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2024 Quarter 2 Newsletter

FDA APPROVAL SPOTLIGHT



On April 24, 2024, Pivya (pivmecillinam) was approved for the treatment of uncomplicated urinary tract infections (UTIs) in adult females by the Food and Drug Administration (FDA). This is indicated specifically for UTIs caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus saprophyticus*.

Uncomplicated or simple UTI is also known as cystitis (infection of the bladder) or pyelonephritis (infection of the kidney), depending on its location. This diagnosis is typically characterized by a symptomatic infection in female patients that are afebrile, immune-competent, and not pregnant. Symptoms may include urinary frequency and/or urgency, dysuria, suprapubic pain, etc. The majority of these infections are caused only by a few bacterial species with *E. coli* and *Klebsiella spp.* being the most common.

In September 2023, the National Institutes of Health (NIH) published a study that found that UTIs affect over 10% of women in the United States annually with over 60% of U.S. women being diagnosed with at least UTI in their lifetime. Due to the prevalence of this disease state, as well as the rise in resistant UTI-causing pathogens, there has been a great need for development of new therapies for this indication. The Infectious Diseases Society of America's (IDSA) 2011 guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis recommend nitrofurantoin or trimethoprim-sulfamethoxazole as first-line therapies for this indication. The guidelines also reference pivmecillinam 400 mg twice daily for 3 to 7 days as an appropriate first-line choice but acknowledge that the product has not been available in the United States.

Pivya is the first formulation of pivmecillinam approved for use in the United States. It is taken as a 185 mg tablet by mouth three times daily for 3 to 7 days, administered without regard to meals. Pivya is contraindicated in patients with hypersensitivity to pivmecillinam, other beta-lactam antibiotics, or any other formulation component. It is also contraindication in patients with primary or secondary carnitine deficiency resulting from inherited disorders of mitochondrial fatty acid oxidation and carnitine metabolism, as well as porphyria. As a penicillin antibiotic, its primary mechanism of action consists of bacterial cell wall interference, but uniquely Pivya performs this action by acting with high specificity against penicillin-binding protein 2 (PBP-2), which is found in gram-negative cell walls.

In three multicentered, randomized, doubled-blinded clinical trials, Pivya was compared to placebo, cephalexin, and ibuprofen, respectively. The primary outcomes composite response rates, clinical cure rates, and microbiological response rates. Pivya outperformed placebo and ibuprofen but fell short of cephalexin in all of these three outcomes. Table 1 describes these outcomes from each trial.

Composite Response Rate (Clinical Cure and Microbiological Response)	Rate (%)	Rate (%)	Difference (95% CI)
Trial 1 Pivya (N=137) Placebo (N=134)	Pivya – 85 (62)	Placebo – 14 (10)	52 (41, 62)
Trial 2 Pivya (N=127) Cephalexin (N=132)	Pivya – 91 (72)	Cephalexin – 100 (76)	-4 (-16, 7)
Trial 3 Pivya (N=105) Ibuprofen (N=119)	Pivya – 69 (66)	Ibuprofen – 26 (22)	44 (31, 57)
Clinical Cure Rates (Micro-ITT Population)	Rate (%)	Rate (%)	Difference (95% CI)
Trial 1 Pivya (N=137) Placebo (N=134)	Pivya – 87 (64)	Placebo – 31 (23)	40 (29, 52)
Trial 2 Pivya (N=127) Cephalexin (N=132)	Pivya – 105 (83)	Cephalexin – 112 (85)	-2 (-12, 8)
Trial 3 Pivya (N=105) Ibuprofen (N=119)	Pivya – 81 (77)	Ibuprofen – 45 (38)	39 (27, 52)
Microbiological Response Rate	Rate (%)	Rate (%)	Difference (95% CI)
Trial 1 Pivya (N=137) Placebo (N=134)	Pivya – 119 (87)	Placebo – 35 (26)	61 (51, 71)
Trial 2 Pivya (N=127) Cephalexin (N=132)	Pivya – 97 (76)	Cephalexin – 106 (80)	-4 (-15, 7)
Trial 3 Pivya (N=105) Ibuprofen (N=119)	Pivya – 78 (74)	Ibuprofen – 64 (54)	21 (7, 34)

Another consideration for Pivya, due to the affected population, is its use in pregnancy and lactation. It is known that mecillinam, the active metabolite of pivmecillinam, does cross the placenta; but is unclear if it is significantly distributed into breastmilk. Because being pregnant and having a UTI automatically constitutes a complicated UTI, Pivya is technically not indicated for treatment in pregnant patients. However, it is worth noting that other penicillin antibiotics are used for the treatment of various infections in pregnancy. So it is likely that additional data for Pivya use in this population will be forthcoming.

