Long-Term Care Updates

June 2024

Pivmecillinam - a new aminopenicillin for the treatment of uncomplicated UTI

PharMerica

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Indications:
Pivmecillinam is FDA-approved for the treatment of females aged 18 years and older with uncomplicated urinary tract infections (uUTI) caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus saprophyticus*.[1]

Pharmacology:
Pivmecillinam is a prodrug of mecillinam, which is the pivaloyloxymethylester of amidinopenicillanic acid. Upon oral administration, pivmecillinam is rapidly hydrolyzed to mecillinam. Mecillinam is a beta-lactam antibacterial that is primarily active against gram-negative bacteria. Like other beta-lactams, mecillinam interferes with the biosynthesis of the bacterial cell wall by binding to penicillin-binding proteins (PBPs). However, mecillinam is unique in that it has high specificity against gram negative PBP-2, while other beta-lactams preferentially bind gram-negative PBP-1A, PBP-1B, or PBP-3.[1]

In vitro, mecillinam has demonstrated activity against Enterobacterales in the presence of some beta-lactamases and extended-spectrum beta-lactamases (ESBL), including CTX-M, SHV, TEM, and AmpC.[1]

Pharmacokinetics:
The pharmacokinetic parameters of pivmecillinam and its active antibacterial moiety mecillinam are listed in Table 1. While taking pivmecillinam with food does not alter its pharmacokinetic profile, the impact of age, body weight, race, and sex on the pharmacokinetics of pivmecillinam or mecillinam has not been evaluated. Hepatic impairment is not expected to alter mecillinam clearance as hepatic metabolism plays a minor role in its elimination. However, the effects of hepatic impairment on mecillinam pharmacokinetics have not been studied. Declining renal function decreases the systemic elimination and urinary excretion of mecillinam, although the clinical significance of these changes on the safety and efficacy of pivmecillinam is unclear. No dosage adjustments are recommended based on hepatic or renal function.[1]

Table 1: Available pharmacokinetic parameters for pivmecillinam[1]

	Pivmecillinam
Absorption	Bioavailability = 25-35% Cmax = 1.7mcg/mL (mecillinam) Tmax = 90 min (mecillinam)
Distribution	<25% plasma protein-bound Vd = 51L
Metabolism	Pivmecillinam is converted to mecillinam and pivalic acid by non-specific esterases; mecillinam undergoes minimal metabolism
Excretion	Renal elimination 80% of dose recovered unchanged in urine $t_{½}$ = 61 min

Standard of Care/Clinical Guidelines:

Guidelines from the Infectious Diseases Society of America (IDSA) on the treatment of acute uncomplicated urinary tract infections and pyelonephritis have not been updated since 2010.[2] They are currently archived, with new guidelines under development.

Generally, experts suggest that empiric antibiotic therapy is appropriate in nonpregnant females with uUTI, with selection of antibiotic based on local antimicrobial resistance patterns, coverage for ESBL-producing strains if concerns for resistance exist, and patient-specific factors, including prior UTIs, allergies, and tolerability issues. First-line options for empiric therapy including nitrofurantoin, fosfomycin, and pivmecillinam. Second-line agents include cefadroxil and cephalexin. Trimethoprim/sulfamethoxazole may be considered if local resistance for *E. coli* is <20%. Fluoroquinolones and aminopenicillins (with the exception of pivmecillinam) are generally not recommended for uUTI. In addition to antibiotic therapy, management of symptoms with nonsteroidal anti-inflammatory drugs (NSAIDS) and urinary analgesics (e.g., phenazopyridine) should be considered. Evidence regarding the use of herbal remedies or cranberry products for uUTI is limited.[3]

Comparative Clinical Efficacy:

Pivmecillinam was approved on the basis of three phase III, double-blind, randomized controlled trials comparing pivmecillinam, taken three times daily for 3-7 days, to placebo, cephalexin, or ibuprofen in over 750 females with uUTI. The primary outcome in each study was composite response, which required both clinical cure and microbiological response at the "test of cure" date, which ranged from day 8 to day 14 across the three trials. Patients analyzed included those in the microbiological intention-to-treat population, which was defined as all randomized subjects with positive baseline urine culture $\geq 10^5$ CFU and no more than 2 species of microorganisms detected. With respect to the primary outcome, pivmecillinam was superior to placebo and ibuprofen. For every 2 patients treated with pivmecillinam over placebo, 1 additional patient achieved both clinical cure and microbiological response. For every 3 patients treated with pivmecillinam over ibuprofen, 1 additional patient achieved the primary outcome. Significant differences between pivmecillinam and placebo or ibuprofen were also observed for clinical cure and microbiological response rates when analyzed separately. No statistically significant differences between pivmecillinam and cephalexin were reported.

Adverse Reactions:
Pivmecillinam was generally well tolerated in all trials that led to its approval. The most common adverse reactions reported in the placebo-controlled trial for pivmecillinam are listed in Table 3. No serious adverse reactions were reported in any patients treated with pivmecillinam in the clinical trials described above.[1]

Table 2: Commonly reported adverse reactions to pivmecillinam

	Pivmecillinam (n = 282)	Placebo (n = 288)
Diarrhea	2.1%	0.7%
Genital pruritus	1.8%	1.4%
Headache	1.4%	0.3%
Nausea	4.3%	2.1%
Vulvovaginal candidiasis	1.8%	0.0%

Boxed Warning:
Pivmecillinam does not carry a Boxed Warning.[1]

QT Prolongation:
No evidence addressing the risk of QT prolongation with pivmecillinam was identified.

