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## Review Article

# Tebipenem pivoxil, the first oral carbapenem for complicated urinary tract infections: a review

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## ABSTRACT

Complicated urinary tract infections (cUTIs) are increasingly difficult to manage because emerging antimicrobial resistance limits conventional oral treatment options. Tebipenem pivoxil hydrobromide is an orally administered prodrug of tebipenem. It was recently approved by the US FDA in June 2026. It represents the first oral carbapenem available for adults with cUTI, including pyelonephritis, caused by specified susceptible organisms when limited or no alternative oral options exist. The pivotal PIVOT-PO trial demonstrated non-inferiority of oral tebipenem pivoxil 600 mg every 6 hours to intravenous imipenem-cilastatin for 7–10 days in hospitalised adults with cUTI or pyelonephritis, building on earlier non-inferiority evidence against intravenous ertapenem from the ADAPT-PO programme. After summarising the pharmacology, microbiology, pharmacokinetics, dosing, efficacy, safety and gut-microbiome data underlying the United States approval, this review offers a critical appraisal of where tebipenem pivoxil fits among the several new oral agents recently introduced for urinary tract infection, and considers its relevance to antimicrobial-resistance settings such as India, where carbapenem resistance among Enterobacterales is substantial and driven predominantly by metallo- $\beta$ -lactamases against which no currently available carbapenem, including tebipenem, retains activity. The clinical value of tebipenem is therefore best understood not as a universal substitute for intravenous carbapenems or for narrower-spectrum oral agents, but as an option for carefully selected patients needing carbapenem-level activity and suitable for oral therapy, guided by local susceptibility data, renal dose adjustments, awareness of carnitine depletion and valproic acid interactions, and proper antimicrobial stewardship.

**Keywords:** Complicated urinary tract infection, Tebipenem pivoxil, Oral carbapenem, Pyelonephritis, Antimicrobial resistance, Carbapenem-sparing therapy, Antimicrobial stewardship, Gut microbiota, Metallo- $\beta$ -lactamase

## INTRODUCTION

Urinary tract infections (UTIs) are among the most frequently encountered bacterial infections in ambulatory and hospital settings.<sup>1</sup> Complicated UTIs (cUTI) includes structural or functional urinary tract abnormalities, instrumentation, comorbidity, or other host factors increase the likelihood of treatment failure and adverse outcomes. Pyelonephritis represents an important upper-

tract manifestation and may be associated with systemic infection and sepsis. Recent reviews highlight that cUTI is not a uniform clinical condition; treatment choices should take into account the severity of the illness, the susceptibility of microorganisms, factors related to the host, any urinary tract abnormalities, and the necessity for source control.

Antimicrobial resistance has further narrowed the available oral treatment options, particularly when

infections are caused by extended-spectrum  $\beta$ -lactamase (ESBL)-producing or multidrug-resistant Enterobacterales.<sup>2</sup> Intravenous carbapenems remain important for severe infections and resistant organisms, but reliance on parenteral treatment can prolong hospitalisation and increase healthcare resource use.<sup>3</sup> Recent reviews of cUTI treatment therefore emphasise patient-centred selection of therapy, antimicrobial stewardship, and appropriately timed intravenous-to-oral transition when an effective oral agent is available. New oral agents may contribute to earlier discharge, but their broad-spectrum activity also creates a need for careful stewardship.

Tebipenem pivoxil addresses this therapeutic gap by providing an orally administered carbapenem prodrug. A 2026 appraisal of the changing landscape of community-acquired UTI in the United States included tebipenem pivoxil alongside pivmecillinam, sulopenem and gepotidacin as new oral agents under review or recently approved, and specifically flagged tebipenem as the prospective first oral carbapenem option for cUTI.<sup>4</sup> On 17 June 2026, the United States Food and Drug Administration (FDA) approved UTEBZI (tebipenem pivoxil), developed by Spero Therapeutics in partnership with GSK, for adults with cUTI, including pyelonephritis, caused by specified susceptible organisms in patients with limited or no alternative oral treatment options. It is the first time an oral carbapenem antibacterial has been made available anywhere in a Western regulatory market. The approval was supported by the PIVOT-PO phase 3 trial, in which oral tebipenem pivoxil was compared with intravenous imipenem-cilastatin. This review therefore focuses not only on the drug's pharmacological and clinical evidence, but also on where it should fit within contemporary cUTI management, how it compares with other recently introduced oral agents for urinary tract infection, and what its approval means for antimicrobial-resistance settings, including India, that were not part of its pivotal development programme.

