal screening tests; severe cutaneous adverse reactions (SCAR).
- *Adverse reactions*: nausea and diarrhea.

Condition: Pregnancy and Urinary Tract Infection (UTI)

- UTIs account for approximately 10 percent of office visits by women, and 15 percent of women will have a UTI at some time during their life. Urinary tract infections are common during pregnancy and may give rise to pyelonephritis which is the most common serious medical condition seen in pregnancy.[2] In pregnant women, the incidence of UTI can be as high as 8 percent.[3] In one study, 3.5% of antepartum admissions were due to UTI.[4]
- During pregnancy, urinary tract changes predispose women to infection. Ureteral dilation is seen due to compression of the ureters from the gravid uterus.[2] Hormonal effects of progesterone may cause smooth muscle relaxation leading to dilation and urinary stasis, and vesicoureteral reflux increases. The organisms which cause UTI in pregnancy are the same uropathogens seen in non-pregnant individuals.[2] A 18-year retrospective analysis found E. coli to be the causative agent in 82.5% of cases of pyelonephritis in pregnant patients.[5]
- Asymptomatic bacteriuria can lead to the development of cystitis or pyelonephritis. All pregnant women should be screened for bacteriuria and subsequently treated with antibiotics, such as nitrofurantoin, sulfamethoxazole or cephalexin.[6] Ampicillin is no longer used in the treatment of asymptomatic bacteriuria because of high rates of resistance. Pregnant women with urinary group B streptococcal infection should be treated and subsequently should receive intrapartum prophylactic therapy. Pyelonephritis can be a life-threatening illness, with increased risk of perinatal and neonatal morbidity. Recurrent infections are common during pregnancy and require prophylactic treatment. Suppressive antibiotic therapy, usually with nitrofurantoin once daily, is commonly recommended especially in cases where patients have had a prior UTI.[2] This is typically continued throughout pregnancy and the early postpartum period.

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[2] Habak PJ, Griggs, Jr RP. Urinary Tract Infection In Pregnancy. [Updated 2022 Jul 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-.

[3] Delzell JE Jr, Lefevre ML. Urinary tract infections during pregnancy. Am Fam Physician. 2000 Feb 1;61(3):713-21. Erratum in: Am Fam Physician 2000 Jun 15;61(12):3567.

[4] Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL. Hospitalizations during pregnancy among managed care enrollees. Obstet Gynecol. 2002 Jul;100(1):94-100.

[5] Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. Am J Obstet Gynecol. 2014 Mar;210(3): 219.e1-6.

[6] Gupta K, et al. Urinary tract infections and asymptomatic bacteriuria in pregnancy. UpToDate.com, accessed 3/4/24.

- Schieve et al.[7] conducted a study involving 25,746 pregnant women and found that the presence of UTI was associated with premature labor (labor onset before 37 weeks of gestation), hypertensive disorders of pregnancy (such as pregnancy-induced hypertension and preeclampsia), anemia (hematocrit level less than 30 percent) and amnionitis. Additionally, randomized trials have demonstrated that antibiotic treatment decreases the incidence of preterm birth and low-birth-weight infants.[8]

DATA REVIEW

PREGNANCY

Nonclinical Experience

Developmental toxicity studies with pivmecillinam or mecillinam administered during organogenesis to rats and mice showed no evidence of embryo-fetal toxicity, including drug-induced fetal malformations, at doses approximately 3.4 or 7.9 times (rats) or 5.1 or 3.9 times (mice) higher than given to patients receiving the maximum recommended daily dose (based on body surface area). Evidence of slight fetotoxicity (reduced ossification) was seen in offspring of rats that were given pivmecillinam during organogenesis at a dose approximately 10.2-fold higher than the maximum recommended daily human dose based on body surface area. For more information, refer to the Nonclinical Review by Amy Ellis, PhD.

Clinical Experience

Applicant's Review Published Literature

Pharmacokinetics

The applicant submitted published literature regarding pivmecillinam use in pregnancy and pharmacokinetics.[9,10] The applicant concluded that pivmecillinam can be administered to pregnant women without need for dosage adjustment. These data have been reviewed by the DAI Clinical Pharmacology Review Team. Refer to the review by Timothy Bensman, PharmD for additional details.

Safety

The applicant performed a systematic search in Embase and MEDLINE to identify relevant published literature regarding the safety of pivmecillinam and mecillinam (see submission for search details).[11] The applicant identified 3 clinical trial studies that evaluated treatment of bacteriuria during pregnancy (see applicant's Table 3 in Appendix

[7] Schieve LA, Handler A, Hershow R, Persky V, Davis F. Urinary tract infection during pregnancy: its association with maternal morbidity and perinatal outcome. Am J Public Health. 1994; 84:405-10.
[8] Romero R, Oyarzun E, Mazor M, Sirtori M, Hobbins JC, Bracken M. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. Obstet Gynecol. 1989; 73:576-82.
[9] Heikkila A, Pykko K, Erkkola R, Iisalo E. The pharmacokinetics of mecillinam and pivmecillinam in pregnant and non-pregnant women. Br J Clin Pharmacol. 1992;33:629- 633.
[10] Kjer JJ, Ottesen B. Pharmacokinetics of pivmecillinam hydrochloride in pregnant and non-pregnant women. Acta Pharmacol Toxicol (Copenh) 1986; 59(5):430-431.
[11] Applicant's NDA submission document "Pivmecillinam Safety SLR: A systematic literature review to identify published evidence on any safety signals associated with the use of the antibiotic, pivmecillinam."

A) and 8 studies that evaluated safety outcomes in pregnant patients exposed to pivmecillinam (see applicant's Table 4 in Appendix B). These studies are briefly summarized below with a focus on pregnancy safety outcomes rather than efficacy:

Clinical Trials (n=3):

- Sanderson et al 1984[12] presented results of a study including 44 pregnant women with bacteriuria in pregnancy treated with pivmecillinam. Pregnancy outcomes included: 3 lost to follow up, 39 healthy livebirths, 1 livebirth with cleft palate, and 1 stillbirth; the authors concluded neither event was related to pivmecillinam treatment.
- Brumfitt et al 1979[13] compared efficacy and safety of pivmecillinam and cephradine in 50 patients with bacteriuria in pregnancy and in acute UTI in 48 nonpregnant women. However, no relevant safety information related to pregnancy outcomes was described.
- Bint et al 1979 compared pivmecillinam with ampicillin in 100 pregnant patients with bacteriuria randomly allocated to receive either treatment. However, no relevant safety information related to pregnancy outcomes was described.[14]

Observational studies (n=8):

- Molgaard-Nielsen et al 2012[15] studied the associated between antibiotic use early in pregnancy and the risk of isolated orofacial clefts in 806,011 livebirths in Denmark from January 1996 to September 2008. Study results showed that maternal use of any antibiotics in early pregnancy was not associated with an increase risk of cleft lip (with or without cleft palate) or cleft palate alone. Further analysis of specific classes of antibiotics showed increased risks for cleft lip with or without cleft palate or cleft palate alone for doxycycline/tetracycline, sulfamethizole, trimethoprim, and pivmecillinam. An increased risk of cleft palate was seen for the third month of use of pivmecillinam (9 exposed cases; prevalence odds ratio [OR], 2.34; 95% confidence interval [CI], 1.20-4.54).

  Reviewer's Comment
  DEPI II determined this study was not of significant rigor for full review.

- Larsen et al 2001[16] performed a Danish cohort study comparing the prevalence of congenital abnormalities, preterm delivery, low birth weight, low Apgar score, and neonatal hypoglycemia in the offspring of 414 women who had at least one

[12] Sanderson P, Menday P. Pivmecillinam for bacteriuria in pregnancy. J Antimicrob Chemother 1984;13:383-388.
[13] Brumfitt W, Hamilton-Miller JM. Pivmecillinam in complicated urinary infections failing to respond to conventional therapy. Infection 1982;10:149-152.
[14] Bint A, et al. A comparative trial of pivmecillinam and ampicillin in bacteriuria of pregnancy. Infection 1979;7:290-293.
[15] Mølgaard-Nielsen D, Hviid A. Maternal use of antibiotics and the risk of orofacial clefts: a nationwide cohort study. Pharmacoepidemiol Drug Saf 2012;21:246-253.
[16] Larsen H, et al. Birth outcome and risk of neonatal hypoglycaemia following in utero exposure to pivmecillinam: a population-based cohort study with 414 exposed pregnancies. Scand J Infect Dis 2001;33:439-444.

prescription for pivmecillinam redeemed during pregnancy with those of the offspring of 7,472 pregnant women for whom no drugs were prescribed during pregnancy. The prevalence of congenital abnormalities was 1.7% among 119 infants exposed in the first trimester and 3.7% among the reference group (OR, 0.46; 95% CI, 0.11-1.86). No significantly increased risks in preterm delivery (OR, 0.91, 95% CI, 0.11-1.86), low birth weight (OR, 0.57; 95% CI, 0.23-1.41), low Apgar score (OR, 2.32, 95% CI, 0.30-18.16), or hypoglycemia (OR, 0.73; 95% CI, 0.18-3.00) induced by carnitine depletion were reported. A total of 24 preterm deliveries were recorded in women who had pivmecillinam prescriptions at any time during pregnancy as compared with 480 in the reference group. The authors concluded that no significantly increased risk in adverse birth outcome was apparent in women treated with pivmecillinam.

Reviewer's Comment
DEPI II determined this study was not of significant rigor for full review.

- Skriver et al 2004[17], examined the risk of adverse birth and neonatal outcomes among pregnant users of pivmecillinam based on population-based registries in Denmark. Of 63, 659 women with a live birth or stillbirth after 28 weeks gestation, a total of 2,031 had redeemed prescriptions for pivmecillinam at any time during pregnancy, 559 in the first trimester, and 371 within 28 days before delivery. Adjusted ORs were: birth defects 0.83 (95% CI, 0.53-1.32) for exposure during the first trimester, preterm delivery 0.96 (95% CI, 0.79-1.18) and low birth weight 0.79 (95% CI, 0.52-1.20) for exposure at any time during pregnancy, and stillbirth 1.19 (95% CI, 0.30-4.80), low Apgar score 1.17 (95% CI, 0.37-3.66), hypoglycemia 1.03 (95% CI, 0.53-2.00), and respiratory distress syndrome 0.79 (95% CI, 0.38-1.68) for exposure within 28 days before delivery. The authors concluded that use of pivmecillinam during pregnancy did not appear to increase the risk of adverse birth and neonatal outcomes; however, the statistical precision of the analysis was low.

  Reviewer's Comment
  DEPI II determined this study was not of significant rigor for full review.

- Damkier et al 2019[18], performed a Danish cohort study comprising all singleton liveborn children (n=932,731) between 2000 and 2015 determined the risk of congenital malformations following first-trimester in utero exposure to 10 commonly prescribed antibiotics. Data on malformations were collected through 2016. In the primary analysis, the exposed cohort was compared to a cohort *exposed to exposed to* any of 4 penicillins considered safe during pregnancy (ampicillin, pivampicillin, benzylpenicillin, and phenoxymethylpenicillin). In sensitivity analysis, the exposed cohort was compared to an unexposed cohort.

[17] Skriver VM, et al. Pivmecillinam and adverse birth and neonatal outcomes: a population-based cohort study. Scand J Infect Dis 2004;36:733-737.
[18] Damkier P, et al. In utero exposure to antibiotics and risk of congenital malformations: a population-based study. Am J Obstet Gynecol 2019;221:648 e641-648 e615.

Covariate adjustments were made for maternal age at delivery, year of delivery, parity, pre-pregnancy body mass index, smoking, educational status, employment status, and annual personal income.

Results indicated no increased risk of congenital malformations to be related to first-trimester exposure to 10 of the most commonly prescribed antibiotics compared to a cohort of pregnant women exposed to penicillins that are considered safe during pregnancy. This large cohort study included more than 36,000 first-trimester exposures to pivmecillinam. In a secondary analysis, compared to unexposed pregnancies, small increased risks of major congenital malformations were apparent for pivmecillinam (OR, 1.13; CI, 1.06-1.19; and OR, 1.15; CI, 1.04-1.28, respectively), sulfamethizole (OR, 1.15; CI, 1.07-1.24; and OR, 1.22; CI, 1.07-1.39, respectively), and azithromycin (OR, 1.19, CI, 1.03-1.38; and OR, 1.29, CI, 0.99-1.67, respectively). The authors noted the study design substantiates that this finding is likely due to confounding by indication.

Reviewer's Comment
DEPI II reviewed this study in detail, refer to conclusions described below.

- Miller et al 2012[19] examined whether maternal use of antibiotics during pregnancy, as a marker of infection, increased the risk of childhood epilepsy in a large population-based cohort using data from the Danish National Birth Registry between January 1996 and September 2004. A total of 2,848 children with a diagnosis of epilepsy in the cohort of 447,629 singletons followed for up to 9.9 years (median, 5.5 years) were identified. Of these, 1,033 cases of epilepsy were diagnosed during the first year of life. The adjusted hazard ratio (HR; 95% CI) for risk of epilepsy in the children was 1.2 (1.1-1.3) for any cystitis antibiotic. The study also examined pivmecillinam, sulfamethizole, and nitrofurantoin specifically. They reported an adjusted HR (95% CI) of 1.2 (1.0-1.4) for pivmecillinam, 1.2 (1.1-1.4) for sulfamethizole, and 1.1 (0.8-1.5) for nitrofurantoin. Associations for pharmacologically different antibiotics were comparable, which may suggest an association with the underlying disease rather than the medications. Whether the association is a direct effect of antibiotics or of maternal infection or uncontrolled confounding remains unclear.

  Reviewer's Comment
  DEPI II determined this study was not of significant rigor for full review.

- Miller et al 2013[20] examined whether maternal use of antibiotics during pregnancy, as a marker of infection, increased the risk of febrile seizures in childhood in the same cohort and observed that the adjusted HR (95% CI) for risk of childhood-onset febrile seizures was 1.08 (1.05-1.11) in the group with

[19] Miller JE, et al. Maternal use of cystitis medication and childhood epilepsy in a danish population-based cohort. Paediatr Perinat Epidemiol 2012;26:589-595.
[20] Miller JE, et al. Maternal use of antibiotics and the risk of childhood febrile seizures: a Danish population-based cohort. PLoS One 2013;8:e61148.

maternal use of any systemic antibiotic. For those maternally exposed to either pivmecillinam or sulfamethizole, the adjusted HR (95% CI) was 1.12 (1.06-1.18); for nitrofurantoin and erythromycin maternal exposure, the adjusted HR (95% CI) was 1.16 (1.04- 1.29) and 1.03 (0.95-1.11), respectively. Weak associations between the redemption of certain antibiotics during pregnancy and febrile seizures in early childhood were found. The authors suggested that the association does not occur due to the exposure of the antibiotic but rather due to the risk of infection.

Reviewer's Comment
DEPI II determined this study was not of significant rigor for full review.

- Nørgaard et al 2008[21], examined the relationship between maternal infection treated with pivmecillinam during pregnancy and risk of miscarriage in a population-based case-control study from 1997-2002. The study included 1,599 first-time pregnant women who had a miscarriage with known gestational age and a control group of 15,990 primiparous women who had a live birth during the study. Five cases (0.3%) and 24 controls (0.15%) were exposed to pivmecillinam in the last week before the miscarriage/index date.

  After adjustment for maternal age, use of antidiabetics, and use of antiepileptics, the OR for miscarriages among pivmecillinam users compared with nonusers was 2.03 (95% CI, 0.77-5.33) and the corresponding OR for use of sulfamethizole was 1.53 (95% CI, 0.76-3.09). Exposure within 2 to 12 weeks before the miscarriage was not associated with an increased risk. The authors concluded that pivmecillinam use was associated with an increased risk of miscarriage, but that the risk was not significantly (p=0.64) different from the risk associated with use of sulfamethizole. The authors noted whether this association is causal, related to the symptoms of UTI or the underlying infection in itself, is not entirely clear as no significant difference in risk between use of sulfamethizole and pivmecillinam was identified.

  Reviewer's Comment
  DEPI II reviewed this study in detail, refer to conclusions described below.

- Nørgaard et al 2012[22] examined maternal infection during pregnancy and the risk of childhood epilepsy in a cohort study of singletons born in Denmark from 1998 through 2008 who survived ≥29 days. Out of 57,826 newborns prenatally exposed to maternal infection, maternal antibiotic use was recorded for 55,743 newborns. The incidence rate for epilepsy among singletons prenatally exposed to maternal infection (defined by exposure to any antibiotic) was higher than in unexposed singletons, with an adjusted incidence rate ratio (IRR) of 1.40 (95% CI, 1.22-

[21] Nørgaard M, et al. Risk of miscarriage for pregnant users of pivmecillinam: a population-based case-control study. APMIS 2008;116:278-283.
[22] Nørgaard M, et al. Maternal use of antibiotics, hospitalization for infection during pregnancy, and risk of childhood epilepsy: a population-based cohort study. PLoS One 2012;7:e30850.

1.61). For the group where prenatal exposure was to pivmecillinam, the adjusted IRR was 1.55 (95% CI, 1.25-1.93). For the other antibiotic groups listed (penicillin V, other penicillins, sulfonamide/trimethoprim, and macrolides), adjusted IRRs ranged from 1.42 to 1.61.

Reviewer's Comment
DEPI II determined this study was not of significant rigor for full review.

Overview of DEPI II Review
DPMH met with the DEPI II Review Team on 1/24/24 and 2/6/24 to discuss the applicant's submitted published literature as described above. DEPI II performed a systemic literature search in PubMed and reviewed the applicant's submitted publications. Only studies considered to have quality design features were considered for final in-depth review by DEPI II. Refer to the DEPI II by Ikponmwosa Osaghae, MD, PhD for details of the search criteria and evaluation of selected studies. In brief, only 4 published studies met criteria for DEPI II review. Two studies were identified by the applicant as already described above (Damkier et al 2019 and Norgaard et al 2008) and 2 additional studies were identified by DEPI II (Nordeng et al 2013[23] and Hjorth et al 2022[24]) that were not submitted by the applicant as described below.