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2024 GUIDELINE UPDATES

In May of 2024, the American Academy of Dermatology (AAD) published an updated guideline for the management of acne vulgaris. Previously, the most recent AAD guideline for this diagnosis had been published in 2016. These guidelines served to update treatment recommendations for acne vulgaris, based on the most recent evidence on the safety and efficacy of available treatments.

Acne vulgaris is in the top ten most prevalent disease states around the world with approximately 85% of adolescents being affected. The pathogenesis of acne vulgaris involves complex relationships between bacterial colonization of the epidermis, immune-mediated inflammatory responses, and follicular hyperkeratinization. Due to its widespread prevalence and impact on quality of life, the emotional, physical, and financial strain is felt by many patients.

Table 1: AAD Acne Vulgaris Treatment – Highlighted Guideline Updates

Guideline Topic	2024 Recommendations
Topical Treatments	Multimodal approach is recommended with the following first-line agents in fixed-dose combinations. - Topical retinoids - Benzoyl peroxide Topical antibiotics
	Clascoterene, salicylic acid, and azelaic acid may also be used as second-line topical treatment options.
Systemic Antibiotics	Limit use when possible. When needed, doxycycline is preferred in combination with topical treatments.

	Minocycline, sarecycline, and azithromycin may also be used as second-line systemic antibiotic options.
Hormonal Agents	Intralesional corticosteroids are preferred as an adjuvant treatment for large acne papules or nodules at risk of scarring.
	Combined oral contraceptives and spironolactone may be used as second-line hormonal agent options.
Isotretinoin	Isotretinoin should be considered for patients with significant psychosocial burden or scarring with daily dosing preferred over intermittent dosing.
Physical Modalities	Use of pneumatic broadband light is recommended against in addition to adapalene.

Key points for these recommendations include the wide range of recommended topical and antibiotic therapies, the role of hormonal therapies such as combined oral contraceptives, and the emphasis on identifying patient at high risk of scarring. Additionally, it is important to note that the evidence points to utilizing multiple mechanisms of action when necessary, including the recommended multiple approach to topical treatments, while still limiting systemic antibiotic use if at all possible to avoid bacterial resistance.

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LEGISLATIVE NEWS



On March 22, 2024, the Health Care Cybersecurity Improvement Act of 2024 was introduced in the Senate. As stated, this bill would require all entities “to meet minimum cybersecurity standards to be eligible for Medicare accelerated and advance payment programs if the reason for the need for such payments is due to a cybersecurity incident.” This bill was likely created in response to the many cyberattacks targeting healthcare entities in recent years.

This is concerning for many reasons but particularly in the arena of patient privacy. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 lays out standards for protecting patient information and hindering its unnecessary disclosure without the patient’s consent. To improve the safety of sensitive health-related information, the Health Care Cybersecurity Improvement Act would require all hospitals to agree to the Medicare Condition of Participation, a set of healthcare-related cybersecurity standards, and would allocate up to \$100 million to these hospitals for the implementation of these standards and access to cybersecurity resources.

The introduction of this bill signals a growing concern in the federal government, as well as the general population they represent, for the negative impacts of misplaced or misused patient information and the need for greater security measures to prevent these impacts. It is expected that similar legislation will be introduced in both the House and the Senate in the coming months, but it is unclear how these may affect the Medicare and Medicaid patient populations specifically or the providers/entities that care for them.

References:

- S.4054 - 118th Congress (2023-2024): Health Care Cybersecurity Improvement Act of 2024. (2024, March 22).
<https://www.congress.gov/bill/118th-congress/senate-bill/4054/text>
- H.R.3103 - 104th Congress (1995-1996): Health Insurance Portability and Accountability Act of 1996. (1996, August 21).
<https://www.congress.gov/bill/104th-congress/house-bill/3103>