## DEVELOPMENT HISTORY: FROM ADAPT-PO TO PIVOT-PO

Tebipenem pivoxil hydrobromide has been in international clinical development for several years before its 2026 US-FDA approval. The trial ADAPT-PO, compared oral tebipenem pivoxil hydrobromide 600 mg every 8 hours with intravenous ertapenem 1 g every 24 hours in adults with cUTI or acute pyelonephritis. The results published in the *New England Journal of Medicine* in 2022, showed adverse events in a similar proportion of patients on tebipenem and ertapenem (25.7% versus 25.6%, mostly mild diarrhoea and headache), with clinical cure rates at test-of-cure of 93.1% and 93.6%, respectively.<sup>5,6</sup> An initial US regulatory submission based on ADAPT-PO was not successful, and the programme was subsequently reworked. The trial supporting the 2026 FDA approval was publicly registered as PIVOT-PO (NCT06059846). This trial used a different intravenous comparator,

imipenem-cilastatin 500 mg every 6 hours, a different tebipenem dosing interval (600 mg every 6 hours rather than every 8 hours), and explicitly included pyelonephritis within the cUTI indication. This distinction matters for clinicians and researchers searching the literature, since the older ADAPT-PO dataset (ertapenem comparator, every-8-hour dosing) and the newer PIVOT-PO dataset (imipenem-cilastatin comparator, every-6-hour dosing, which forms the basis of the current FDA label) are not interchangeable and represent different stages of the drug's development.

## PHARMACOLOGY OF TEBIPENEM PIVOXIL

### *Chemistry and formulation*

Tebipenem pivoxil is administered as the hydrobromide salt, a white-to-off-white powder that is sparingly soluble in water, with a molecular weight of approximately 578.5 g/mol.<sup>7</sup> Each film-coated tablet contains 300 mg of tebipenem pivoxil (equivalent to approximately 348.8 mg of the hydrobromide salt), along with inactive excipients including crospovidone, magnesium stearate, microcrystalline cellulose and silicon dioxide, and a coloured film coat. Tebipenem pivoxil itself is pharmacologically inactive and is not detectable in plasma following oral administration; it functions solely as an orally absorbable prodrug that is hydrolysed to the active moiety, tebipenem during intestinal absorption.

### *Pharmacokinetics*

Tebipenem pivoxil is rapidly hydrolysed to tebipenem by intestinal esterases during absorption, with plasma exposure increasing in an approximately dose-proportional manner across the therapeutic dose range and no meaningful accumulation on repeated dosing every six hours.<sup>7</sup> Mass-balance studies using radiolabelled drug confirm that absorption and elimination occur predominantly through hydrolysis and renal excretion, with minimal hepatic contribution.<sup>8</sup> A systematic review of dietary effects on beta-lactam bioavailability found no clinically important reduction in tebipenem exposure with food, consistent with the FDA label's guidance that it may be taken with or without meals.<sup>9</sup>

A dedicated pharmacokinetic study across renal impairment patients, including end-stage renal disease, demonstrated declining eGFR, with high exposure to Tebipenem pivoxil, which suggested dose reduction in renal failure patients.<sup>10</sup> The drug-drug interaction studies showed no clinically meaningful interaction between tebipenem pivoxil and antacids (aluminium hydroxide/magnesium hydroxide/simethicone) or the proton pump inhibitor, omeprazole.<sup>11</sup> Tissue-penetration studies using micro-dialysis have demonstrated good distribution of tebipenem into skin and soft tissue, including in patients with diabetic foot infections and into intrapulmonary compartments after oral dosing, suggesting pharmacokinetic properties favourable for

infections beyond the urinary tract.<sup>12,13</sup> For patients unable to swallow tablets, bioavailability of crushed tebipenem administered via nasogastric tube is preserved both with and without concurrent enteral feeding.<sup>14</sup> Urinary pharmacokinetic analyses further indicate that the duration and concentration of tebipenem in urine influence the timing of recurrent bacteriuria after treatment, a consideration relevant to relapse risk in cUTI.<sup>15</sup>