- *Nordeng et al 2013: A population-based cohort study using the Norwegian Prescription Database linked to data on all live births, stillbirths, and induced abortions after 12 weeks of gestation from The Medical Birth Registry of Norway. The study population consisted of 180,120 pregnancies in 2004-2008. The pregnancy outcomes of women who were dispensed nitrofurantoin during pregnancy were compared with the outcomes of women who were dispensed pivmecillinam (disease comparison group) and unexposed women. The pivmecillinam group consisted of 5,800 (3.2%) exposed during the first trimester, 16,363 (9.1%) during the second trimester, third trimester, or second and third trimester, and 20,643 (11.5%) in total during pregnancy.*

  5,794 (3.2%) filled prescriptions for nitrofurantoin during pregnancy, 1,334 women (0.7%) in the first trimester and 979 women (0.5%) in the last 4 weeks of pregnancy. Dispensing nitrofurantoin during the first trimester was not associated with increased risk of major malformations (31 of 1,334 [2.3%]) compared with disease controls (162 of 5,800 [2.8%], OR 0.79, 95% CI (0.51-1.23). No increased risk for secondary adverse pregnancy outcomes was observed when compared with the disease comparison group. Dispensing nitrofurantoin the last 30 days before delivery was associated with increased risk of neonatal jaundice (103 of 959 [10.8%]) compared with unexposed women (10,336 of 127,507 [8.1%], OR 1.31, 95% CI 1.02-1.70).

[23] Nordeng et al., 2013. Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol. 2013 Feb;121(2 Pt 1):306-313. doi: 10.1097/AOG.0b013e31827c5f88. PMID: 23344280.
[24] Hjorth et al., 2022. Prenatal exposure to nitrofurantoin and risk of childhood leukaemia: a registry-based cohort study in four Nordic countries. International Journal of Epidemiology, 2022, 778-788. 2021.

- *Hjorth et al 2022: A population-based cohort study of children born in Denmark, Finland, Norway or Sweden from 1997 to 2013, prenatal exposure to nitrofurantoin or pivmecillinam (active comparator) was ascertained from national Prescription Registries. Childhood leukaemia was identified by linkage to national Cancer Registries. Poisson regression was used to estimate incidence rate ratios (IRRs) and incidence rate differences (IRDs) with inverse probability of treatment weights applied to account for confounding.*

  A total of 44,091 children prenatally exposed to nitrofurantoin and 247,306 children prenatally exposed to pivmecillinam were included. The children were followed for 9.3 years on average (standard deviation 4.1). There were 161 cases of childhood leukaemia. The weighted IRR for prenatal nitrofurantoin exposure when compared with pivmecillinam was 1.34 (95% confidence interval 0.88, 2.06), corresponding to an IRD of 15 per million person-years. Higher point estimates were seen for first- and third-trimester exposure. There was no evidence of a dose–response relationship.

DEPI II noted the four observational studies reviewed found no evidence of increased risk of adverse pregnancy, maternal, and infant outcomes among pregnant women exposed to pivmecillinam. Among the two cohort studies that assessed the risk of malformations following pivmecillinam use during pregnancy, either found an association between first trimester exposure and the risk of congenital malformations when compared to penicillin duratives or nitrofurantoin. One of the cohort studies assessed several infant outcomes following in utero exposure to pivmecillinam and reported no association with the risk of stillbirth, neonatal death, low birth weight, preterm deliveries, NICU admissions, Apgar score lower than 7 at 5 minutes, and neonatal jaundice compared to nitrofurantoin. The single case control study suggested pivmecillinam may be associated with increased risk of miscarriage. The other cohort study reported no association between in utero exposure to pivmecillinam and the risk of childhood leukemia compared to nitrofurantoin. DEPI II stated the four reviewed studies are limited by biases such as exposure misclassification, outcome misclassification, and unmeasured confounding, to different extent. Overall, DEPI II concluded the data on malformations seems to have better quality than data on other outcomes. Refer below to the DEPI II and DPMH recommendations for 8.1 Pregnancy labeling.

DPMH's Review of Published Literature

DPMH performed a literature search in PubMed, Embase, Micromedex[25], TERIS[26], Reprotox[27], and Briggs[28] to find any relevant articles regarding pivmecillinam use during pregnancy. Search terms included: "pivmecillinam" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage."

[25]Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 2/5/2024.
[26]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 2/5/2024.
[27]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 2/5/2024.
[28] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide, 9th Ed. 2011.

- Reprotox database states "amdinocillin exposure during pregnancy as amdinocillin pivoxil (pivmecillinam) was not associated with an increase in congenital anomalies in human reports. A suspected increase in miscarriage risk has not been confirmed as causally related to the drug exposure. Studies already reviewed above are described.

- No additional relevant publications were identified.

Applicant's Review of Pharmacovigilance Database

On January 8, 2024, the applicant responded to DPMH IR to provide a cumulative review of available pharmacovigilance data related to use of pivmecillinam in pregnancy. The applicant noted that UTILITY therapeutics Ltd. Acquired the safety database from LEO Pharma A/S on May 15, 2018. UTILITY is not in possession of case report forms from the safety database and pharmacovigilance data is only available up until the transfer data of February 28, 2021. Thus, the applicant reviewed public data from the European Medicines Agency (EMA) and aggregate data from the marketing authorization holder outside the US (Karo Pharma, Sweden) to include data from February 28, 2021 to until present. A line listing of suspected adverse drug reactions for pivmecillinam covering the period of January 1, 2019 to November 9, 2023 was downloaded and included in the review. The applicant noted that "only a low number of events related to Pregnancy, Lactation, and Females and Males of Reproductive Potential have been reported cumulatively and no specific areas of concern have been identified.

- Stillbirths and miscarriages (N=5): the MedDRA SMQ "Termination of pregnancy and risk of abortion" was used when searching for stillbirths (n=2) and miscarriages (n=2) or abortions (n=1). Cases are briefly described below.
    - Abortion: anencephaly (maternal UTI at 11 weeks, pivmecillinam treatment x 1 day, ultrasound at 16 weeks identified anencephalic fetus which was aborted. No additional information provided.
    - Miscarriage: 10 weeks gestation, patient treated with mecillinam and doxycycline during pregnancy. No additional information provided.
    - Miscarriage: maternal treatment with pivmecillinam for UTI, 1 day later experienced miscarriage at 6 weeks gestation. No additional information provided.
    - Stillbirth: maternal treatment with pivmecillinam at 23 weeks for bacteriuria; underlying maternal disease (hypertension, diabetes, and anemia); concomitant medications (methyldopa, nitrazepam, cyanocobalamin, folic acid, and ferrous fumarate); stillbirth at 36 weeks (postmortem reported indicated congenital heart disease-enlarged right ventricle).
    - Stillbirth: literature report of maternal treatment with pivmecillinam for UTI. Underlying medical history of miscarriage, prior stillbirth, maternal chronic disease, recurrent UTI in pregnancy, and smoking. No additional details provided.

- Livebirths with congenital anomalies (N=10): the MedDRA SMQ "Congenital, familial and genetic disorders" was used when searching for congenital anomalies (n=10 cases with a total of 14 congenital anomalies events). Refer to applicant's Table 1 below for details.[29]

Table 1: Number of reported congenital anomalies by MedDRA SOC and PT

MedDRA SOC / PT	Spontaneous	Spontaneous, literature	Total
Congenital, familial and genetic disorders	**7**	**7**	**14**
Atrial septal defect	0	1	1
Cleft lip	0	1	1
Cleft palate	1	1	2
Congenital anomaly	0	1	1
Congenital eye disorder	1	0	1
Congenital hand malformation	1	0	1
Deafness congenital	1	0	1
Ductus arteriosus stenosis foetal	1	0	1
Epilepsy congenital	0	1	1
Multiple congenital abnormalities	1	1	2
Syndactyly	1	0	1
Ventricular septal defect	0	1	1
Total	**7**	**7**	**14**

- Interference with neonatal screening tests: In the PSUR covering 01Jul2020 to 30Jun2021 Karo Pharma commented: "During this review period 13 non-serious cases were received from the same reported (other healthcare professional) in UK via the MRHA portal within 2 days reporting "laboratory test interference" in neonates. The laboratory test interference resulted in no medical side effects in the babies. Limited information was available for these cases." The applicant noted that interference with neonatal screening tests for isovaleric acidemia is listed in the proposed USPI.

Reviewer's Comment
DPMH Maternal Health Team defers the review of the reported cases of laboratory test interference and labeling recommendations to the DPMH Pediatrics Team who is also consulting on this application. Briefly, DPMH Pediatrics Team is recommending adding a Warning and Precaution to labeling to alert healthcare providers that treatment of pregnant individuals with pivmecillinam prior to delivery may cause a false positive for isovaleric acidemia in the newborn as part of newborn screening. For details, refer to the DPMH Pediatrics Review Memo by Sonaly McClymont, MD.

- Perinatal Complications: the MedDRA SMQ "Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth)" was used when searching for perinatal complications. No events were identified in Utility's safety

[29] Table 1 from Applicant's Response to FDA IR dated 12/6/23.

database, the Karo aggregate Safety Update Reports or in the Eudravigilance database line listing.

LACTATION

Nonclinical Experience

In a study of lactating cows given 8 mg/kg mecillinam IV, an amount corresponding to the human dose, the concentration in milk was 0.1 and 0.7 µg/mL at 2 and 6 hours, respectively, and the total excretion in milk over the first 6 hours was 0.03% of the injected dose. For more information, refer to the Nonclinical Review by Amy Ellis, PhD.

Clinical Experience

Applicant's Review of Published Literature

The applicant did not perform a review of published literature for lactation data.

DPMH's Review of Published Literature

DPMH performed a literature search in LactMed[30], *Medications and Mother's Milk*[31], Micromedex,[25] Reprotox[27], PubMed, and Embase to find any relevant articles related to pivmecillinam use during lactation. Search terms included: "pivmecillinam "lactation" OR "breastfeeding." The following articles were identified:

- The **LactMed** database summary of use during lactation for pivmecillinam (alternative name: amdinocillin) states: "limited information indicates that amdinocillin produces low levels in milk that are not expected to cause adverse effects in breastfed infants. Monitor the breastfed infant for diarrhea and thrush." The following additional information is provided:
    - Maternal drug levels: Four women who were 4 or 6 days postpartum were given a single 100 mg dose of amdinocillin. The drug was not detectable in breastmilk 1 or 3 hours after the dose, although the sensitivity of the assay is unknown.[32,33]
    - No relevant published information was found on infant drug levels, effects in breastfed infants, or effects on lactation and breastmilk.

- The Reprotox database for amdinocillin states: "We have not located information on possible lactation effects of amdinocillin or pivmecillinam. According to product labeling for pivmecillinam, amdinocillin is excreted into human milk.[34]"

[30] Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501922/.
[31] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.
[32] Seiga K, Minagawa M, Yamaji K, et al. Studies on pivmecillinam. Chemotherapy (Tokyo). 1977;25:347–51.
[33] Neu HC, Amdinocillin: A Novel Penicillin. Antibacterial Activity, Pharmacology and Clinical Use. Pharmacotherapy 1985;5:1-10.
[34] Karo Pharma AB. 2019. Selexid tablets product information. Available at https://www.medicines.org.uk/emc/product/3799/smpc

Reviewer's Comment
The applicant's proposed labeling states that (b) (4)

(b) (4)

Applicant's Review of Pharmacovigilance Database
The safety database was searched using the MedDRA PT "Exposure via breast milk" to identify relevant cases. Four relevant cases were identified and classified as non-serious as described below. The applicant stated that relevant case information was identified in the Karo aggregate Safety Update Reports or in the Eudravigilance database line listing.

- Diarrhea, regurgitation, stomachache, drug exposure via breastmilk in a 2.5 month old infant exposed to pivmecillinam (strength 200 mg x 1 day) via breastmilk.
- Fever and generalized rash reported in a female baby whose mother was using pivmecillinam during breastfeeding. The baby also began breathing quickly such that the mother sought emergency care.
- Drug exposure via breastmilk in a newborn with no additional information
- Drug exposure via breastmilk with no adverse event reported in a neonate whose mother was treated with pivmecillinam for 5 days while breastfeeding.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Mecillinam had no adverse effect on fertility in male or female rats at subcutaneous doses up to 450 mg/kg/day (approximately 7.9-fold higher than the maximum recommended daily human dose based on body surface area). Pivmecillinam had no adverse effect on fertility in male or female rats at oral doses up to 582 mg/kg/day (approximately 10.2-fold higher than the maximum recommended daily human dose based on body surface area). For more information, refer to the Nonclinical Review by Amy Ellis, PhD.

Clinical Experience
Applicant's Review of Published Literature
The applicant did not perform a review of published literature regarding the use of pivmecillinam and effects on male or female fertility.

DPMH's Review of Published Literature
DPMH performed a literature search in PubMed, Embase, and Reprotox[27] to find any relevant articles regarding pivmecillinam use and effects on fertility. Search terms included: "pivmecillinam" AND "fertility," "contraception," "oral contraceptives," OR "infertility."

- Reprotox database summary on reproduction for amdinocillin states "we have not located information on possible effects on fertility in men or women. Pivmecillinam therapy can alter vaginal flora.[35]

Applicant's Review of Pharmacovigilance Database

The applicant searched the safety database using the MedDRA SMQ "Fertility disorders." Two relevant cases were identified as described below. The applicant stated that no relevant case information was identified in the Karo aggregate Safety Update Reports or in the Eudravigilance database line listing.

- Bladder pain, aggravated cystitis, irregular menstruation, and urethral irritation was reported in a 13-year-old female treated with pivmecillinam for cystitis. Co-suspected medications included nitrofurantoin, sulfametizol, trimethoprim and ciprofloxacin all for cystitis. Medical history included hyperactive bladder, stomach pain, painful urination, irregular and painful menstruation. Concomitant medications included morphine and mirabegron. After treatment with pivmecillinam, the patient experienced aggravated cystitis, pain in bladder, bladder cramps, irregular menstruation and irritation in the urethra. The patient suspected the cause was all the products used throughout the years. The former sponsor noted the patient also had MRI and CT scans suggestive of alternative etiologies for her symptoms.
- Pregnancy on oral contraceptive and premature delivery were reported in a 19 year-old female whose treatment with pivmecillinam occurred before the last menstrual period. Compliance with the oral contraceptive was not reported.

Reviewer's Comment

The 2 pharmacovigilance cases above are unlikely related to pivmecillinam treatment. Regarding the case of bladder pain, aggravated cystitis, irregular menstruation, and urethral irritations, the patient was treated with several concomitant medications and per history likely has an underlying medical condition causing symptoms as opposed to medication side effects. For the case of contraceptive failure, the treatment with pivmecillinam occurred prior the LMP and the compliance with oral contraceptive was not reported.

DISCUSSION/CONCLUSIONS

Pregnancy

Available data from four published epidemiologic studies (including 3 cohort studies and 1 case-control study) were determined to be robust for review by DEPI II. DEPI II and DPMH discussed the available data and have concluded published literature from observational studies on pivmecillinam use during the first trimester do not indicate an increased risk of major birth defects. There are limited studies on pivmecillinam use during pregnancy and the risk of miscarriage or other adverse maternal or fetal outcomes, which have methodological limitations hindering interpretation. DPMH recommends including this information in subsection 8.1 Risk Summary and Human Data sections. Nonclinical data do not indicate an increased risk for adverse pregnancy outcomes and

[35] Sullivan A, Fianu-Jonasson A, Landgren BM, Nord CE. Ecological effects of perorally administered pivmecillinam on the normal vaginal microflora. Antimicrob Agents Chemother. 2005 Jan;49(1):170-5.

will be described in the Risk Summary and Animal Data sections of pivmecillinam labeling.

DPMH discussed submitted published pregnancy PK data with the Clinical Pharmacology Team who recommends including a statement in the Risk Summary and Clinical Considerations that no dose adjustment is required in pregnant women. The Clinical Pharmacology Team noted the available data from published literature indicate no clinically significant differences in mecillinam pharmacokinetics were observed in pregnant compared to non-pregnant women. Additionally, the DPMH Pediatrics Team also recommends including a Clinical Considerations heading "Interference with Newborn Screening Test" based on their review of available data which indicates intake of pivmecillinam administration prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening.

Regarding postmarketing requirements (PMRs), pivmecillinam is anticipated to be widely used in females of reproductive potential, including pregnant women. There is over 40 years of postmarketing experience outside of the US and several published studies that do not indicate an increased risk of congenital malformation or other adverse maternal or fetal outcomes. Given the overall reassuring human safety data from outside the US over several decades of use of pivmecillinam, DPMH and DEPI II do not recommend issuing a PMR for pregnancy registry or claims study.

Lactation

Approved labeling outside of the US for pivmecillinam states "mecillinam is present in human milk" however the source of this information is unclear. No published literature were identified that describe the presence of mecillinam in human milk. Review of the published literature identified 1 publication indicating pivmecillinam was not detected in the milk of 4 lactating women at 1 to 3 hours after a single dose, however, the available data are insufficient to exclude the presence of pivmecillinam in human milk given the small study size, limited timepoints of evaluation, and inadequate description of the bioanalytical methods. Therefore, DPMH recommends labeling subsection 8.2 for pivmecillinam include a statement that there are insufficient data regarding the presence of mecillinam in human milk.