Contraindications, Warnings & Precautions:
The labeled contraindications, warnings, and precautions for pivmecillinam are provided in Table 3. Pivmecillinam is contraindicated in patients who have experienced a serious hypersensitivity reaction to pivmecillinam, penicillins, or cephalosporins. Because pivmecillinam has been associated with acute attacks of porphyria, it is contraindicated in patients suffering from porphyria. It is also contraindicated in patients with primary or secondary carnitine deficiency.[1]

Pivmecillinam is a pivalate-containing compound, and clinical manifestations of carnitine depletion can occur in patients using these compounds. While carnitine depletion is unlikely with short courses of pivmecillinam therapy, long-term treatment has been linked to clinically significant hypocarnitinemia. Symptoms include hypoglycemia, muscle aches, fatigue, and confusion. Concomitant treatment with valproic acid or other pivalate-generating drugs can increase the risk of carnitine depletion.[1]

Table 3: Contraindications, warnings, and precautions of pivmecillinam[1]

	Pivmecillinam
Contraindication	
Acute porphyria	X
Carnitine deficiency	X
Serious hypersensitivity reactions	X
Warning/Precaution	
Carnitine depletion	X
Clostridioides difficile-associated diarrhea	X
Development of drug-resistant bacteria	X
Hypersensitivity reactions	X
Interference with newborn screening test	X
Severe cutaneous adverse reactions	X

Drug Interactions:
Drug interactions do not appear to be a major concern with pivmecillinam. Due to the potential for carnitine depletion (see Contraindications, Warnings, and Precautions), concomitant treatment with valproic acid, valproate, or other pivalate-generating drugs should be avoided. If the use of pivmecillinam with these drugs is necessary, patients should be monitored for symptoms associated with carnitine depletion. Penicillins, including pivmecillinam, can reduce the clearance of methotrexate, and alternative therapy should be considered when possible.[1]

Recommended Monitoring:
Beyond monitoring patients for improvement in symptoms associated with uUTI, laboratory monitoring is not necessary.[1,4]

Geriatric/Nursing Considerations:
In the phase III clinical trials for pivmecillinam, 14% and 3% of patients were aged ≥65 years and ≥75 years, respectively. No differences in safety or efficacy of pivmecillinam were observed between older and younger patients, and no dosage adjustment based on age is required. Pivmecillinam is renally eliminated and older adults are more likely to have decreased renal function; however, the clinical significance of these changes is unknown.[1]

Pivmecillinam may be taken with or without food.[1]

Dosing and Availability:
Pivmecillinam is available in oral tablets providing 185mg of pivmecillinam (equivalent to 200mg of pivmecillinam hydrochloride).

Usual Adult Dosage**:** 185mg by mouth 3 times daily for 3-7 days as clinically indicated.

Renal Dosing: No adjustment necessary.

Hepatic Dosing: No adjustment necessary.

Geriatric Dosing: Refer to Usual Adult Dosing.

Summary:

1. Pivmecillinam, a prodrug of mecillinam, is FDA-approved for the treatment of adult females with uUTI caused by susceptible isolates of *Escherichia coli, Proteus mirabilis,* and *Staphylococcus saprophyticus.*

2. Clinical practice guidelines on the management of uUTI have not been updated since 2010; however, experts suggest that pivmecillinam may be considered a first-line empiric treatment option.

3. In phase III clinical trials, pivmecillinam was superior to both placebo and ibuprofen, with similar results when compared with cephalexin, in female patients with uUTI. For every 2 or 3 patients treated with pivmecillinam over placebo or ibuprofen, respectively, 1 additional patient achieved both clinical cure and microbiological response.

4. Pivmecillinam does not carry a Boxed Warning and has limited potential for drug-drug interactions.

5. While rare, pivmecillinam may cause severe hypersensitivity reactions, porphyria, severe cutaneous adverse reactions, or *Clostridioides difficile*-associated diarrhea.

6. Because pivmecillinam is a pivalate-containing compound, it can cause carnitine depletion, especially when used long-term or in combination with valproic acid or other pivalate-generating drugs. Carnitine depletion is unlikely when pivmecillinam used short-term, as labelled, for uUTI. Its use should be avoided in patients with primary or secondary carnitine deficiency.

7. No laboratory monitoring or dose adjustments for renal or hepatic impairment are necessary.

References:

1. Pivya [package insert]. Florham Park, NJ: Utility Therapeutics Ltd.; April 2024.
2. Gupta K, Hooton TM, Naber KG, 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;52(5):e103-e120.
3. Uncomplicated Urinary Tract Infection (UTI) (Pyelonephritis and Cystitis). DynaMed. EBSCO Information Services. https://www.dynamed.com/condition/uncomplicated-urinary-tract-infection-uti-pyelonephritis-and-cystitis. Updated May 15, 2024. Accessed June 16, 2024.
4. Pivmecillinam. Clinical Pharmacology. Tampa, FL: Elsevier/Gold Standard; 2024. https://www.clinicalkey.com/pharmacology/monograph/5532?sec=monmp. [subscription required]. Updated May 13, 2024. Accessed June 16, 2024