### Mechanism of action and spectrum of action

Tebipenem is an oral carbapenem antibiotic with a broad spectrum of antibacterial activity. It binds to penicillin-binding proteins (PBPs) in bacteria and inhibits transpeptidation/cross-linking of peptidoglycan. Therefore, bacterial cell-wall synthesis is inhibited, leading to cell lysis and death. It is bactericidal and has activity against many Gram-positive and Gram-negative bacteria, including some  $\beta$ -lactamase-producing organisms.

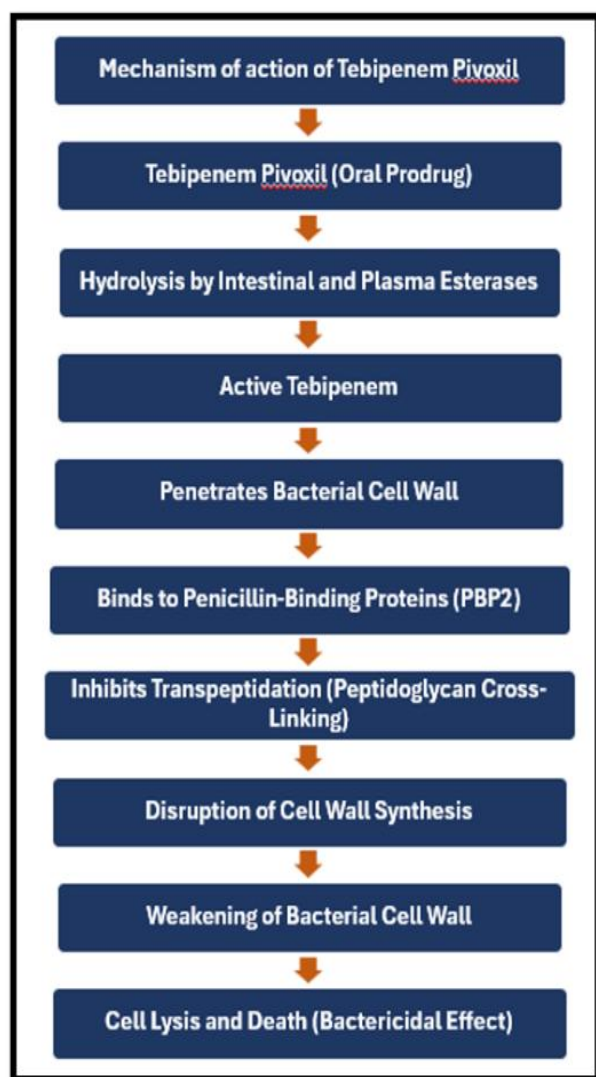


Figure 1: Mechanism of action of tebipenem pivoxil.

### Mechanism of action and microbiology

Following absorption, tebipenem pivoxil is converted to active tebipenem, a carbapenem that exerts bactericidal activity by binding to penicillin-binding proteins (PBPs), with preferential affinity for PBP2 in *Escherichia coli* and *Klebsiella pneumoniae*. This inhibits peptidoglycan cross-linking, disrupts bacterial cell-wall synthesis, and leads to cell lysis and death. Tebipenem is stable against several ESBLs and AmpC  $\beta$ -lactamases, including TEM, SHV, CTX-M, and some OXA variants, but may be hydrolysed by certain serine and metallo-carbapenemases. It demonstrates broad in-vitro activity against Enterobacterales, including ESBL-producing strains. The FDA-approved indication includes susceptible *E. coli*, *K. pneumoniae*, *Enterobacter cloacae* complex, *K. oxytoca*, and *Enterococcus faecalis*; several other organisms show in-vitro susceptibility, although clinical efficacy has not been established in controlled trials.<sup>16-19</sup>