Review of the pharmacovigilance database from approval outside of the US noted 4 reported cases of pivmecillinam exposure in breastfed infants (2 with no adverse events; 2 cases with non-serious adverse events: 1 case of diarrhea, regurgitation, stomachache and 1 case of fever and rash with rapid breathing). DPMH recommends including a description of the postmarketing cases of rash and diarrhea in subsection 8.2 of labeling, to alert prescribers to monitor for these potential adverse reactions in the breastfed infant exposed to pivmecillinam. There are no data on the effects of pivmecillinam on milk production.

Regarding the overall breastfeeding recommendation, DPMH recommends including the following benefit/risk statement regarding use pivmecillinam use during lactation: "The developmental and health benefits of breastfeeding should be considered along with the

mother's clinical need for pivmecillinam and any potential adverse effects on the breastfed infant from pivmecillinam or from the underlying maternal condition."

Considering pivmecillinam is anticipated to be widely used in females of reproductive potential, including lactating women, and there are insufficient data regarding the presence of mecillinam in human milk, DPMH recommends the applicant perform a clinical lactation study. The objective of the lactation study is to evaluate concentrations of pivmecillinam and its active metabolite (mecillinam) in human milk and any adverse effects on the breastfed infant. Therefore, DPMH recommends DAI issue a PMR for a milk-only lactation study at approval.

Fertility

DPMH recommends omitting subsection 8.3 of pivmecillinam labeling. Available nonclinical data to not indicate pivmecillinam adverse effects fertility in animal studies. Further, DPMH did not identify any human data to suggest pivmecillinam use would have an adverse effect on male or female fertility. Pregnancy testing and contraception headings will not be included.

LABELING RECOMMENDATIONS

DPMH proposed labeling recommendations for subsections 8.1 and 8.2 of pivmecillinam labeling for compliance with the PLLR (see below). DPMH discussed the labeling recommendations below with DAI on February 13, 2024. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pivmecillinam Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published observational studies on pivmecillinam use during the first trimester do not indicate an increased risk of major birth defects. There are limited studies on pivmecillinam use during pregnancy and the risk of miscarriage or other adverse maternal or fetal outcomes, which have methodological limitations hindering interpretation *(see Data).* No dose adjustment is required in pregnant women *(see Clinical Considerations).*

Developmental toxicity studies with pivmecillinam or mecillinam administered during organogenesis to rats and mice showed no evidence of embryo-fetal toxicity, including drug-induced fetal malformations, at doses approximately 3.4 or 7.9 times (rats) or 5.1 or 3.9 times (mice) higher than given to patients receiving the maximum recommended daily dose (b) (4). Evidence of slight fetotoxicity (reduced ossification) was seen in offspring of rats that were given pivmecillinam during organogenesis at a dose approximately 10.2-fold higher than the maximum recommended daily human dose (b) (4).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, and other

adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Interference with Newborn Screening Test

Treatment of a pregnant individual with pivmecillinam prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening *[see Warnings and Precautions (5.6) aDrug Interactions (7.2)]*.

Dose Adjustment During Pregnancy and Postpartum

[redacted]

Data

Human data

Two cohort studies in 42,223 pregnant women who were exposed to pivmecillinam during the first trimester did not observe an increased risk of major birth defects when compared to 50,099 pregnant women exposed to other antibacterial drugs. These two studies were limited by potential exposure misclassification.

Animal data

Pivmecillinam administered during the period of organogenesis had no adverse effects on embryofetal development in rats or mice at oral doses up to [redacted] mg/kg/day in rats and [redacted] mg/kg/day in mice. These doses are approximately [redacted]-fold and [redacted]-fold higher than the maximum recommended daily human dose based on body surface area, respectively. There was a skeletal variation (reduced ossification of sternebrae, possibly indicating slight fetotoxicity) in offspring of rats treated at [redacted] mg/kg/day (approximately [redacted]-fold higher than the maximum recommended daily human dose based on body surface area). Mecillinam did not cause adverse effects on embryofetal development in rats and mice when administered by subcutaneous injection at doses up to 450 mg/kg/day (approximately 7.9-fold and 3.9-fold higher than the maximum recommended daily human dose based on body surface area, respectively). In pre- and postnatal studies in rats where maternal animals were dosed beginning during gestation (Day 15) and continuing throughout the weaning period, neither pivmecillinam nor mecillinam had adverse effects on the maternal animals or on the survival and development of the offspring. Pivmecillinam was given orally at doses up to [redacted] mg/kg/day and mecillinam was given subcutaneously at doses up to 450 mg/kg/day (approximately [redacted]-fold and 7.9-fold higher than the maximum recommended daily human dose of Pivya, based on body surface area, respectively).

8.2 Lactation

Risk Summary

There are insufficient data to exclude the presence of mecillinam in human milk. Mecillinam is present in animal milk *(see Data)*. When a drug a present in animal milk, it is likely to be present in human milk. There are pharmacovigilance reports of adverse

reactions with mecillinam exposure in breastfed infants, including rash and diarrhea. There are no data on the effects of mecillinam on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pivmecillinam and any potential adverse effects on the breastfed infant from pivmecillinam or from the underlying maternal condition.

Data

Animal data

In a study of lactating cows given 8 mg/kg mecillinam IV, the concentration in milk was 0.1 and 0.7 µg/mL at 2 and 6 hours, respectively, and the total excretion in milk over the first 6 hours was 0.03% of the injected dose.

Appendix A: Applicant's Table 3: Comparative Studies Reporting Safety Outcomes For Pivmecillinam Regimens

Reference, study design, country	Safety population	Treatment dose and duration	Overall safety, n (%)	Specific safety events, n (%)				Discontinued due to AEs, n
				GI tract related	Skin related	Reproductive related	Other	
Pivmecillinam in pregnancy‡								
Sanderson et al 1984[32] Clinical trial UK	PIV: 44 PIV prophylactically: 12 **Mean (range) age:** PIV: 25.5 (17-44) y Women with bacteriuria in pregnancy (treated from between 10 and 28 wk of pregnancy)	PIV 200 mg tid 7 d PIV prophylactically100 mg alternate days	PIV: 2 PIV prophylactically: 2	**PIV:** •Diarrhea: 1 •Nausea and vomiting: 1 **PIV prophyl-actically:** •Nausea: 1 •Vomiting: 1	NR	NR	NR	**PIV:** 2 (nausea and vomiting: 1, diarrhea: 1) **PIV prophyl-actically:** 1
Brumfitt et al 1979[26] Clinical trial England	PIV: n=49 Cephradine: n=49 **Mean (SD) age:** **PIV:** Nonpregnant: 35.0 (14.5) y Pregnant: 26.2 (5.9) y **Cephradine:** Nonpregnant: 33.5 (12.4) y Pregnant: 26.1 (5.1) y Nonpregnant and pregnant women treated for bacteriuria	PIV 400 mg q6h for 7 d Cephradine 500 mg q6h for 7 d	PIV: 16 (33) Cephradine: 25 (51)	**PIV:** •GI: 10 **Cephradine:** •GI: 11	NR	NR	**PIV:** •Vaginal irritation: 3 •Others: 4 **Cephradine:** •Vaginal irritation: 15 •Others: 5	**PIV:** 4 (8) **Cephradine:** 3 (6)
Bint et al 1979[52] Clinical trial	N=100 (total patients), *Comparative arm:* Ampicillin: n=48	*Comparative arm:* PIV 400 mg qid 7 d	*Comparative arm:*	*Comparative arm:* **Ampicillin:**	**Ampicillin** •Pruritus: 1 (2)	NR	*Comparative arm:* **Ampicillin:** •Felt unwell: 1 (2)	NR

Reference, study design, country	Safety population	Treatment dose and duration	Overall safety, n (%)	Specific safety events, n (%)				Discontinued due to AEs, n
				GI tract related	Skin related	Reproductive related	Other	
UK	PIV: n=37 PIV tablets: n=12 *Low-dose follow-up:* PIV 200 mg: n=20 Women with bacteriuria of pregnancy	Ampicillin 500 mg qid 7 d *Low-dose follow-up:* PIV 200 mg tid 7 d	Ampicillin 500 mg: 11 (23) PIV 400 mg: 21 (57) PIV 400 mg tablets: 7 (58) *Low-dose follow-up:* PIV 200 mg: 5 (25)	•Anorexia and/or nausea: 5 (10) •Vomiting: 3 (6) •Diarrhea: 2 (4) **PIV 400 mg:** •Vomiting: 13 (35) •Anorexia and/or nausea: 5 (14) •Diarrhea: 1 (3) •Indigestion: 1 (3) •Epigastric fullness: 1 (3) **PIV 400 mg tablets:** •Anorexia and/or nausea: 3 (25) •Vomiting: 1 (8) *Low-dose follow-up:* **PIV 200 mg**			**PIV 400 mg:** •Headache: 2 (6) •Dizzy and lightheaded: 1 (3) **PIV 400 mg tablets:** •Headache: 2 (16) •Dizzy and light headed: 1 (8) *Low-dose follow-up:* •Others: 2 (10)	

Reference, study design, country	Safety population	Treatment dose and duration	Overall safety, n (%)	Specific safety events, n (%)				Discontinued due to AEs, n
				GI tract related	Skin related	Reproductive related	Other	
				•Vomiting: 1 (5) •Anorexia and/or nausea: 4 (20)				

* Age for efficacy population.
† Denotes that this study is included within the UTILITY Therapeutics FDA New Drug Application for pivmecillinam.
‡ Three studies analyzing safety outcomes in pregnancy are reported in this table while the remaining eight studies are reported in Table 4.
AE, adverse event; bid, twice daily; BUN, blood urea nitrogen; d, days; GI, gastrointestinal; h, hours; IM, intramuscular; IV, intravenous; MEC, mecillinam; mo, months; NR, not reported; PIV, pivmecillinam; q6h, every 6 hours; qday, once daily; qid, four times daily; RCT, randomized controlled trial; RTI, respiratory tract infection; SAE, serious adverse event; SD, standard deviation; SGOT, serum glutamic-oxaloacetic transaminase; tid, three times daily; TMP-SMX, trimethoprim-sulfamethoxazole; UK, United Kingdom; US, United States; UTI, urinary tract infection; wk, weeks; y, years.

APPENDIX B: Applicant's Table 4. Studies Reporting Safety Outcomes in Pregnancy

Reference, study type, country	Safety population	Treatment name	Safety outcomes
Molgaard-Nielsen et al 2012[36] Registry Denmark	First trimester (cleft lip with or without cleft palate): n=18 First trimester (cleft palate alone): n=13 Second month (cleft lip with or without cleft palate): n=6 Third month (cleft palate alone): n=9 Singleton live births	Pivmecillinam*	**Risk of isolated orofacial clefts, adjusted POR (95% CI):** •First trimester (cleft lip with or without cleft palate): NR •First trimester (cleft palate alone): NR •Second month (cleft lip with or without cleft palate): NR •Third month (cleft palate alone): 2.34 (1.20-4.54)
Larsen et al 2001[31] Population based follow-up study Denmark	N=414 **Mean (range) age:** Pivmecillinam prescriptions during first trimester: 25.8 (17-41) y Pivmecillinam prescriptions at any time during pregnancy: 25.6 (16-43) y Pregnant women who had redeemed prescriptions for pivmecillinam	Pivmecillinam	**Pivmecillinam prescriptions during first trimester:** •Number of congenital abnormalities: 2 •Number of children with low birth weight: 4 •Number of preterm deliveries: 5 •Number of stillborn babies (before birth): 1 •Number of stillborn babies (during birth): 1 **Pivmecillinam prescribed at any time during pregnancy:** •Number of congenital abnormalities: 12 •Number of children with low birth weight: 17 (5) •Number of preterm deliveries: 24 •Number of stillborn babies (before birth): 1 •Number of stillborn babies (during birth): 1
Skriver et al 2004[33] Observational study Denmark	Prescriptions taken up during entire pregnancy: n=2031 Prescriptions taken up within first trimester: n=559 Prescriptions taken up 28 d before delivery: n=371 Women with a live birth, or stillbirth after the 28th week of gestation	Pivmecillinam	**Risk of adverse birth and neonatal outcomes, adjusted OR (95% CI); exposure 28 d before delivery** •Birth defects for exposure during first trimester: 0.83 (0.53-1.32) •Birth defects without chromosomal abnormalities: 0.83 (0.53-1.32) •Preterm delivery: 0.96 (0.79-1.18) •Low birth weight for exposure at any time during pregnancy: 0.79 (0.52-1.20) •Stillbirth: 1.19 (0.30-4.80) •Low Apgar score: 1.17 (0.37-3.66)

Reference, study type, country	Safety population	Treatment name	Safety outcomes
			•Hypoglycemia: 1.03 (0.53-2.00) •Respiratory distress syndrome: 0.79 (0.38-1.68)
Damkier et al 2019[60] Cohort study Denmark	Overall population: Exposed to study antibiotic: n=82 318 Exposed to reference penicillin: 48 765 Unexposed population: 801 648 Singleton pregnancies resulting in a live birth of an infant without chromosomal abnormalities	Pivmecillinam, sulfamethizole, and azithromycin	Exposed to study antibiotic: inferential analysis did not identify any association between exposure and any of the three outcomes (major congenital malformations, cardiac malformation, and any malformation), compared with the primary control cohort (penicillin group) in the fully adjusted model •Any malformations: 2291 •Major malformations: 1286 •Cardiac malformations: 380 **Compared with unexposed pregnancies:** *Pivmecillinam* •Risks for major malformations: OR, 1.13; 95% CI, 1.06-1.19 •Risk for cardiac malformations: OR, 1.15; 95% CI, 1.04-1.28 *Sulfamethizole* •Risks for major malformations: OR, 1.15; 95% CI, 1.07-1.24 •Risk for cardiac malformations: OR, 1.22; 95% CI, 1.07-1.39 *Azithromycin* •Risks for major malformations: OR, 1.19; 95% CI, 1.03-1.38 •Risk for cardiac malformations: OR, 1.29; 95% CI, 0.99-1.67
Miller et al 2012[34] Registry Denmark	•Mothers exposed, at any time during pregnancy, to any cystitis antibiotic: n=68 820 •Mothers exposed, at any time during pregnancy to pivmecillinam: n=34 609 •One redeemed prescription (pivmecillinam, sulfamethizole, and nitrofurantoin): n=36 072 •One redeemed prescription (pivmecillinam): n=15 975 •>1 redeemed prescriptions (pivmecillinam, sulfamethizole, and nitrofurantoin): n=32 748 •>1 redeemed prescriptions (pivmecillinam): n=18 634 Children diagnosed with epilepsy	Pivmecillinam, sulfamethizole, nitrofurantoin	**Risk of childhood epilepsy, n (%)** •Mothers exposed, at any time during pregnancy, to any cystitis antibiotic: 500 (18) •Mothers exposed, at any time during pregnancy to pivmecillinam: 233 (8) •One redeemed prescription (pivmecillinam, sulfamethizole, and nitrofurantoin): 232 (8) •One redeemed prescription (pivmecillinam): 96 (3) •>1 redeemed prescriptions (pivmecillinam, sulfamethizole, and Nitrofurantoin): 268 (9) •>1 redeemed prescriptions (pivmecillinam): 137 (5) **Risk of childhood epilepsy, OR (95% CI)**

Reference, study type, country	Safety population	Treatment name	Safety outcomes
			•Mothers exposed, at any time during pregnancy, to any cystitis antibiotic: 1.2 (1.1-1.3) •Mothers exposed, at any time during pregnancy, to pivmecillinam: 1.2 (1.0-1.4) •One redeemed prescription (pivmecillinam, sulfamethizole, and nitrofurantoin): 1.1 (0.9-1.2) •One redeemed prescription (pivmecillinam): 1.1 (0.9-1.3) •>1 redeemed prescriptions (pivmecillinam, sulfamethizole, and nitrofurantoin): 1.3 (1.2-1.5) •>1 redeemed prescriptions (pivmecillinam): 1.3 (1.1-1.5)
Miller et al 2013[35] Registry (population-based cohort) Denmark	Exposed to: •Pivmecillinam: n=34 596 •Penicillin V: n=79 063 •Sulfamethizole: n=37 648 •Erythromycin: n=15 886 •Nitrofurantoin: n=6926 Children with a diagnosis of febrile seizures and children born to women who took at least one type of antibiotic during pregnancy (exposed) Unexposed: N=378 639 Children of women who did not take any antibiotics during pregnancy (unexposed)	Pivmecillinam, penicillin V, sulfamethizole, erythromycin, nitrofurantoin	**1. Risk of febrile seizures in the children, according to antibiotic exposure, n; adjusted HR (95% CI):** •Pivmecillinam: 1508; 1.12 (1.06-1.18) •Penicillin V: 3242; 1.06 (1.02-1.10) •Sulfamethizole: 1649; 1.12 (1.06-1.18) •Erythromycin: 638; 1.03 (0.95-1.11) •Nitrofurantoin: 312; 1.16 (1.04-1.29) •Unexposed: 14 550; 1.08 (1.05-1.11) **2. Risk of febrile seizures for children born at term with a birth weight >2500 g, no congenital malformations, and an Apgar score at 5 minutes of >10, n; adjusted HR (95% CI):** •Pivmecillinam: 1142; 1.13 (1.06-1.20) •Penicillin V: 2472; 1.06 (1.02-1.11) •Sulfamethizole: 1219; 1.11 (1.05-1.18) •Erythromycin: 470; 1.00 (0.92-1.10) •Nitrofurantoin: 235; 1.16 (1.02-1.32) •Unexposed: 10 942; reference, any systemic antibiotic: 1.08 (1.04-1.11) **3. Risk of febrile seizures in the children, by number of redeemed prescriptions during pregnancy, one redemption, n; adjusted HR (95% CI):** •Pivmecillinam: 814; 1.12 (1.04-1.20) •Penicillin V: 1826; 1.03 (0.98-1.08)

