

**Short Communication**

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A Milestone in Antimicrobial Therapy: Oral Tebipenem Pivoxil for Complicated Urinary Tract Infections

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Complicated urinary tract infections (cUTIs), including acute pyelonephritis, increasingly involve multidrug-resistant Gram-negative pathogens for which effective oral treatment options are limited. Oral tebipenem pivoxil hydrobromide (tebipenem pivoxil) represents an important therapeutic advance as the first orally administered carbapenem approved by the U.S. Food and Drug Administration for adults with cUTIs, including pyelonephritis, who have limited or no suitable oral treatment alternatives. The Phase III PIVOT-PO trial demonstrated that oral tebipenem was noninferior to intravenous imipenem-cilastatin, with a comparable safety profile, supporting its potential to facilitate intravenous-to-oral transition and reduce prolonged parenteral therapy. However, its use should remain restricted to appropriately selected patients to preserve carbapenem effectiveness and support antimicrobial stewardship. Important populations, including patients with severe renal impairment, severe hepatic impairment, seizure history, or carnitine deficiency, were excluded from pivotal trials, limiting the generalizability of current evidence. Gastrointestinal adverse effects, particularly diarrhea, nausea, and headache, were among the most frequently reported treatment-emergent events. Although tebipenem offers a promising oral alternative for selected resistant cUTIs, further real-world and outpatient studies are needed to evaluate its long-term safety, effectiveness, resistance development, and impact on healthcare utilization. Its role should therefore be guided by culture and susceptibility results, clinical status, patient-specific factors, and established stewardship principles.

Short Communication

Urinary tract infections (UTIs), particularly acute pyelonephritis and other complicated urinary tract infections (cUTIs), remain among the most common serious bacterial infections requiring hospitalization. Their management has become increasingly challenging because of the rising prevalence of antimicrobial-resistant pathogens [1]. Extended-spectrum β -lactamase (ESBL)-producing Enterobacterales and fluoroquinolone-resistant Gram-negative organisms are often resistant to conventional oral

antibiotics, leaving intravenous (IV) carbapenems as the mainstay of treatment [2]. Although patients frequently improve clinically within a few days, many must continue prolonged IV therapy because no reliable oral alternative is available. This dependence on parenteral treatment contributes to longer hospital stays, increased healthcare costs, and catheter-related complications, highlighting the need for an effective oral agent with activity against multidrug-resistant Gram-negative uropathogens while maintaining the efficacy of carbapenems [3].

The choice of therapy for cUTIs, including acute pyelonephritis, depends on disease severity, previous antibiotic exposure, local antimicrobial resistance patterns, and urine culture susceptibility results [4]. Current guidelines recommend transitioning clinically improving patients from IV to oral therapy when an effective oral agent is available [2,4]. However, this strategy is often not feasible when infections are caused by resistant Gram-negative organisms, particularly ESBL-producing Enterobacterales [2].

For susceptible isolates, oral trimethoprim-sulfamethoxazole (TMP-SMX) or fluoroquinolones may be used as step-down therapy, provided susceptibility has been confirmed and prior antibiotic exposure has not compromised their effectiveness [2,4]. In contrast, agents commonly used for lower UTIs, such as nitrofurantoin, are unsuitable for pyelonephritis because they do not achieve adequate renal parenchymal concentrations [4]. Consequently, carbapenems including ertapenem, meropenem, and imipenem-cilastatin remain essential treatment options for resistant infections but require intravenous administration [2].

This creates an important therapeutic gap: patients may be clinically stable but remain dependent on hospital-based or outpatient parenteral antimicrobial therapy solely because no effective oral alternative exists. Oral tebipenem pivoxil addresses this unmet need by providing the first oral carbapenem option for selected adults with cUTIs and pyelonephritis who have limited or no suitable oral treatment alternatives [3].