### Dosage and administration

The recommended adult dose of tebipenem pivoxil is 600 mg (two 300 mg tablets) orally every 6 hours for 7–10 days in patients with eGFR 60–150 ml/min, taken with or without food. The dose should be adjusted according to renal function. Use is not recommended when eGFR >150 ml/min, and data are insufficient for patients undergoing haemodialysis. Prolonged treatment should be avoided because of the risk of carnitine depletion associated with pivalate-containing compounds.<sup>7</sup> Dosage should be reduced according to renal function as summarised in Table 2.

Table 1: Pharmacokinetic parameters of tebipenem (600 mg every 6 hours, steady state).

| Parameter                      | Value (mean $\pm$ SD, or range)                  |
|--------------------------------|--------------------------------------------------|
| C <sub>max</sub> (mcg/ml)      | 5.0 ( $\pm$ 1.3)                                 |
| AUC <sub>0–24</sub> (mcg·h/ml) | 64.5 ( $\pm$ 20.4)                               |
| T <sub>max</sub> (hours)       | 0.6–1.5                                          |
| Terminal half-life (hours)     | 1.6 ( $\pm$ 0.16)                                |
| Apparent clearance (L/hour)    | 34.2 ( $\pm$ 8.1)                                |
| Plasma protein binding         | ~42%                                             |
| Urinary excretion              | Unchanged drug ~62%; ring-opened metabolite ~22% |

Table 2: Recommended dosage of tebipenem pivoxil in renal impairment.

| eGFR             | Dose   | Frequency      |
|------------------|--------|----------------|
| 60 to <90 ml/min | 600 mg | Every 6 hours  |
| 30 to 59 ml/min  | 300 mg | Every 6 hours  |
| 15 to 29 ml/min  | 300 mg | Every 12 hours |

**Clinical efficacy: the PIVOT-PO trial**

The efficacy of tebipenem pivoxil was evaluated in the phase III PIVOT-PO trial, a randomised, double-blind study involving 1,690 hospitalised adults with complicated urinary tract infection (cUTI) or pyelonephritis. Patients received either oral tebipenem pivoxil 600 mg every 6 hours or intravenous imipenem-cilastatin 500 mg every 6 hours for 7–10 days. The overall clinical and microbiological response was 58.5% with tebipenem and 60.2% with imipenem-cilastatin, confirming non-inferiority. Clinical cure was achieved in 93.5% and 95.2% of patients, respectively. Similar outcomes were observed in patients with ESBL-producing and other resistant *Enterobacterales*. However, in patients with bacteraemia, the response was lower with tebipenem than with imipenem-cilastatin (40.6% vs 61.8%), suggesting that caution is needed when treating bacteraemic cUTI (Table 3).<sup>15,20,21</sup>

**Safety and tolerability**

In the pivotal PIVOT-PO trial, 843 patients received tebipenem pivoxil and 844 received imipenem-cilastatin, for a median treatment duration of about 7.5 days in each arm. Discontinuation due to adverse reactions was infrequent and similar between groups (0.6% versus 0.8%). In the earlier ADAPT-PO programme against ertapenem, overall adverse event rates were likewise comparable between arms (25.7% versus 25.6%), with mild diarrhoea and headache predominating.<sup>5,7</sup> The most common adverse reactions with tebipenem pivoxil in the PIVOT-PO trial, each occurring in at least 1% of patients, are summarised in Table 4; diarrhoea was more frequent with tebipenem pivoxil than with imipenem-cilastatin, while *Clostridioides difficile* infection was numerically less frequent (Table 4).