Reference, study type, country	Safety population	Treatment name	Safety outcomes
			•Sulfamethizole: 758; 1.08 (1.00-1.16) •Erythromycin: 274; 1.06 (0.94-1.19) •Nitrofurantoin: 94; 1.17 (0.95-1.43) •Unexposed: 14 550; reference, any systemic antibiotic: 1.06 (1.03-1.09) **4. Risk of febrile seizures in the children, by number of redeemed prescriptions during pregnancy, >1 redemption, n; adjusted HR (95% CI):** •Pivmecillinam: 694; 1.12 (1.04-1.21) •Penicillin V: 1416; 1.10 (1.04-1.16) •Sulfamethizole: 891; 1.16 (1.08-1.24) •Erythromycin: 364; 1.00 (0.90-1.11) •Nitrofurantoin: 218; 1.16 (1.01-1.32) •Unexposed: 14 550; reference, any systemic antibiotic: 1.11 (1.06-1.15)
Norgaard et al 2008[38] Case-control study Denmark	**Cases:** **Pivmecillinam:** •Overall: N=1599 Exposure to pivmecillinam: •Within 1 wk before hospitalization: n=5 •Within 2-3 wk before hospitalization: n=5 •Within 4-7 wk before hospitalization: n=4 •Within 8-12 wk before hospitalization: n=3 **Sulfamethizole:** Overall: N=1599 Exposure to sulfamethizole: •Within 1 wk before hospitalization: n=9 •Within 2-3 wk before hospitalization: n=9 •Within 4-7 wk before hospitalization: n=15 •Within 8-12 wk before hospitalization: n=4 **Penicillin V:**	Pivmecillinam, sulfamethizole, penicillin V, NSAIDs	**Risk of miscarriage, adjusted OR (95% CI):** **Pivmecillinam:** •Within 1 wk before hospitalization: 2.03 (0.77-5.33) •Within 2-3 wk before hospitalization: 1.10 (0.44-2.78) •Within 4-7 wk before hospitalization: 0.75 (0.27-2.10) •Within 8-12 wk before hospitalization: 1.27 (0.38-4.22) **Sulfamethizole:** •Within 1 week before hospitalization: 1.53 (0.76-3.09) •Within 2-3 wk before hospitalization: 0.92 (0.47-1.82) •Within 4-7 wk before hospitalization: 1.04 (0.61-1.77) •Within 8-12 wk before hospitalization: 0.52 (0.19-1.43) **Penicillin V:** •Exposure to penicillin V in the wk before the miscarriage was not associated with an increased risk of miscarriage (OR, 1.03; 95% CI, 0.41-2.61) Penicillin V (controls: reference)

Reference, study type, country	Safety population	Treatment name	Safety outcomes
	•Exposure to penicillin V within 12 wk before hospitalization: n=47 **NSAIDs:** •Exposure to NSAIDs within 12 wk before hospitalization: n=45 **Controls:** **Pivmecillinam:** •Overall: N=15 990 Exposure to pivmecillinam: •Within 1 wk before hospitalization: 24 •Within 2-3 wk before hospitalization: 44 •Within 4-7 wk before hospitalization: 52 •Within 8-12 wk before hospitalization: 25 **Sulfamethizole:** Overall: N=15 990 Exposure to sulfamethizole: •Within 1 week before hospitalization: n=62 •Within 2-3 wk before hospitalization: n=100 •Within 4-7 wk before hospitalization: n=151 •Within 8-12 wk before hospitalization: n=81 **Penicillin V:** •Exposure to penicillin V within 12 wk before hospitalization: n=463 **NSAIDs:** •Exposure to NSAIDs within 12 wk before hospitalization: n=297 **Cases** - defined as women who, during the study period, had a first-time recorded miscarriage and no previously recorded birth		**NSAIDs:** •When including use of NSAIDs, the risk estimates did not change substantially in any of the analyses (data not shown)

Reference, study type, country	Safety population	Treatment name	Safety outcomes
	Control - women with a first live birth during the study period and no previous recorded miscarriage in the Hospital Discharge Registry		
Norgaard et al 2012[37] Registry Denmark	Pivmecillinam: n=17 756 Penicillin V: n=27 150 Other penicillins: n=12 259 Sulfonamides/trimethoprim: n=12 748 Macrolides: n=5847 Unexposed: n=13 1307 Singletons born	Pivmecillinam, penicillin V, sulfonamides/ trimethoprim, macrolide, other penicillin	**Pivmecillinam:** •Risk of childhood epilepsy, n=106 •Adjusted IRR (95% CI): 1.55 (1.25-1.93) **Penicillin:** Penicillin V: •Risk of childhood epilepsy, n=177 •Adjusted IRR (95% CI): 1.56 (1.30-1.87) Other penicillins: •Risk of childhood epilepsy, n=79 •Adjusted IRR (95% CI): 1.46 (1.15-1.87) **Sulfonamides/trimethoprim:** •Risk of childhood epilepsy, n=83 •Adjusted IRR (95% CI): 1.42 (1.12-1.82) **Macrolides:** •Risk of childhood epilepsy, n=46 •Adjusted IRR (95% CI): 1.61 (1.15-2.25) **Unexposed:** •Risk of childhood epilepsy, n=587 •Adjusted IRR (95% CI): 1.0

* Study reports data for other antibiotics also.

CI, confidence interval; d, days; HR, hazard ratio; IRR, incidence rate ratio; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; POR, prevalence odds ratio; wk, weeks; y, years.

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LYNNE P YAO
03/20/2024 05:17:15 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 18, 2024

To: Joseph Nguyen, Regulatory Project Manager
Division of Anti-Infectives (DAI)

Leslie Ball, Clinical Reviewer, DAI

Abimbola Adebowale, Associate Director for Labeling, DAI

From: Qumerunnisa Syed, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for PIVYA (pivmecillinam) tablets, for oral use

NDA: 216483

Background:
In response to DAI's consult request dated December 11, 2023, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original NDA submission for PIVYA (pivmecillinam) tablets, for oral use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 12, 2024, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on March 12, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Qumerunnisa Syed at 301-796-8897 or Qumerunnisa.syed@fda.hhs.gov.

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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Clinical Inspection Summary

Date	14 March 2024
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Joseph Nguyen, PharmD, Regulatory Project Manager Leslie Ball, MD, Medical Officer Mayurika Ghosh, MD, Medical Team Lead Peter Kim, MD, Division Director
NDA #	216483
Applicant	Utility Therapeutics, LTD
Drug	Pivmecillinam
NME	No
Proposed Indication	For the treatment of uncomplicated urinary tract infections (uUTI), caused by susceptible (b) (4) and Staphyloccocus saprophyticus.
Consultation Request Date	5 December 2023
Summary Goal Date	24 March 2024
Action Goal Date	24 April 2024
PDUFA Date	24 April 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The applicant, Utility Therapeutics, LTD, was inspected in support of NDA 216483 covering one clinical trial, Protocol MET-9401 (Ferry Study).

During the inspection, uncertified scanned copies of case report forms, microbiology laboratory test results, and drug accountability and compliance logs were reviewed and verified against the legacy data line listings (i.e., that Utility submitted to the NDA) in all 113 randomized subjects at Site 45. Data related to the primary efficacy endpoint of overall success (i.e., microbiological and clinical success) were reviewed and verified and included signs and symptoms of infection, urine culture and susceptibility testing results, and urine culture concentrations documented at Visits 1, 2 and 3, as well as concomitant antibiotics other than antibiotics permitted in the protocol. Minor discrepancies were noted that had no impact on the subjects' overall response assessment of success, failure, or indeterminate. More information about review of these records and these discrepancies are described in more detail in Section III of this Clinical Inspection Summary (CIS).

Also noted during inspection was a data reliability concern related to changes Utility made to the original legacy dataset that Leo Pharma (the original sponsor of Protocol MET 9401) transferred to them. Utility performed verification of the original legacy dataset against scanned copies of the subject case report forms (CRFs) during the timeframe between the statistical analysis plan (SAP) Version 3 (dated 10 February 2021) and final SAP Version 4 (dated 13 December 2021). The source data verification entailed review of the microbiology data (e.g., culture, urine culture concentration in CFUs/mL, and susceptibility testing results) and clinical data (i.e., signs and symptom scores and adverse event data) at Visits 1, 2, and 3 in 91 (10%) randomly identified subjects.

As a result of this source data verification, Utility made 138 data changes in 55 subjects. The data changes included corrections made to subject initials, susceptibility results, signs and symptoms of infection at Visit 3, and follow-up adverse event information. Utility provided a listing of data changes made to the microbiology and clinical data; however, audit trails that tracked these and potentially other changes were not available for inspectors to review. After the inspection, each of the 138 data changes were reviewed and verified against the original scanned copies of the CRFs for the 55 subjects. No discrepancies were noted. Furthermore, none of the data changes appear to impact the individual subject's overall response assessment (i.e., success, failure, or indeterminate) at the test of cure (TOC) visit or inclusion in or exclusion from the micro-ITT analysis set. See Section III of this CIS for more information about these data changes.

More importantly, there was a lack of audit trails available for review and verification purposes to ensure that no other changes were made to the data beyond the changes Utility identified in their listing of data changes. In a 4 March 2024 IR response, Utility further explained that the data changes were applied in the creation and incorporated directly into the ADaM datasets created by them and a formal audit trail to track the data changes was not available. In addition, Utility explained the difficulty in comparing the original legacy study data (transferred to them by Leo Pharma) to the ADaM dataset because there is not a one-to-one match between the variables contained in original dataset and the ADaM dataset (e.g., variable AEYN in the original dataset does not exist in the ADaM dataset). The review division should be aware that the lack of audit trails and comparability between the datasets (i.e., legacy dataset and ADaM dataset) make it difficult to verify whether any additional changes were potentially made to other study data beyond those that Utility identified as being made in 55 of the 91 subjects whose data underwent the source data verification. The review division should consider the lack of adequate tracking of data changes via audit trails in ADaM datasets in the review of the overall efficacy and safety results as presented in the applicant's overall summary of efficacy.

II. BACKGROUND

NDA 216483 was submitted to support the use of pivmecillinam (an oral prodrug of mecillinam) for the treatment of uncomplicated urinary tract infections (uUTI) caused by susceptible (b) (4)
and Staphyloccocus saprophyticus. Pivmecillinam tablets was first approved in 1977 in the

UK, Denmark, and Sweden. The 200 mg tablets are currently marketed in 9 European countries and Sri Lanka. The 200 mg tablets were approved but not marketed in Portugal, Canada and Morocco. The 400 mg tablets are marketed in Denmark, Sweden, Iceland, Norway, Finland, Malaysia, Belgium, Italy, and Germany. The 400 mg tablets are approved but not marketed in Spain, Netherlands, Poland, Luxembourg, Ireland and Canada.

The following three legacy clinical trials submitted to the NDA were considered pivotal in supporting the efficacy of pivmecillinam for the treatment of uUTI:

- MET-9401, "The natural history and the effect of pivmecillinam in lower urinary tract infection." (Ferry 2007 publication)
- Protocol 2641, "Comparison of Amdinocillin-pivoxil (Ro 10-9071) Three Days of Therapy Versus Seven Days of Therapy With Cephalexin in the Treatment of Uncomplicated Urinary Tract Infections." (Menday 2000 publication)
- EudraCTnr: 2012-002776-14, "Ibuprofen versus mecillinam for uncomplicated cystitis in adult, non-pregnant women." (Vik 2018 publication)

The inspection covered MET-9401 (Ferry 2007 publication), only one of the three legacy studies identified above. MET-9401, conducted from 1995 to 1997, was sponsored by Leo Pharma, the company who held the licensing rights at that time. In 2018, Utility Therapeutics, LTD licensed the rights to market mecillinam and pivmecillinam in the U.S. from Leo Pharma and trial data and records held by Leo Pharma were transferred to them.

Protocol MET-9401 (Ferry 2007 publication):
This was a multi-center, randomized, double-blind study evaluating the efficacy of three different dosage regimens of pivmecillinam tablets compared to placebo in women 18 years of age or older with symptoms of lower UTI (i.e., urgency, dysuria, suprapubic pain, or loin pain). The primary objectives of the study were to compare the cumulated effect of 4 different treatment alternatives in lower urinary infections on symptoms and bacterial counts after 8- 10 days and one month's follow-up.

Subjects: A total of 1162 subjects were enrolled and randomized
Sites: 18 sites in Northern Sweden
Study Initiation and Completion Dates: April 1995 to December 1997

The trial consisted of 3 visits:
- Visit 1 (Baseline Visit)
- Visit 2 (Test of Cure Visit)
- Visit 3 (Follow-Up Visit).

At Visit 1, eligible subjects were randomized to one of four different treatment groups in a 1:1:1:1 ratio:
- Treatment Group A: pivmecillinam 200 mg TID for 7 days
- Treatment Group B: pivmecillinam 200 mg BID for 7 days
- Treatment Group C: pivmecillinam 400 mg BID for 3 days followed by placebo for 4 days
- Treatment Group D: placebo 2 tablets TID for 7 days

To blind the study, each subject, based on their randomized treatment group, took a combination of 200 mg tablets and/or placebo three times a day for 7 days (i.e., 2 tablets in the morning, one at mid-day, and 2 tablets in the evening).

At Visits 1, 2 and 3, urine culture and susceptibility tests were performed as well as an assessment of the subject's clinical signs and symptoms (i.e., frequent urination, burning sensation during urination, low abdominal pain, and pain across loins) as strong, moderate, mild, or none.

The ***primary efficacy endpoint*** was the treatment difference (pivmecillinam vs placebo) in the overall success at Test of Cure (Visit 2) in the microbiological Intent-to-Treat (micro-ITT) analysis set. The micro-ITT analysis set consisted of all subjects regardless of whether or not the subject received study drug and who had a positive baseline urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen and no more than 2 species of microorganisms, regardless of colony count.

Because the original MET-9401/analysis population and overall response endpoint of MET-9401 (as conducted by Leo Pharma) was not consistent with FDA's 2019 guidance on uUTI, for the purposes of the integrated summary of efficacy, Utility Therapeutics redefined the following after data transfer from Leo Pharma:

- Subject eligibility criteria: to include only females ≥18 years, with evidence of pyuria, if the data was provided in the study and with ≥2 of the following symptoms: dysuria, urinary frequency, urinary urgency and suprapubic pain. In addition, subjects were excluded if they had signs or symptoms of systemic illness such as fever (>38°C), shaking chills or other clinical manifestations suggestive of complicated UTI or had received antibiotics for the uUTI in the 72 hours prior to first dose of study drug.
- Primary efficacy endpoint of overall success: Per-pathogen microbiological response at TOC (Day 7 to Day 15) was assessed for each baseline pathogen using the definitions in the 2019 FDA Guidance on uUTI.
    - Microbiological eradication was defined as $<10^3$ CFU/mL of uropathogen. A subject was considered a microbiological success if all baseline pathogens were eradicated.
    - Clinical success was defined as all symptoms present at baseline being resolved (i.e., absence of symptoms) with no new UTI symptoms present and no antibiotics other than the study drug used to treat the uUTI. Subjects with new or persistent symptoms were considered clinical failures.

Clinical response (which was classified as success, failure or indeterminant/missing) was determined programmatically by Utility from the clinical signs and symptoms and microbiologic data.

III. RESULTS (by site):

1. Utility Therapeutics, LTD
   3rd Floor, Ashley Road
   Altrincham, Cheshire, WA14 2DT
   United Kingdom
   PDUFA Inspection Dates: 29 January to 2 February 2024

The inspection of the applicant, Utility Therapeutics, focused on the following:

1. Utility's management and oversight of legacy datasets and records received from Leo Pharma (the sponsor of Protocol MET-9401) after Utility licensed the rights to market the product in the U.S
2. Review of the MET-9401 Trial Master File (TMF) records (e.g., monitoring reports and scanned copies of the original case report forms [CRFs])
3. Review and verification of legacy data line listings (DLL) submitted to the NDA with MET-9401 records maintained in the TMF for Site 45

Records reviewed included those related to the roles and responsibilities of the Utility Therapeutics and its statistical service providers; the organization and its personnel; service provider agreements; quality control activities (i.e., performed initially by Leo Pharma during the conduct of the legacy trial and then performed by Utility after receipt of the legacy datasets and records from Leo Pharma); data management; record retention; and relevant communication and correspondence. The following issues were noted during the inspection:

1. Inadequate tracking of data changes (via audit trails) made to the legacy study data.
2. Data discrepancies were noted between the legacy DLL and the scanned copies of the CRFs.

1. Inadequate tracking of data changes (via audit trails) made to the legacy study data

In a 14 November 2023 response to an Information Request (IR), Utility described their quality control (QC) activities (i.e., source data verification) that they undertook on a random sample of approximately 91 subjects (10% of subjects) to ensure the accuracy of data in the legacy dataset (i.e., the original dataset that they received from Leo Pharma). In this response, Utility also provided a listing of the data changes that were made as a result of the QC activity. These changes made were further investigated during the inspection.

Utility stated during the inspection that they received the original unblinded datasets and scanned copies of the CRFs from Leo Pharma approximately in April 2019. Without establishing a pre-specified and formal quality control plan, Utility performed source data verification of the original legacy dataset against scanned copies of the subject CRFs in September/October 2021, during the timeframe between SAP Version 3 (dated 10 February 2021) and the final SAP Version 4 (dated 13 December 2021). The source data verification entailed review of the microbiology data (e.g., culture, urine culture concentration in CFUs/mL, and susceptibility testing results) and clinical data (i.e., signs and symptom scores and adverse event data) at Visits 1, 2, and 3. As a result of this QC activity, Utility made data changes to reflect data as defined in the scanned copies of the CRFs when discrepancies were

identified between the original dataset and subject CRFs. The applicant provided a listing of the changes made to the microbiology and clinical data, but audit trails that tracked the data changes were not made available for inspectors to review. The applicant instead provided copies of the tables, listings, and figures that were generated after each of the 4 versions of the SAP to demonstrate that the data changes had minimal impact on the overall study results.