On June 17, 2026, the U.S. Food and Drug Administration (FDA) approved tebipenem pivoxil hydrobromide (Utebzi), making it the first orally administered carbapenem approved for the treatment of complicated urinary tract infections, including pyelonephritis, in adults with limited or no alternative oral treatment options [5]. Tebipenem pivoxil is an orally administered prodrug that is rapidly hydrolyzed to its active form, tebipenem, after absorption. Tebipenem inhibits bacterial cell wall synthesis by binding to multiple penicillin-binding proteins (PBPs), resulting in bactericidal activity. As with other β -lactam antibiotics, its efficacy is best correlated with the percentage of time that free plasma concentrations remain above the minimum inhibitory concentration (%fT>MIC) [5]. Its spectrum includes many ESBL- and AmpC-producing Enterobacterales, as well as isolates resistant to trimethoprim-sulfamethoxazole and fluoroquinolones, making it particularly relevant in regions where multidrug-resistant uropathogens are increasingly prevalent [3].

The efficacy and safety of oral tebipenem were demonstrated in the Phase III PIVOT-PO trial, which formed the basis for FDA approval. In this study, oral tebipenem was noninferior to intravenous imipenem-cilastatin in hospitalized adults with cUTIs or acute pyelonephritis and exhibited a comparable safety profile [6]. As the first oral carbapenem available for clinical use, tebipenem has the potential to facilitate earlier hospital discharge, expand outpatient management, and reduce dependence on prolonged intravenous antibiotic therapy [5,6].

Despite this important therapeutic advance, several limitations should be considered. The FDA indication is restricted to adults with limited or no suitable oral treatment alternatives and is

not intended for routine first-line use, reflecting principles of antimicrobial stewardship and efforts to minimize the emergence of resistance [5]. Furthermore, important patient populations were excluded from the PIVOT-PO trial, including individuals with creatinine clearance ≤ 30 mL/min, severe hepatic impairment (ALT/AST $> 5\times$ the upper limit of normal), a history of seizures, or carnitine deficiency. Consequently, the safety and efficacy of tebipenem in these groups remain uncertain [6].

The most frequently reported treatment-emergent adverse events were diarrhea (4.9%), headache (3.0%), and nausea (2.7%), which were generally mild to moderate in severity [6]. Additionally, because the trial enrolled only hospitalized patients, its findings cannot be directly extrapolated to patients managed entirely in the outpatient setting [6].

Pharmacokinetic-pharmacodynamic analyses further demonstrated that tebipenem exposure was not predictive of either clinical or microbiological response, suggesting that the dosing regimen was appropriately optimized [7]. Instead, treatment outcomes were more strongly influenced by patient-specific factors, including anatomical or functional urinary tract abnormalities, rather than by plasma antibiotic exposure [7]. These observations may help refine future clinical trial design and improve identification of patients most likely to benefit from therapy [7].

In conclusion, oral tebipenem pivoxil represents a significant advancement in the management of complicated urinary tract infections by providing the first effective oral carbapenem for appropriately selected adults. Its availability may facilitate earlier transition from intravenous therapy, reduce healthcare resource utilization, and improve patient convenience without compromising efficacy. Nevertheless, its use should remain guided by culture and susceptibility data, antimicrobial stewardship principles, and the approved FDA indication.

Future development should focus on addressing the remaining evidence gaps surrounding oral carbapenem therapy. Additional studies could characterize tebipenem across broader patient populations, particularly patients with renal impairment, recurrent or structurally complicated urinary tract infections, and those managed entirely in outpatient settings. Real-world pharmacokinetic and pharmacodynamic studies may also help determine whether the currently approved regimen provides adequate exposure across diverse patient characteristics and infecting organisms. Longer-term surveillance will be important to characterize the emergence of tebipenem resistance, cross-resistance with other carbapenems, and the potential ecological consequences of wider oral carbapenem use. Comparative effectiveness studies incorporating hospitalization duration, outpatient parenteral antibiotic therapy, readmissions, adverse events, and healthcare costs could further clarify its clinical and health-system value. Such evidence may ultimately inform future regulatory decisions regarding the populations in which tebipenem can be used and the conditions under which its benefits outweigh antimicrobial stewardship concerns.

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