Reviewer's comment: *These data changes that Utility made were further reviewed and assessed after inspection. Of note, Utility made 138 data changes in 55 of the 91 randomly identified subjects whose microbiology and clinical data underwent the QC data check. The data changes included corrections made to subject initials, susceptibility results, signs and symptoms of infection at Visit 3, and follow-up adverse event information. Each of the 138 data changes were reviewed and verified with the original scanned copies of the CRFs for the 55 subjects. No discrepancies were noted (i.e., the listing of data changes provided by Utility matched the documentation in the original scanned copy of the CRFs). In addition, none of the data changes appear to impact the individual subject's overall response assessment (i.e., success, failure, or indeterminate) at the TOC visit or inclusion in or exclusion from the micro-ITT analysis set for the following reasons:*

a) *All data changes made to signs and symptom scores were made at Visit 3. The primary efficacy endpoint was assessed at the TOC Visit, which was Visit 2. However, in Utility's 4 March 2024 IR response, they noted that the signs/symptom variables that were changed at Visit 3 to missing as a result of the QC of the data should have remained 0 (i.e., absent) or should have been re-derived using an imputation for missing data that would set these to 0. Visit 3 signs and symptoms data were used in various secondary efficacy endpoints, and the review division should note this inconsistency in this Visit 3 signs/symptoms data for subjects who underwent the QC data review versus the Visit 3 signs/symptoms data for rest of the subjects who did not undergo this review.*

b) *Changes made to the microbiology data involved changes to susceptibility results only. Susceptibility results were not used as inclusion/exclusion criteria for the micro-ITT analysis set.*

The data changes were also discussed with Utility personnel during and at the closeout meeting of the inspection. Utility also responded in part to the inspection observations in a letter dated 22 February 2022 by further summarizing the changes that were made and their impact on the overall statistical results. In their letter, they classified these changes as linguistic clarification (n=12), missing field (n=8), last observation carried forward (n=105), and value to correct (n=13), and concluded that data changes made had minor to no impact on the overall results of the trial.

Audit trails to track data changes are critical for traceability and verification purposes to ensure that no other changes were made to dataset beyond the changes Utility identified in their listing of data changes. Thus, the issue related to the lack of audit trails was further reviewed and assessed after the inspection. In a 4 March 2024 IR response, Utility further explained that the data changes were incorporated directly into the ADaM datasets created by them. Because the data changes were applied in the creation of these ADaM datasets, a formal audit trail to track the data changes was not available. In addition, Utility explained that it

would be difficult to compare the original legacy dataset to the ADaM dataset because there is not a one-to-one match between the variables contained in each dataset (e.g., variable AEYN in the original dataset does not exist in the ADaM dataset).

The review division should be aware that the lack of audit trails and comparability between the datasets (i.e., original legacy dataset and ADaM datasets) make it difficult to verify whether additional changes were made to other subject data beyond those that Utility identified as being made in 55 of the 91 subjects whose data underwent the QC check. The review division should consider the lack of adequate tracking of data changes via audit trails in ADaM datasets in the review of the overall efficacy and safety results as presented in the applicant's overall summary of efficacy.

2. Data discrepancies noted between the legacy DLL and the scanned copies of the CRFs

During the inspection, uncertified scanned copies of case report forms, microbiology laboratory test results, and drug accountability and compliance logs maintained in Utility's TMF were reviewed and verified against the legacy data line listings (DLL) in all 113 randomized subjects at Site 45. Data reviewed and verified was related to the primary efficacy endpoint of overall success and included the signs and symptoms of infection, urine culture and susceptibility testing results, and urine culture concentrations documented at Visits 1, 2 and 3, as well as concomitant antibiotics other than antibiotics permitted in the protocol. Of note, the legacy DLL that Utility submitted to the NDA were originally generated by Leo Pharma and represented the original legacy dataset that Leo Pharma transferred to Utility. These DLL were not representative of the data changes Utility made to the ADaM dataset. Seven minor discrepancies were noted as follows:

- Five discrepancies were noted in the Subjects (b) (6) for signs and symptom scores at Visit 3
- One discrepancy was noted in Subject (b) (6) for urine culture test result (i.e., from missing culture test results in DLL to E. coli at 10^4 CFU/mL found in source case history) at Visit 1
- One discrepancy was noted in Subject (b) (6) for urine culture test results (i.e., from culture identification of blank/missing at 10^3 CFU/mL to yeast at 10^3 CFU/mL found in the source case history) at Visit 2

Reviewer's comment: *These discrepancies had no impact on the subjects' overall response assessment or inclusion in the micro-ITT analysis set because:*

- *5 of the 7 discrepancies occurred at Visit 3, a visit which was not involved in assessment of the primary efficacy endpoint.*
- *The urine culture concentration count of $<10^4$ CFUs/mL in Subject (b) (6) (randomized to pivmecillinam 200 mg BID) was not $\geq 10^5$ CFU/mL, a criterion that had to be met for inclusion in the micro-ITT analysis set.*
- *Subject (b) (6) (randomized to pivmecillinam 200 mg BID) culture report identified yeast and not bacteria.*

{See appended electronic signature page}

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine
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MEMORANDUM

From: Sonaly R. McClymont, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Shetarra Walker, MD, MSCR, Clinical Team Leader, DPMH

John J. Alexander, MD, MPH, Deputy Director, DPMH

NDA Number: 216483

Applicant: UTILITY Therapeutics Ltd.

Drug: Pivmecillinam hydrochloride (HCl) 200 mg, oral tablets

Proposed Indication: Treatment of adults with uncomplicated urinary tract infections caused by susceptible [redacted] (b) (4) and *Staphylococcus saprophyticus*.

Division Consult Request: The Division of Anti-Infectives (DAI) requests assistance with reviewing pediatric information in labeling for this application. Specifically, the Applicant submitted draft prescribing information describing drug interference with the newborn screening test for isovaleric acidemia in the setting of *in utero* exposure. DAI requested the DPMH Pediatric Team review this section for accuracy.

Background

Brief Regulatory Background

Pivmecillinam received its first marketing authorization in the United Kingdom in May 1977 as an antimicrobial agent for the treatment of susceptible gram-negative infections. It is marketed outside the United States (US) by Karo Pharma AB under the proprietary name Selexid®. The Applicant reports that as of May 2021, Selexid® has been approved as a 200-mg tablet in 13 countries (marketed in 10) and as a 400-mg tablet in 15 countries (marketed in 8);[1] and used in both adults and pediatric patients > 6 years of age.[2]

The Applicant was granted Qualified Infectious Disease Product designation by the FDA on 6/29/2018 for Pivmecillinam hydrochloride tablet for oral use for treatment of uncomplicated urinary tract infections (uUTI).[3] The Applicant submitted Pivmecillinam hydrochloride 200-mg tablets as an original 505(b)(1) NDA on 10/24/2023. It was filed on 12/22/2023 and classified as Priority with a PDUFA goal date on 4/24/2024.

An Agreed Initial Pediatric Study Plan (iPSP) was issued in February 2022[4] and was included in the NDA submission. The Agreed iPSP includes a plan for partial waiver in ages birth to less than 2 months of age because studies are impossible or highly impracticable and deferral in ages 2 months to less than 18 years of age because adult studies are completed and ready for approval. This NDA was reviewed at the Pediatric Review Committee (PeRC) Meeting on 1/30/24 at which time the PeRC agreed with issuing PMRs as planned based on the Agreed iPSP.[5]

Brief Pivmecillinam Overview

Pivmecillinam is an orally active prodrug of mecillinam, an extended spectrum penicillin used only for treatment of urinary tract infection. Compared to other β-lactams it has specificity for the urinary tract, minimal resistance or propensity for collateral damage, and reasonable treatment efficacy. It is recommended by the Infectious Disease Society of America and the European Society for Microbiology and Infectious Diseases as a first-line empiric treatment option for uUTI where available.[6]

Metabolism of pivmecillinam to its active component, mecillinam, results in the formation of pivalate. Pivalate is eliminated by conjugation with carnitine to form pivaloylcarnitine which is excreted in urine.[7] Because the presence of pivaloylcarnitine may interfere with the newborn screening test for isovaleric acidemia, the Applicant submitted draft prescribing information that

[1] NDA 216483 Cover Letter included in eCTD section 1.2
[2] IND 118650 Agreed Initial Pediatric Study Plan – Agreement dated 02/25/2022. DARRTS Reference ID: 4943428.
[3] IND 118650 Grant QIDP Designation Request – uUTI dated 6/29/2018. DARRTS Reference ID: 4284773
[4] See footnote #2.
[5] 1-30-2024 PeRC Meeting Minutes. DARRTS Reference ID: 5331941
[6] Gupta et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011 Mar 1;52(5):e103-20. doi: 10.1093/cid/ciq257. PMID: 21292654.
[7] Boemer et al. Surprising causes of C5-carnitine false positive results in newborn screening. Mol Genet Metab. 2014 Jan;111(1):52-4. doi: 10.1016/j.ymgme.2013.11.005. Epub 2013 Nov 19. PMID: 24291264.

describes the drug's potential for interference with newborn screening testing in the setting of *in utero* exposure. DPMH recommendations on draft labeling language will be discussed later in our review.

Isovaleric Acidemia Overview

Isovaleric Acidemia (IVA) is a rare genetic condition estimated to affect at least 1 in 250,000 people in the United States. It causes a deficiency of isovaleryl CoA dehydrogenase, an enzyme necessary to metabolize leucine (an essential amino acid). This enzyme deficiency inhibits the proper breakdown of leucine containing proteins[8] which leads to a buildup of isovalerylcarnitine, isovalerylglycine, isovaleric acid, and 3-hydroxyisovaleric acid ultimately causing metabolic ketoacidosis in those affected.[9]

Severe IVA presents in the first 1 to 2 weeks of life with lethargy, poor feeding, vomiting, "sweaty feet" odor, hyperammonemia, hypoglycemia, and neutropenia. If not promptly identified and treated, the condition can lead to metabolic crisis, irreversible brain damage and possibly death. Milder variants without neonatal illness can occur. Treatment should be initiated under the guidance of a specialist and includes the avoidance of fasting, protein restriction and supplementation with L-carnitine. The prognosis of IVA with appropriate therapy is good. [10]

Newborn Screening Overview

Newborn screening (NBS) in the US is a state public health service performed soon after birth (typically between 24-48 hours of life) designed to identify treatable congenital disorders.[11] The system of NBS consists of three parts: 1) blood spot screening for certain genetic, endocrine and metabolic disorders, 2) pulse oximetry screening for critical congenital heart defects (CCHDs), and 3) hearing screening for hearing loss.[12,13]

The part of NBS pertinent to this review is the blood spot screening. While every state requires NBS, each state manages its own NBS program and chooses which conditions to include on its NBS panel (for which the blood spot undergoes testing). To help states decide which conditions to include in their NBS panels, the US Secretary of Health and Human Services has created a list of recommended conditions for inclusion called the Recommended Uniform Screening Panel

[8] National Library of Medicine, MedlinePlus, Genetics, Genetic Conditions, Isovaleric Acidemia. Accessed 2/13/2024 from: https://medlineplus.gov/genetics/condition/isovaleric-acidemia/#references
[9] Murko et al. Neonatal screening for isovaleric aciduria: Reducing the increasingly high false-positive rate in Germany. JIMD Rep. 2022 Oct 28;64(1):114-120. doi: 10.1002/jmd2.12345. PMID: 36636590
[10] American College of Medical Genetics ACT Sheet: Newborn Screening ACT Sheet, [Elevated C5 Acylcarnitine], Isovaleric Acidemia. Accessed 2/13/2024 from: https://www.acmg.net/PDFLibrary/C5.pdf
[11] Newborn Screening 101. Baby's First Test.org. Accessed 2/16/24 from: https://www.babysfirsttest.org/newborn-screening/screening-101
[12] About Newborn Screening. Newborn Screening Information Center. Health Resources & Services Administration (HRSA) Newborn Screening. Accessed 2/16/24 from: https://newbornscreening.hrsa.gov/about-newborn-screening
[13] Newborn Screening Portal. Centers for Disease Control and Prevention (CDC). Accessed 2/16/24 from: https://www.cdc.gov/newbornscreening/

(RUSP).[14] Most states include most of the conditions on the RUSP in their NBS panel. IVA is included on the RUSP.

Most states perform blood spot screening once shortly after birth. Some states include a second blood spot screening at age 1-2 weeks of life. NBS results are reported directly to the health care provider for the newborn who is identified at the time of blood sample collections. Results of blood spot screening are typically reported to the health care provider (HCP) within five to seven days. The method and timing of reporting results vary by state NBS program.

Pivmecillinam Interference with Newborn Screening for Isovaleric Acidemia
Newborn screening for IVA is performed by mass spectrometry to quantify C5 carnitines. Isovalerylcarnitine is a C5 carnitine that accumulates in the blood of patients with IVA (described above); however, it is only one of several C5 carnitines that are collectively detected as a group in this screening test. Pivaloylcarnitine, a metabolic product of pivmecillinam (described above), is isomeric with isovalerylcarnitine and therefore contributes to the quantification of C5 carnitines thereby allowing for the possibility of a false positive result for this screening test for IVA.[15]

When a positive screening test result is reported for IVA, several immediate actions are recommended to ensure safety of the newborn. First, the HCP for the newborn should contact the caregiver and assess the clinical status of the newborn. If the newborn is symptomatic (poor feeding, vomiting, lethargy, tachypnea, etc.), they should be transported to the hospital immediately for treatment and consultation with a metabolic specialist. If the newborn is asymptomatic, the health care provider should consult with a pediatric metabolic specialist the same day and schedule a prompt evaluation of the newborn. Confirmatory testing should be initiated which requires blood and urine samples be collected from the newborn.[16]

In the setting of *in utero* exposure to pivmecillinam prior to delivery; if pivaloylcarnitine is determined to be the only elevated C5 carnitine and all other confirmatory tests are normal in an asymptomatic patient, then the screening test would be considered a false positive. The *in utero* exposure may or may not be known prior to confirmatory testing; however, based on either the initial positive screening result or the results of confirmatory testing, the exposure can be investigated.

The first false positive NBS result for IVA due to an antibiotic containing a pivalate derivative was reported as early as 1998.[17] Several publications describe more recent clinical experience with this phenomenon in Europe. Boemer et al (2014) described an 18-month period in which 50 newborns, all from one unique maternity unit in Belgium, presented with elevated C5 carnitine levels on newborn screening for IVA. Ultimately all blood samples were determined to

[14] Newborn Screening Process. Newborn Screening Information Center. Health Resources & Services Administration (HRSA) Newborn Screening. Accessed 2/16/24 from: https://newbornscreening.hrsa.gov/newborn-screening-process#nbs-same
[15] See footnote #9.
[16] See footnote #10.
[17] See footnote #9.

be false positives due to presence of pivaloylcarnitine and absence of other C5 carnitines. At that time, no pivalic-ester prodrugs were commercially distributed in Belgium; however, it was found that a nipple-fissure unguent containing neopentanoate, a pivalate derivative, was systematically provided to mothers in the unique maternity unit from which all 50 newborns were delivered. Introduction of the moisturizing agent in the maternity unit and the increase of false positives for IVA screening were well correlated chronologically. Ultimately, removing the cream from the maternity ward resulted in a significant reduction in the false positive rate back to the prior initial positivity proportion.[18]

Bonham et al (2018) informally surveyed European countries to determine the extent of interference from pivaloylcarnitine in NBS for IVA. An email survey was sent to NBS programs in 17 European countries, responses were received from nine. Seven of the nine countries reported that pivalate-containing medications contributed to false positive diagnoses in their NBS programs. Three of the seven reported a predominant etiology from creams, three reported a predominant etiology from antibiotics (two of which specifically cited pivmecillinam), and one country reported a mixed etiology from both sources.[19]

In a publication more specifically describing the pivmecillinam experience, Murko et al (2022) report that false positive IVA screening in German newborns was first reported in 2019, three years after approval of pivmecillinam in Germany. This prompted a systematic study on its occurrence in two German screening centers from January 2019 to December 2021, during which time 156,772 newborns were screened for IVA. A total of 100 newborns screened positive for an elevated C5 carnitine level. Ultimately one was genetically proven to have IVA and the other 99 were determined to have pivaloylcarnitine as the only cause for C5 elevation. Contact with mothers was possible in more than 80% of the cases and always confirmed intake of antibiotics at the end of pregnancy, however, the exact trade names and indications were often unknown to the mothers at the time of contact. Impacts of the increase in false positive results included increased parental anxiety and increased hospital admissions.[20]

The increasing findings of false positive newborn screening tests for IVA in various countries have led to the development of second-tier testing for the condition. Second-tier testing can isolate the distinct C5 carnitines and specifically identify pivaloylcarnitine in the original blood spot sample during the routine NBS process. In the survey reported by Bonham et al (2018), of the seven countries that reported pivalate-containing medications contributed to false positive diagnoses in their NBS programs, four reported use of second-tier testing to identify pivaloylcarnitine in the blood spot sample to avoid clinical referral and confirmatory testing. At the time of Bonham et al (2018) survey, Germany reported that pivalate-containing medications did not contribute to false positives in their NBS program. That scenario subsequently changed for Germany after increased use of pivmecillinam in the country. Murko et al (2022) reported development of a second-tier testing method to differentiate C5 carnitines which was used in

[18] See footnote #7.
[19] Bonham et al. Raising Awareness of False Positive Newborn Screening Results Arising from Pivalate-Containing Creams and Antibiotics in Europe When Screening for Isovaleric Acidaemia. Int J Neonatal Screen. 2018 Feb 10;4(1):8. doi: 10.3390/ijns4010008. PMID: 33072934; PMCID: PMC7510208.
[20] See footnote #9.

their analysis of German newborns described above. They ultimately recommended that second-tier testing should be included in their NBS program.

Second-tier testing for IVA within the NBS process is not currently available in the US.

DPMH Labeling Recommendations

The DPMH labeling recommendations for relevant sections are below. Recommended information to be added to selected sections is underlined. Information to be deleted has a strikethrough.

Highlights

Warnings and Precautions

Interference with (b) (4) Newborn Screening Tes (b) (4) (b) (4) Treatment of a pregnant individual with pivmecillinam (b) (4) prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of (b) (4) newborn screening.

Reviewer comments:

- *In the United States, the commonly used term for the type of testing described is "newborn screening," therefore we recommend changing the language from "(b) (4) screening" to "newborn screening" throughout the labeling. Additionally, because the effect on only one test is being described we recommend using the singular "test" instead of the plural "tests" throughout labeling.*

- *To be more specific about the affected patient population and to use active (as opposed to passive) language, we recommend the phrase "(b) (4) be revised to "treatment of a pregnant individual with pivmecillinam..." throughout labeling.*

- *There is no available evidence to support a specific time frame prior to delivery during which in utero exposure to pivmecillinam is associated with interference with NBS for IVA. The language proposed by the applicant, (b) (4) (b) (4). We recommend the phrase "(b) (4)" be revised to "prior to delivery..." throughout labeling to reflect the lack of specificity currently known about this time frame.*

5 Warnings and Precautions

5 (b) (4) Interference with (b) (4) Newborn Screening Tests (b) (4) Treatment of a pregnant individual with pivmecillinam (b) (4) prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of (b) (4) newborn screening. (b) (4) Prompt follow-up of a positive newborn screening result for isovaleric acidemia is recommended.

Reviewer comments:

- [redacted] (b) (4) *; therefore, removal of this information is recommended.*

- [redacted] (b) (4) *therefore, we recommend removal of reference to it.*

- *Isovaleric acidemia is a genetic condition that can lead to metabolic crisis causing risk of irreversible brain damage and death within the first 1 to 2 weeks of life if not identified and treated promptly. Due to the severity of the disease and the risk associated with a true positive NBS result, addition of the last sentence (with practical guidance for the HCP) is recommended to ensure safety of affected newborns.*

- *In the US, the clinical risk to the newborn of a false-positive IVA NBS result would likely be pain and/or distress related to blood and urine confirmatory testing. While the newborn is expected to be asymptomatic in the setting of a false positive, there may be variability in clinical decision-making surrounding hospitalization and treatment while awaiting results of confirmatory testing.*

  Additional risks to consider in this scenario may include emotional distress for the family, medical resource utilization [e.g., time sensitive notification from NBS lab to pediatric HCP and HCP to family, consultation of pediatric metabolic specialist, additional laboratory testing, etc.], and potential cost to family (potential medical bills, potential cost of transportation to medical appointments and/or lost days of work, etc.).

  Based on this risk assessment, as compared to the other conditions in Sections 5 and 6 (Hypersensitivity Reactions, Carnitine Depletion, Clostridioides Difficile-Associated Diarrhea, Development of Drug-Resistant Bacteria, and Severe Cutaneous Adverse Reactions), we recommend consideration of moving 'Interference with Newborn Screening Test' to be the last condition listed in Highlights (Warnings and Precautions), Section 5, [redacted] (b) (4)

[redacted] (b) (4)

7 Drug Interactions

7.2 Drug Interference with Newborn Screening Test

Treatment of a pregnant individual with pivmecillinam prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening. Prompt follow-up of a positive newborn screening result for isovaleric acidemia is recommended.

Reviewer comment:
Per the Labeling Review Tool (LRT)[21], Section 7 must include practical guidance on known interference of the drug with laboratory tests. Therefore, we recommend creating a subsection within Section 7 to include this information.

8 Use in Specific Population
8.1 Pregnancy
Clinical Considerations
Interference with Newborn Screening Test
Treatment of a pregnant individual with pivmecillinam prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening [see *Warnings and Precautions (5.6)* and *Drug Interactions* (7.2)].

Reviewer comment:
- *Due to the perinatal circumstances of the drug's potential for interference with NBS, we recommend adding this sentence to Section 8.1, directed towards the HCP for the pregnant individual. This information may impact the HCP's clinical decision making on the choice of treatment and counseling provided to the pregnant individual. This information may also promote notification to the HCP for the newborn in a timely manner.*

- *We recommend cross-reference to Sections 5 and 7 due to additional information in those sections with practical guidance for management of the test result.*

8.4 Pediatric Use
Interference with Newborn Screening Test
Newborns exposed to pivmecillinam *in utero* prior to delivery may have a false positive newborn screening test for isovaleric acidemia. Prompt follow-up of a positive newborn screening result for isovaleric acidemia is recommended.

Reviewer comments:
- *Due to the drug's potential for interference with NBS, we recommend adding this information to Section 8.4. This information will directly impact clinical decision making for the HCP of the newborn who is responsible for managing the NBS test results.*

- *The language in the first sentence is altered slightly from previous sections to address the pediatric impact directly; however, the content is similar enough that we do not believe a cross-reference to Section 5 or 7 is necessary.*

17 Patient Counseling Information
Interference with (b) (4) Newborn Screening Tests

[21] FDA Labeling Review Tool (for internal use only) Version September 2023.

Advise patients [redacted] that [redacted] treatment of a pregnant individual with PIVYA [redacted] prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of [redacted] newborn screening and prompt follow-up of a positive result is recommended [see *Warnings and Precautions (5* [redacted]

Reviewer comment:
Rationale for these revisions is described above.

Conclusions and Recommendations

The labeling changes recommended in this review have been shared with DAI. Labeling negotiations are ongoing. The final labeling may differ (see approval letter for final approved labeling).

Additionally, due to the potential for a false positive test result that will trigger prompt clinical follow-up for the affected infant; we recommend consulting CDER's Office of Communications to discuss an appropriate strategy to disseminate this information to relevant organizations involved in the NBS process.

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 5, 2024
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216483
Product Name, Dosage Form, and Strength:	Pivya (pivmecillinam) tablet, 185mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	UTILITY therapeutics, Ltd
FDA Received Date:	January 31, 2024
TTT ID #:	2023-6865
DMEPA 1 Safety Evaluator:	Kristine Needleman, RPh
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

REASON FOR REVIEW

As part of the approval process for Pivya (pivmecillinam) tablet, the Division of Anti-Infectives (DAI) requested that we review the proposed Pivya prescribing information (PI), unit-dose blister-sheet label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 216483 is a 505(b)(1) application submitted on October 24, 2023.

MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Information Requests	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

1 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), unit-dose blister-sheet label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for UTILITY therapeutics, Ltd.

RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented in the DOSAGE AND ADMINISTRATION section of the HIGHLIGHTS OF PRESCRIBING INFORMATION and the FULL PRESCRIBING INFORMATION, no information is provided regarding administration of the tablets in relationship to food/meals.	Lack of this information may lead to confusion regarding medication administration for healthcare providers.	For clarity, add the appropriate administration instruction in relationship to food/meals. *See Draft Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (Jan 2023)*
			(b) (4)
Full Prescribing Information – Section 2 Dosage and Administration			
1.			(b) (4)
2.	The missed dose statement, “If a dose of this medicine is missed, take it	Lack of clarity of when to take a missed dose leads to confusion.	If appropriate, consider revising for clarity. For example, "If a dose of PIVYA is missed, take it

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	as soon as possible. Do not double the dose," is lacking clarity.		as soon as possible unless more than X hours have passed. Do not take 2 doses of PIVYA at the same time to make up for the missed dose."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	An imprint code on the tablet is missing.	Per 21 CFR 206.10(a), *Unless exempted under § 206.7, no drug product in solid oral dosage form may be introduced or delivered for introduction into interstate commerce unless it is clearly marked or imprinted with a code imprint that, in conjunction with the product's size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product. Identification of the drug product requires identification of its active ingredients and its dosage strength. Inclusion of a letter or number in the imprint, while not required, is encouraged as a more effective means of identification than a symbol or logo by itself.* Absence of the imprint code or an imprint code that is difficult to see or	We recommend adding an imprint code to the tablet and including the identifying information in the *How Supplied/Storage and Handling* section in the PI labeling to facilitate product identification.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		identical or similar to imprint codes of other products have contributed to the dispensing and administration of the wrong drug product and wrong strength.[a]	
2.	As currently presented, the description of the packaging configuration "...film-coated in aluminum-aluminum push-through blisters with 10 tablets per Blister" is incomplete.	Inclusion of "...*units in which the dosage form is ordinarily available for prescribing by practitioners*..." is required by 21 CFR 201.57(c)(17)(ii).	Revise Section 16 of the Prescribing Information to comply with the content requirements in accordance with 21 CFR 201.57(c)(17)(ii). For example: PIVYA is supplied as film-coated tablets in aluminum-aluminum push-through blisters with 10 tablets per blister-sheet and five blister-sheets per carton.
3.	The NDC number is missing from this section.	Section 16 How Supplied/Storage and Handling should contain information suitable for product identification in accordance with 21 CFR 201.57(c)(17)(iii).	When finalized, ensure the NDC number is included in Section 16 in accordance with 21 CFR 201.57(c)(17)(iii).
4.	Currently subsection 16.2 Storage and Handling states "PIVYA tablets should be stored at 20°C to 25°C (68°F to 77°F)." The information stated here is not consistent with the information on the carton labeling, which includes the	The presentation of the storage statement should be consistent and clearly stated to avoid storage errors.	Revise to say "PIVYA tablets should be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

[a] Safety Considerations for Product Design to Minimize Medication Errors Guidance for Industry

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	statement "[see USP Controlled Room Temperature]."		
5.	Currently section 16.2 Storage and Handling does not state if the tablets can be removed from the blister package prior to dispensing.	In consultation with our Office of Pharmaceutical Quality colleagues, we note that Pivmecillinam tablets are sensitive to high humidity. Additionally, we note that the long-term stability studies were conducted with the tablets remaining in the blister packaging.	Add the statement "Store and dispense tablets in the unit-dose blisters (b) (4) (b) (4) ." For consistency, the storage information would need to be updated on the carton labeling.

RECOMMENDATIONS FOR UTILITY THERAPEUTICS, LTD

Table 3. Identified Issues and Recommendations for UTILITY therapeutics, Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
Unit-Dose Blister-Sheet Label			
1.	The blister sheet will require cutting to provide the correct number of tablets for the 3-to-7-day duration of therapy.	To ensure stability of the tablets in the blister cells it is important that the health care practitioner does not cut into the blister cells.	We recommend adding grid lines on the blister sheet label to indicate where to cut between the blister cells.
2.	Each unit-dose blister cell is required to have a barcode.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2).	Add the product's linear barcode to the blister packaging in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation). Consider removing the (b) (4) .
3.	We note that the blister-sheet labels do not state the NDC number.	Per 21 CFR 201.2, the NDC is "requested but not required to appear on all drug labels and in all drug labeling", however, FDA strongly encourages the NDC appear on all drug labels and in all drug labeling.	To help identify the product consider adding the NDC to the blister-sheet labels.

Table 3. Identified Issues and Recommendations for UTILITY therapeutics, Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	The format for the expiration date is not defined.	Clearly defining the expiration date will minimize confusion and the risk of deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
2.	The strength statement on the principal display panel lacks prominence.	Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6), which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and	Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Consider all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical

Table 3. Identified Issues and Recommendations for UTILITY therapeutics, Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.	(e.g., net quantity statement, NDC code, etc.).
3.	The established name is not at least half the size of the proprietary name.	We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
4.	Currently the dosage form "tablet, (b) (4) (b) (4)" is placed beneath the equivalency statement.	Critical product information such as the proprietary name, established name, dosage form, and product strength, should appear as the most prominent displayed information on	We recommend relocating the dosage form, so it directly follows the established name on the same line or the following line.

Table 3. Identified Issues and Recommendations for UTILITY therapeutics, Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		the PDP. The side or back panels should be used for information such as the equivalency statement, each tablet contains statement, lot number, expiration date, and recommended dosage to maximize the prominence of the information listed above.	Additionally, we recommend relocating the equivalency statement to the side or back panel.
5.	Currently the storage information on the rear panel does not state if the tablets can be removed from the blister package prior to dispensing.	Based on discussion with our Office of Pharmaceutical Quality colleagues, we note that Pivmecillinam tablets are sensitive to high humidity. Additionally, we note that the long-term stability studies were conducted with the tablets remaining in the blister packaging.	Add the statement "Store and dispense tablets in the unit-dose blisters to protect from moisture," to the storage information on the carton.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Pivya that UTILITY therapeutics, Ltd submitted on October 24, 2023.

Table 4. Relevant Product Information for Pivya	
Initial Approval Date	N/A
Active Ingredient	pivmecillinam
Indication	treatment of adults with uncomplicated urinary tract infections (uUTI) caused by susceptible (b) (4) and Staphylococcus saprophyticus
Route of Administration	oral
Dosage Form	tablet
Strength	185 mg
Dose and Frequency	185 mg three times daily for 3 to 7 days (b) (4)
How Supplied	PIVYA tablets are supplied as 185 mg pivmecillinam tablets (equivalent to 200 mg pivmecillinam hydrochloride), film-coated in aluminum-aluminum push-through blisters with 10 tablets per blister and five blister sheets per carton.
Storage	20°C to 25°C (68°F to 77°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 29, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms pivmecillinam and NDA 216483. Our search identified no previous reviews.

Appendix E. Information Request

Response to Agency Information Request received on February 9, 2024, available at: \\CDSESUB1\EVSPROD\nda216483\0028\m1\us\111-information-amendment\response-ir-feb5.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error experiences with similar products, we reviewed the following Pivya labels and labeling submitted by UTILITY therapeutics, Ltd.

- Unit-Dose Blister-Pack Label received on January 31, 2024
- Unit-Dose Blister-Pack Carton Labeling received on January 31, 2024
- Prescribing Information (Image not shown) received on January 31, 2024, available from \\CDSESUB1\EVSPROD\nda216483\0023\m1\us\114-labeling\draft\labeling\pivmecillinam-uspi.pdf

F.2 Label and Labeling Images

Unit-Dose Blister-Pack Label

(b) (4)

[redacted]

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

KRISTINE P NEEDLEMAN
03/05/2024 04:55:50 PM

VALERIE S VAUGHAN
03/05/2024 05:01:49 PM

Memorandum

To:	Leslie Ball, MD, Medical Officer, Division of Anti-infectives
	Mayurika Ghosh, MD, Medical Team Lead, Division of Anti-infectives
From:	Ikponmwosa Osaghae, MD, PhD, Epidemiologist, Division of Epidemiology II
Through:	Yan Li, PhD, Team Lead (Acting), Division of Epidemiology II
	Natasha Chihying Pratt, PhD, Master Epidemiologist, Division of Epidemiology II
	Adebola Ajao, PhD, Deputy Director (Acting), Division of Epidemiology II
Date:	March 01, 2024
Subject:	Literature Review on the Risk of Adverse Pregnancy, Maternal, and Infant Outcomes Associated with Pivmecillinam Use During Pregnancy
Drug name:	Pivmecillinam Oral Tablets
Application #:	NDA 216483
Applicant:	Utility Therapeutics

BACKGROUND

Pivmecillinam is an oral prodrug of mecillinam, a beta-lactam antibiotics. A New Drug Application (NDA) was submitted by Utility Therapeutics (Applicant) for pivmecillinam under NDA 216483 on October 24, 2023. The Applicant is seeking approval of pivmecillinam with the proposed indication of treatment of adults with uncomplicated urinary tract infections (uUTI) caused by susceptible (b) (4) (b) (4) and Staphylococcus saprophyticus. Pivmecillinam has been on the market for several decades with published observational studies conducted in pregnant women. The Applicant conducted a review of the literature on pivmecillinam use in pregnant women with uUTI to inform safety of pivmecillinam use in pregnancy.

The Division of Anti-Infectives (DAI) consulted the Division of Epidemiology (DEPI) to review the published literature related to the use of pivmecillinam in pregnancy to support labelling. To support this request, DEPI reviewed the NDA package submitted by the applicant and conducted a search of the PubMed database to identify additional observational studies that evaluated the association between in utero exposure to pivmecillinam and the risk of adverse pregnancy, maternal, and infant outcomes. This memo summarizes DEPI's assessment of the evidence derived from retrieved observational studies.

REVIEW METHODS AND MATERIALS

We conducted a literature search in the PubMed database on January 3, 2024. The search strategy included a combination of Medical Subject Headings (MeSH) and free-text terms for the exposure (pivmecillinam), outcome (maternal and infant outcomes), and population (pregnant women) of interest. Filters were applied to limit retrieved articles to only studies conducted in humans. A detailed description of the search strategy is presented in Appendix 1. We also screened references of retrieved studies and all studies included in the Applicant's application package to identify additional potentially relevant studies. At the stage of title and abstract screening, we included studies for full text review if it, a) was a cohort study or case-control study, b) assessed maternal pivmecillinam use during pregnancy, c) assessed the risk of adverse pregnancy, maternal,

and infant outcomes, and d) reported a measure of association between the exposure and outcome, such as relative risk (RR) or odds ratio (OR). We excluded studies for full text review if it, a) was a descriptive study, b) was a narrative or systematic review, c) was a randomized clinical trial, d) did not assess the risk of adverse pregnancy, maternal, and infant outcomes, e) did not report a measure of association between the exposure and outcome, such as RR or OR, or f) assessed only pharmacokinetic properties of pivmecillinam.

Only studies with the following design features were considered to have relatively higher quality for a final full in-depth review.

- Used population-based controls, instead of controls from selected samples (e.g., database of teratogenic information center), to avoid potential selection bias.
- If cohort study – included an active comparator group (i.e., women using other antibiotics) to minimize the effect of confounding due to infections, and/or accounted for infections as potential confounders.
- If case control study – accounted for infections as potential confounders.

REVIEW RESULTS

We identified 30 articles from our PubMed search and two additional articles from the Applicant's application package for a total of 32 articles. Our literature search included six of the eight studies reporting safety outcomes in pregnancy captured by the Applicant's literature search and identified two additional studies not reported by the Applicant.[a] After screening titles and abstracts of the retrieved articles, we excluded 22 articles and10 met the initial inclusion criteria for a full text review. Six of the ten articles were excluded for lack of active comparators or lack of control for maternal infection, and four were selected for an in-depth review (Appendix 2). Among these four studies, three were cohort studies[1-3] and one was a case control study[4]. All included studies were conducted in the Nordic countries of Denmark, Norway, Finland, and Sweden. A summary of study details is described below and in Appendix 3.

The Damkier study[1] was conducted using four Danish National Registries (Registry of Medicinal Product Statistics, Medicinal Birth Registry, National Patient Registry, and Civil Registration System) between 2000 and 2015. In the primary analysis, first trimester exposure to pivmecillinam (n=36,423) was compared to any of four penicillin derivatives (ampicillin, pivampicillin, benzylpenicillin, and phenoxymethylpenicillin, [n=48,765]), which are considered to be safe with respect to congenital malformations. Multivariable logistic regression analyses were used to account for potential confounders. Compared to pregnant women exposed to any of four penicillins, exposure to pivmecillinam in the first trimester was not associated with increased risk of any malformations (adjusted OR [aOR]: 0.97; 95% CI: 0.92 to 1.03), major congenital malformations (aOR: 1.02; 95% CI: 0.94 to 1.10), or cardiac malformations (aOR: 0.99; 95% CI: 0.86 to 1.14). However, in sensitivity analyses, compared to pregnant women unexposed to any antibiotics, exposure to pivmecillinam in the first trimester was associated with small increased risk of any malformation (aOR: 1.12; 95% CI: 1.07 to 1.17), major congenital malformations (aOR: 1.13: 95% CI: 1.06 to 1.19), and cardiac malformations (aOR: 1.15; 95% CI: 1.04 to 1.28).

The Nordeng study[2] was conducted using data from the Medical Birth Registry of Norway and the Norwegian Prescription Database between 2004 to 2008. Authors compared 5,794 nitrofurantoin users (n=1,334 for first trimester exposure) to 20,643 pivmecillinam users (n=5,800 for first trimester exposure). Multivariable conditional generalized estimation equations were used to adjust for confounders.[b] There was no increased risk of major malformations among pregnant women exposed in the first trimester to pivmecillinam compared to nitrofurantoin (nitrofurantoin vs. pivmecillinam: 2.3% vs. 2.8%; aOR: 0.79; 95% CI: 0.51 to 1.23).[b] Also,

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[a] For the two studies included in the applicant search but missed by our search strategy, one assessed the risk of childhood febrile seizures and the other assessed the risk of childhood epilepsy. Both studies did not meet our in-depth review criteria.

[b] In the Nordeng study, pivmecillinam was used as the active comparator to assess the risk of major malformations and other secondary outcomes including stillbirth or neonatal deaths, low birth weight, preterm deliveries, neonatal intensive care unit (NICU) admissions, and Apgar score lower than 7 at 5 minutes, and neonatal jaundice among pregnant women exposed to nitrofurantoin. Thus, all results are reported comparing nitrofurantoin to pivmecillinam exposed pregnant women.

compared to nitrofurantoin, exposure to pivmecillinam in the last 30 days of pregnancy was not associated with increased risk of neonatal jaundice requiring treatment (nitrofurantoin vs. pivmecillinam: 10.8% vs. 8.1%; aOR: 1.25; 95% CI 0.93 to 1.69). Null results were observed for other secondary outcomes including stillbirth or neonatal deaths, low birth weight, preterm deliveries, neonatal intensive care unit (NICU) admissions, and Apgar score lower than 7 at 5 minutes.

The Hjorth study[3] was a pooled analysis using national registries from four Nordic countries (Denmark, Norway, Finland, and Sweden) between 1997 and 2003. Pregnancies exposed to nitrofurantoin (n=44,091) were compared with those exposed to pivmecillinam (n=247,306) at any time of pregnancy and at each trimester.[c] Inverse probability of treatment weighting based on propensity scores was used to account for potential confounders. In the main analyses, there was no significantly increased risk of any leukemia among women exposed at any time of pregnancy to pivmecillinam compared to nitrofurantoin (nitrofurantoin vs. pivmecillinam[c]: 72.6 vs. 52.2 per 100,000 person-years; weighted incidence rate ratio [wIRR]: 1.34, 95% CI: 0.88 to 2.06; weighted incidence rate difference [wIRD]: 1.49, 95% CI: -1.92 to 4.90). Results of the subgroup analysis among women with two or more prescriptions fills were similar to the main analysis but with wider confidence intervals (wIRR: 1.57, 95% CI: 0.54 to 4.55; wIRD: 3.09, 95% CI: -5.92 to 12.10). The authors also conducted other subgroup and sensitivity analyses, including trimester specific analyses, analysis restricted to women who were unexposed to other systemic antibiotics, and analysis restricted to women who had contacts with the healthcare system before pregnancy. Results of these analyses supported findings of the main analyses.

The Norgaard study[4] was conducted between 1997 and 2002 using the County Hospital Discharge Registry, Pharmaco-epidemiological Prescription Database of the Danish County of North Jutland, and Danish Medical Birth Registry. Cases were defined as women with a first-time recorded hospitalization with diagnoses for miscarriage who had no previous birth record, while eligible controls were selected among women with first live birth without any previous record of a miscarriage. For each case, 10 controls were sampled in the year of conception from the risk set of pregnancies with the same gestational age. Thus, the index date for controls was set as the date when they had the same gestational age as their corresponding cases at the time of miscarriage. A total of 1,599 cases and 15,990 controls were included in the final analyses. Multivariable conditional logistic regression was used to account for potential confounders. To account for potential confounding by underlying infections, the authors also estimated the risk of miscarriage following exposure to sulfamethizole, a common antibiotic used to treat acute urinary tract infection in Denmark, and penicillin V, which is used for other types of infections. The ORs for exposure to pivmecillinam within 1 week, 2-3 weeks, and 4-7 weeks before hospitalization for miscarriage were 2.03 (95% CI: 0.77 to 5.33), 1.10 (95% CI: 0.44 to 2.78), and 0.75 (95% CI: 0.27 to 2.10), respectively. The ORs for exposure to sulfamethizole within 1 week, 2-3 weeks, and 4-7 weeks before hospitalization for miscarriage were 1.53 (95% CI: 0.76 to 3.09), 0.92 (95% CI: 0.47 to 1.82), and 1.04 (95% CI: 0.61 to 1.77), respectively. The OR for exposure to penicillin V in the week before the hospitalization for miscarriage was 1.03 (95% CI: 0.41 to 2.61).

DISCUSSION

We reviewed four observational studies that found no evidence of increased risk of adverse pregnancy, maternal, and infant outcomes among pregnant women exposed to pivmecillinam. Among these, two cohort studies assessed the risk of malformations following pivmecillinam use during pregnancy. None of the two studies found an association between first trimester exposure to pivmecillinam and the risk of congenital malformations when compared to penicillin derivatives or nitrofurantoin. One case control study assessed the risk of miscarriage which suggested pivmecillinam use during pregnancy may be associated with increased risk of miscarriage. One cohort study assessed several infant outcomes following in utero exposure to

[c] In the Hjorth study, pivmecillinam was used as the active comparator to assess the risk of any leukemia among pregnant women exposed to nitrofurantoin. Thus, all results are reported comparing nitrofurantoin to pivmecillinam exposed pregnant women.

pivmecillinam and reported no association between pivmecillinam use and the risk of stillbirth, neonatal death, low birth weight, preterm deliveries, NICU admissions, Apgar score lower than 7 at 5 minutes, and neonatal jaundice when compared to nitrofurantoin. One cohort study assessed the risk of a long-term outcome (i.e., childhood leukemia) following in utero exposure to pivmecillinam and reported no association between pivmecillinam use and the risk of childhood leukemia when compared to nitrofurantoin. It is important to note that while penicillin use is generally considered safe during pregnancy, the risk profile of nitrofurantoin is less clear.[d] The reviewed studies are limited by biases such as exposure misclassification, outcome misclassification, and unmeasured confounding, to different extent.

Exposure misclassification

In all four studies reviewed, pivmecillinam exposure was ascertained from prescription dispensing records, which may be subject to exposure misclassification since prescription fills do not always reflect actual drug use or exposure. Although prescription registries in the Nordic countries provide complete and prospectively collected exposure data, they are prone to false positive exposure information. A previous study examined the consistency between self-reported medication use during pregnancy and prescription dispensing records and found there were no corresponding self-reported records for about one third of antibiotic dispensing records.[5] The resulting bias from misclassification of the exposure typically depends on the study comparator. For studies utilizing unexposed as comparators, results can be biased towards the null. On the other hand, for studies that utilize an active comparator, the direction of the resulting bias is unpredictable. It is possible that some null findings could be contributed by exposure misclassification. One way to address this challenge is to restrict the study population to those with multiple prescription fills. Of the four studies reviewed, only the Hjorth study conducted subgroup analysis to assess the risk of any leukemia among women exposed to two or more prescriptions fills, with results supportive of the primary analysis.

Outcome misclassification

All four reviewed studies were based on national registries of a Nordic country and relied on diagnostic codes for the ascertainment of outcome. This approach could predispose these studies to misclassification of the outcome. However, disease registrations in national registries of Nordic countries are well established with linkable patient level data, providing great capture of outcomes of interest. For instance, a validation study reported 94% completeness for cleft lip and palate registrations in the Medical Birth Registry of Norway (N=3,616).[6] In another validation study of cardiac malformation diagnoses recorded in the Danish National Patient Registry, a positive predictive value (PPV) of 90% (N=2,952, gold standard: patients' clinical record) was reported.[7] A similar PPV for congenital malformation diagnoses has also been reported in the Medical Birth Registry of Denmark (N=24,147; PPV: 89%).[8] Given the low prevalence of malformations and the high PPV of algorithms used, we expect the specificity of the algorithms to be high. Assuming non-differential misclassification of the outcome between the treatment groups, the relative risk estimates are expected to be unbiased.

The Finnish Cancer Registry (FCR) used by the Hjorth study has 96% completeness for childhood-leukemia registrations[9], we consider the capture of childhood leukemia in the FCR to be adequate.

The Medical Birth Registry of Norway used by the Nordeng study has a PPV of 90% for preterm delivery and a PPV of 100% for low birth weight (N=786, gold standard: hospital records).[10] We expect a similarly high PPV for other infant outcomes evaluated by the Nordeng study. Assuming potential misclassification of infant outcomes assessed by the Nordeng study, if any, to be non-differential between the pivemcillinam and nitrofurantoin groups, risk estimates are likely unbiased.

In the Norgaard study, miscarriage was ascertained from the County Hospital Discharge Registry of Jutland while live births were ascertained from the Danish Medical Birth Registry. Danish registries have almost 100% coverage for all hospital discharges with a PPV of 97% (N=114, gold standard: review of discharge records) for spontaneous abortion.[11] Nevertheless, non-hospitalized miscarriages occurring in early stages of pregnancy are likely to be missed and not captured in the registry. In fact, 30% of self-reported spontaneous abortions in

[d] DEPI has conducted a literature review on the risk of adverse pregnancy, maternal, and infant outcomes associated with nitrofurantoin use during pregnancy previously (Reference ID: 5243444). The reviewed studies reported mixed findings regarding the risk of adverse pregnancy and infant outcomes associated with nitrofurantoin use during pregnancy, which cannot definitively establish the presence or absence of risk during pregnancy.

Denmark are not captured in the Danish Hospital Discharge Registry.[12] Assuming pivmecillinam exposed pregnant women are also more likely to have non-hospitalized miscarriages compared to unexposed, the resulting estimates could be underestimated.

Residual confounding

Maternal urinary tract infections (UTIs) have been linked with the risk of adverse pregnancy outcomes.[13-15] Thus, only studies which accounted for maternal infections, either with active comparators or direct adjustment of infections in regressions were included in our review. For the Damkier and Nordeng studies which assessed the risk of malformations, the influence of residual confounding from underlying maternal infection might be small given that both studies used active comparators and accounted for important confounders. Notably, in the Damkier study when pivemcillinam was compared to the unexposed group, ORs, although elevated, remained close to 1, similar to ORs in the main analysis where pivemcillinam was compared to penicillins. This suggests the influence of UTI might be limited in the assessment of malformations. Nevertheless, residual confounding from unmeasured confounders such as concomitant medication use, illicit drug use, or exposure to known teratogens could bias estimates.

In the case control study by Norgaard, the risk of miscarriage was compared between those exposed to pivmecillinam versus those unexposed in the main analysis, raising concerns about potential confounding by underlying infection. To account for such a possibility, authors compared ORs from the main analysis to ORs of another analysis in which the risk of miscarriage was compared between those exposed to sulfamethizole versus those unexposed. While the authors concluded there was no difference in risk between pivmecillinam and sulfamethizole exposed pregnancies after comparing the two sets of ORs, the validity of this unconventional approach is unknown. Therefore, it is unclear to what extent this study addressed the issue of confounding by underlying maternal UTI. Moreover, the Norgaard study did not account for socioeconomic and lifestyle factors (e.g., smoking), important confounders in the estimation of miscarriage risks.

Similarly, the Hjorth study did not account for environmental and socio-economic factors which are important confounders in estimation of leukemia risks, failure to account for these factors precludes a definitive determination of leukemia risk.

CONCLUSION

It is our view that the data on malformation seems to have better quality than data on other outcomes.

Malformations

Although the two reviewed studies were limited by potential exposure misclassification, they generally do not support an association between pivmecillinam use during the first trimester and the risk of malformations.

Miscarriage

Given the lack of control for potential underlying maternal infection, socioeconomic, and lifestyle factors, and potential exposure and outcome misclassifications of the review study, there is insufficient evidence in the literature to confirm or refute increased risk of miscarriage following in utero exposure to pivmecillinam.

Stillbirth, or neonatal deaths, low birth weight, preterm deliveries, NICU admissions, Apgar score lower than 7 at 5 minutes, and neonatal jaundice

Given the less clear risk profile of nitrofurantoin as the comparator, the reviewed study cannot definitively establish the presence or absence of increased risks of stillbirth or neonatal deaths, low birth weight, preterm deliveries, NICU admissions, Apgar score lower than 7 at 5 minutes, and neonatal jaundice following exposure to pivmecillinam during pregnancy.

Childhood leukemia

Given the small effect size, potential residual confounding by environmental and socioeconomic factors, lack of evidence of dose response relationship, and unknown biological mechanism, the reviewed study cannot definitively confirm or refute the risk of childhood leukemia following in utero exposure to pivmecillinam.

RECOMMENDATIONS

We recommend the following languages in Section 8.1 of the pivmecillinam labeling.

Risk summary

Published observational studies on pivmecillinam use during the first trimester do not indicate an increased risk of major birth defects. There are limited studies on pivmecillinam use during pregnancy (b) (4)

Data

Human Data

Two cohort studies in 42,223 pregnant women who were exposed to pivmecillinam during the first trimester did not observe an increased risk of major birth defects when compared with 50,099 pregnant women exposed to other antibiotics. These two studies were limited by potential exposure misclassification.

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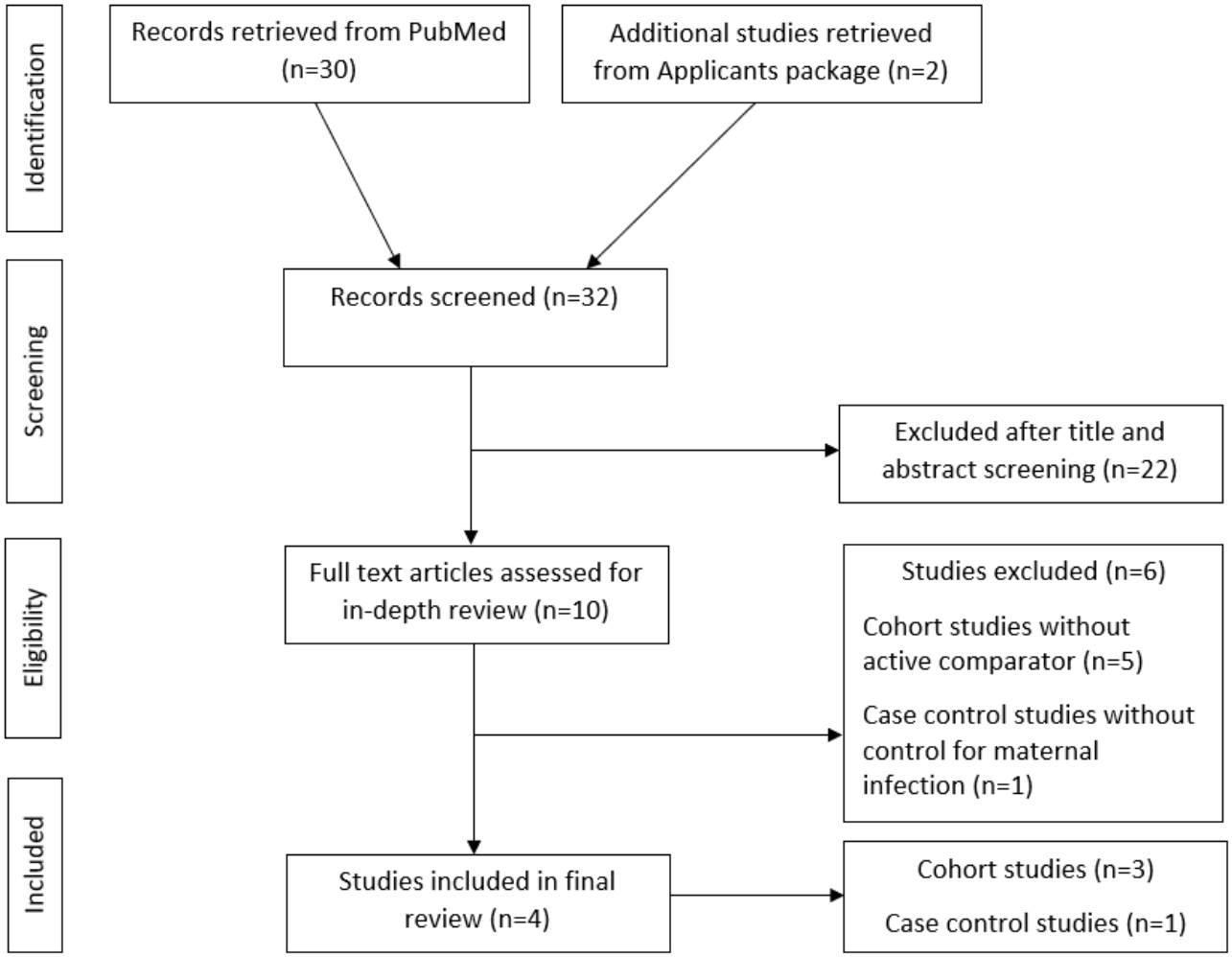
APPENDIX 1: Search Strategy

Strategy	ID#	Query	Hits
Intervention or exposure (Pivmecillinam)	#1	((((((((((Pivmecillinam[Text Word]) OR ("Amdinocillin Pivoxil"[Text Word])) OR (pivamdinocillin[Text Word])) OR ("mecillinam pivaloyl ester"[Text Word])) OR (Selexid[Text Word])) OR ("pivmecillinam hydrochloride"[Text Word])) OR ("FL-1039"[Text Word])) OR ("FL 1039"[Text Word])) OR (coactabs[Text Word])) OR (mecillinam[Text Word])) OR ("Amdinocillin Pivoxil"[MeSH Terms])) OR (Pivmecillinam[MeSH Terms])	869
Outcome (Pregnancy outcome)	#2	((((((((((((("Pregnancy outcome*"[Text Word]) OR "Pregnancy complication*"[Text Word]) OR "Congenital malformation*"[Text Word]) OR ("congenital disorder*"[Text Word])) OR ("congenital abnormalit*"[Text Word])) OR ("fetal disease*"[Text Word])) OR (inborn[Text Word])) OR (infant[Text Word])) OR (newborn[Text Word])) OR (disorder*[Text Word])) OR ("birth defect*"[Text Word])) OR ("congenital abnormalities"[MeSH Terms])) OR ("fetal diseases"[MeSH Terms])) OR ("Pregnancy Complications"[MeSH Terms])) OR ("Congenital, Hereditary, and Neonatal Diseases and Abnormalities"[MeSH Terms])	4,829,313
Population	#3	((((("Pregnant women"[Text Word]) OR (gestation[Text Word])) OR (pregnanc*[Text Word])) OR ("Pregnancy"[MeSH Terms])) OR ("Pregnancy Trimesters"[MeSH Terms])	1,171,210
#1 AND #2 AND #3	#4	((((((((((((Pivmecillinam[Text Word]) OR ("Amdinocillin Pivoxil"[Text Word])) OR (pivamdinocillin[Text Word])) OR ("mecillinam pivaloyl ester"[Text Word])) OR (Selexid[Text Word])) OR ("pivmecillinam hydrochloride"[Text Word])) OR ("FL-1039"[Text Word])) OR ("FL 1039"[Text Word])) OR (coactabs[Text Word])) OR (mecillinam[Text Word])) OR ("Amdinocillin Pivoxil"[MeSH Terms])) OR (Pivmecillinam[MeSH Terms])) AND ((((((((((((("Pregnancy outcome*"[Text Word]) OR "Pregnancy complication*"[Text Word]) OR "Congenital malformation*"[Text Word]) OR ("congenital disorder*"[Text Word])) OR ("congenital abnormalit*"[Text Word])) OR ("fetal disease*"[Text Word])) OR (inborn[Text Word])) OR (infant[Text Word])) OR (newborn[Text Word])) OR (disorder*[Text Word])) OR ("birth defect*"[Text Word])) OR ("congenital abnormalities"[MeSH Terms])) OR ("fetal diseases"[MeSH Terms])) OR ("Pregnancy Complications"[MeSH Terms])) OR ("Congenital, Hereditary, and Neonatal Diseases and Abnormalities"[MeSH Terms]))) AND (((((("Pregnant women"[Text Word]) OR (gestation[Text Word])) OR (pregnanc*[Text Word])) OR ("Pregnancy"[MeSH Terms])) OR ("Pregnancy Trimesters"[MeSH Terms]))	30

Appendix 2: Flow chart of article screening process



APPENDIX 3: Study Summary

Author, country, year, setting	Study type	Exposure and comparator	Index time	Outcome	Methods for confounding adjustment, covariates adjusted	Main results	Other analyses	Comments
Damkier, Denmark, 2019, Danish National Registries, 2000-2015	Cohort study	**Exposed:** Exposure to pivmecillinam which was defined as filling of a prescription for pivmecillinam at a Danish Pharmacy within the first trimester. **Comparator:** Exposure to any of four specific penicillins: ampicillin, pivampicillin, benzylpenicillin, or phenoxymethylpenicillin. This was defined as filling of prescription for one of four specific penicillins at a Danish Pharmacy within the first trimester. **Unexposed:** Pregnant women who did not fill any prescriptions during pregnancy. The Danish Registry of Medicinal Product Statistics (RMPS) was used to identify pregnant women's antibiotics prescription redemptions within the first trimester based on Anatomical Therapeutic Chemical (ATC) classification system.	**Index date:** Defined as the date of prescription fill within first trimester of pregnancy. First trimester was defined as the first 90 days from the first day of the last menstrual period.	**Malformations:** All malformations, major congenital malformations (MCM), and cardiovascular malformations. Malformations were identified in the Danish National Patient Registry (DNPR) and Danish Medicinal Birth Registry (DMBR) where malformations are coded based on the European Surveillance of Congenital Anomalies coding system (EUROCAT).	Logistic regression models used to adjust for maternal age, year of delivery, body mass index, parity, smoking, income, employment status, and level of education.	**Comparators** Pivmecillinam (n=36,423) vs. Penicillin (ampicillin, pivampicillin, benzylpenicillin, or phenoxymethylpenicillin, n=48,765) **Results** <u>Any malformations</u> Events: Pivmecillinam (6.3%) vs. Penicillin (NA). aOR: 0.97; 95% CI: 0.92 to 1.03 <u>Major congenital malformations</u> Events: Pivmecillinam (3.5%) vs. Penicillin (NA). aOR: 1.02; 95% CI: 0.94 to 1.10 <u>Cardiac malformations</u> Events: Pivmecillinam (1.0%) vs. Penicillin (NA) aOR: 0.99; 95% CI: 0.86 to 1.14	Sensitivity analysis compared exposure to pivmecillinam (n=36,423) with unexposed to any antibiotics (n=801,648). **Results** <u>Any malformations</u> aOR: 1.12; 95% CI: 1.07 to 1.17 <u>Major congenital malformations</u> aOR: 1.13: 95% CI: 1.06 to 1.19 <u>Cardiac malformations</u> aOR: 1.15; 95% CI: 1.04 to 1.28	1. Exposure misclassification as prescription fill may not truly reflect actual use. 2. Residual confounding by indication from other maternal infections, concomitant medication, illicit drug use, or exposure to known teratogens.
Nordeng, Norway, 2013, Medical Birth Registry of Norway and Norwegian Prescription Database, 2004-2008.	Cohort study	**Exposed:** Pregnant women dispensed nitrofurantoin. **Comparator:** Pregnant women dispensed pivmecillinam. Norwegian Prescription Database was used to identify pregnant women who were dispensed antibiotics in pregnancy.	**Index date:** Defined as the date in which antibiotics was dispensed. To assess risk of adverse pregnancy outcomes within different time windows (first, second or third trimester, any time during pregnancy, and last 30 days), timing of exposure was defined in relation to the date antibiotics was dispensed, date of delivery, and gestational age.	**Primary Outcome:** Malformations (All, Major, and cardiovascular). **Secondary adverse neonatal outcomes:** Stillbirth or neonatal deaths, low birth weight, preterm deliveries, Neonatal Intensive Care Unit (NICU) admissions, Apgar score lower than 7 at 5 minutes, and neonatal jaundice. Outcomes were ascertained from Medical Birth Registry of Norway based on ICD-10 code categorization of diagnoses.	Multivariable generalized estimating equations Models for malformations: maternal age, parity, previous miscarriage or stillbirth, smoking in the beginning of pregnancy, folic acid use, recurrent urinary tract infections, and maternal chronic disease. Model for neonatal jaundice: prematurity, neonatal sex, year of birth, use of oxytocin to induce labor, neonatal systemic antibiotic treatment, maternal age, parity, and smoking at the end of pregnancy.	**Comparators** *First trimester* Nitrofurantoin (n=1,334) vs. pivmecillinam (5,800) **Results** <u>All Malformations</u> Events: 4.0% vs. 5.0% aOR: 0.80; 95% CI: 0.58 to 1.12 <u>Major malformations</u> Events: 2.3% vs. 2.8%. aOR: 0.79; 95% CI: 0.51 to 1.23 <u>Cardiovascular malformations</u> Events: 1.0% vs. 1.0% aOR: 0.82; 95% CI: 0.40 to 1.67 **Comparators** *Any use during pregnancy* Nitrofurantoin (n=5,794) vs. pivmecillinam (20,643) **Results** <u>Stillbirth and neonatal mortality</u> Events: 0.9% vs. 0.9% aOR: 0.68; 95% CI: 0.38 to 1.24 <u>Low birth weight</u> Events: 4.1% vs. 4.0% aOR: 1.08; 95% CI: 0.76 to 1.56 <u>Preterm delivery</u> Events: 6.7% vs. 6.3% aOR: 1.04; 95% CI: 0.78 to 1.40 <u>NICU admission</u> Events: 9.6% vs. 9.3%. aOR: 0.97; 95% CI: 0.75 to 1.25 <u>Apgar score < 7 at 5 minutes</u> Events: 1.8% vs. 1.8% aOR: 0.84; 95% CI: 0.50 to 1.41 **Comparators**	None	1. Accuracy of neonatal jaundice and hemolytic anemia definitions is unknown. 2. For neonatal jaundice, residual confounding from over-the-counter co-medication in pregnancy or breast feeding.

Author, country, year, setting	Study type	Exposure and comparator	Index time	Outcome	Methods for confounding adjustment, covariates adjusted	Main results	Other analyses	Comments
						Last 30 days of pregnancy Nitrofurantoin vs. pivmecillinam **Results** <u>Neonatal jaundice requiring treatment</u> Events: 10.8% vs. 8.8%. aOR 1.25; 95% CI 0.93 to 1.69 <u>Hemolytic anemia</u> Events: 0.42% vs. 0.41%. aOR and 95% CI (not provided)		
Hjorth, Norway, 2022, National registries in Nordic countries (Denmark, Norway, Finland, Sweden), 1997-2003.	Cohort study	**Exposed:** Women who redeemed prescription for nitrofurantoin during pregnancy. **Comparator:** Women who redeemed prescription for pivmecillinam during pregnancy. Prescription Registries of four Nordic countries (Denmark, Norway, Finland, and Sweden) was used to identify pregnant women's antibiotics prescription fills during pregnancy based on the ATC classification system.	**Index date:** Defined as the date in which antibiotics was redeemed. To assess risk of adverse pregnancy outcomes within different time windows (first, second or third trimester), day zero of pregnancy was defined as the first day of the last menstrual period. First trimester: Days 0 to 89. Second trimester: Days 90 to 179 or birth if born within second trimester. Third trimester: Days 180 to birth.	**Leukemia:** Ascertained from Nordic Cancer Registries based on the International Classification of Childhood Cancer codes.	Inverse probability of treatment weighting based on propensity scores. Calendar year at birth, maternal age, parity, maternal history of cancer before pregnancy, prescription fills for immunosuppressants, systemic corticosteroids and systemic antibiotics before start of pregnancy, maternal smoking status during first trimester, and child sex.	**Comparators** First trimester exposure to nitrofurantoin (n=44,091) vs. pivmecillinam (n=247,306) **Results** <u>Any leukemia</u> *Any prenatal exposure* Events: 72.6 vs. 52.2 per 100,000 person-years wIRR: 1.34; 95% CI: 0.88 to 2.06 wIRD: 1.49; 95% CI: –1.92 to 4.90 per 100,000 person-years *First trimester exposure* Events: 59.9 vs. 34.6 per 100,000 person-years wIRR: 1.92; 95% CI: 0.84 to 4.41 wIRD: 3.53; 95% CI: –2.60 to 9.65 per 100,000 person-years *Second trimester exposure* Events: 38.3 vs. 54.4 per 100,000 person-years wIRR: 0.53; 95% CI: 0.19 to 1.47 wIRD: –2.77; 95% CI: –5.97 to 0.43 per 100,000 person-tears *Third trimester exposure* Events: 102.6 vs. 57.4 per 100,000 per person-years wIRR: 1.73; 95% CI: 1.00 to 2.98 wIRD: 4.77; 95% CI: –1.37 to 10.90 per 100,000 person-years	Results of sensitivity analyses were similar and supported findings of the main analyses. 1. Complete case analyses (instead of analyses in imputed dataset). 2. Analysis with follow-up beginning at 1 year of age to account for the fact that infant leukemia may have different etiology than late-onset childhood leukemia. 3. Analysis restricted to those who were unexposed to systemic antibiotics in utero other than pivmecillinam or nitrofurantoin. 4. Analysis restricted to those who had contact with the healthcare system before pregnancy.	1. Nordic cancer registry has coverage of close to 100%. A validation study in the Finnish Cancer Registry showed 95.7% completeness of childhood-leukemia registrations.
Norgaard, Denmark, 2008, Danish Registry, 1997-2002.	Case control study	**Exposed:** a) Women who redeemed prescription for pivmecillinam during pregnancy, b) women who redeemed prescription for sulfamethizole during pregnancy, and c) women who redeemed prescription for penicillin V during pregnancy. Exposure to antibiotics was assessed during four separate periods (within 1 week, 2-3 weeks, 4-7 weeks, and 8-12 weeks) prior to the day of hospitalization for cases (miscarriage) and the index date for controls. **Unexposed:** Women who did not redeem antibiotic prescription during pregnancy. Pharmaco-epidemiological Prescription Database of North Jutland was used to identify antibiotic prescriptions redeemed by pregnant women based on the ATC classification system.	**Index date:** Defined as the date in which antibiotics was redeemed.	**Cases:** Cases were defined as women who, during the study period, had a first-time recorded miscarriage and no previously recorded birth. All cases were ascertained from the County Hospital Discharge Registry of North Jutland (from which data are transferred to the Danish Hospital Discharge Registry) based on ICD-10 codes. **Controls:** Controls were defined as women with a first live birth during the study period and no previous recorded miscarriage in the Hospital Discharge Registry were eligible as controls. All controls were ascertained from the Medical Birth Registry of Denmark.	Conditional logistic regression model adjusted for maternal age, use of antidiabetics, and antiepileptics.	**Comparators** Pivmecillinam vs. Sulfamethizole **Results** **<u>Miscarriage</u>** **Pivmecillinam** *Exposure within 1 week before hospitalization* aOR: 2.03; 95% CI: 0.77 to 5.33 *Exposure within 2-3 weeks before hospitalization* aOR: 1.10; 95% CI: 0.44 to 2.78 *Exposure within 4-7 weeks before hospitalization* aOR: 0.75; 95% CI: 0.27 to 2.10 *Exposure within 8-12 weeks before hospitalization* aOR: 1.27; 95% CI: 0.38 to 4.22 **Sulfamethizole** *Exposure within 1 week before hospitalization* aOR: 1.53; 95% CI: 0.76 to 3.09 *Exposure within 2-3 weeks before hospitalization*	Sensitivity analysis was conducted to assess the risk of miscarriage from other maternal infections. Exposure to penicillin V (often prescribed in pregnancy for other types of infections) was not associated with an increased risk of miscarriage (OR=1.03; 95% CI: 0.41 to 2.61).	1. Misclassification from potential under reporting of non-hospitalized miscarriages that occurred at early stages of pregnancy in registry. 2. Unmeasured confounding from socioeconomic and lifestyle factors (e.g., smoking). 3. Statistical imprecision from infrequent use of pivmecillinam among selected cases and controls.

Author, country, year, setting	Study type	Exposure and comparator	Index time	Outcome	Methods for confounding adjustment, covariates adjusted	Main results	Other analyses	Comments
						aOR: 0.92; 95% CI: 0.47 to 1.82 *Exposure within 4-7 weeks before hospitalization* aOR: 1.04; 95% CI: 0.61 to 1.77 *Exposure within 8-12 weeks before hospitalization* aOR: 0.52; 95% CI: 0.19 to 1.43 **Pivmecillinam vs. Sulfamethizole** *Within 1 week before hospitalization:* p=0.64 *Within 2-3 weeks before hospitalization:* p=0.75		

aOR: adjusted odds ratio; NICU: neonatal intensive care unit; wIRR: weighted incident risk ratio; wIRD: weighted incident risk difference.

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