**Table 3: Composite response rate at test-of-cure by baseline pathogen (micro-ITT population, PIVOT-PO).**

| Pathogen                                           | Tebipenem Pivoxil<br>n/N (%) | Imipenem-Cilastatin<br>n/N (%) |
|----------------------------------------------------|------------------------------|--------------------------------|
| <b><i>Enterobacterales</i> (overall)</b>           | 261/446 (58.5)               | 291/483 (60.2)                 |
| <b><i>Escherichia coli</i></b>                     | 193/333 (58.0)               | 213/348 (61.2)                 |
| <b><i>Klebsiella pneumoniae</i></b>                | 44/81 (54.3)                 | 60/106 (56.6)                  |
| <b><i>Enterobacter cloacae</i> complex</b>         | 9/11 (81.8)                  | 7/11 (63.6)                    |
| <b><i>Klebsiella oxytoca</i></b>                   | 6/10 (60.0)                  | 3/5 (60.0)                     |
| <b><i>Proteus mirabilis</i></b>                    | 3/6 (50.0)                   | 4/6 (66.7)                     |
| <b><i>Enterococcus faecalis</i> (co-infection)</b> | 10/23 (43.5)                 | 11/22 (50.0)                   |

**Table 4: Adverse reactions occurring in ≥1% of patients (PIVOT-PO trial).**

| Adverse reaction                                 | Tebipenem Pivoxil<br>(n=843) N (%) | Imipenem-Cilastatin<br>(n=844) N (%) |
|--------------------------------------------------|------------------------------------|--------------------------------------|
| <b>Diarrhoea</b>                                 | 68 (8)                             | 23 (3)                               |
| <b>Headache</b>                                  | 25 (3)                             | 29 (3)                               |
| <b>Nausea</b>                                    | 11 (1)                             | 6 (1)                                |
| <b>Abdominal pain</b>                            | 11 (1)                             | 7 (1)                                |
| <b>Hepatic enzyme increased</b>                  | 10 (1)                             | 7 (1)                                |
| <b><i>Clostridioides difficile</i> infection</b> | 9 (1)                              | 13 (2)                               |

**Warnings and precautions****Hypersensitivity reactions**

Serious, occasionally fatal anaphylactic reactions have been reported with beta-lactam and carbapenem antibacterials. Patients with a history of hypersensitivity to carbapenems, penicillins, or cephalosporins should be identified before initiating therapy, and the drug should be discontinued if a reaction occurs.

**Seizures and other CNS adverse reactions**

These have been reported with beta-lactam and carbapenem antibacterials, more commonly in patients with pre-existing CNS disorders or renal impairment; neurological evaluation is warranted if such reactions occur.

**Interaction with valproic acid**

Concomitant carbapenem use, including tebipenem pivoxil, may lower plasma valproic acid or divalproex

sodium concentrations, increasing the risk of breakthrough seizures; concurrent use is best avoided.

#### *Carnitine depletion*

As a pivalate-generating prodrug, tebipenem pivoxil can reduce serum carnitine levels, particularly with prolonged use; it is contraindicated in patients with primary or secondary carnitine deficiency, and treatment beyond the recommended duration should be avoided.

#### *Clostridioides difficile infection (CDI)*

As with nearly all antibacterial agents, CDI has been reported, ranging from mild diarrhoea to fatal colitis, and should be considered in any patient who develops diarrhoea during or after therapy.

#### *Interference with newborn screening*

Maternal treatment with tebipenem pivoxil before delivery may cause a false-positive newborn screening result for isovaleric acidemia, warranting prompt confirmatory follow-up.

#### *Development of drug-resistant bacteria*

As with other antibacterials, use in the absence of a proven or strongly suspected bacterial infection offers no benefit and promotes resistance.<sup>7</sup>

#### *Effect on gut microbiota*

An area not addressed in detail within the FDA label but explored in the independent literature is the impact of tebipenem pivoxil on the intestinal microbiome. A randomised controlled trial in healthy Swedish adults compared the effect of tebipenem pivoxil hydrobromide with amoxicillin-clavulanic acid on gut microbial composition. The finding suggests significant and sustained reductions in both microbial richness and evenness during and after tebipenem treatment, comparable in magnitude to those seen with the comparator agent. Animal studies have also shown changes in gut microbial diversity that may increase susceptibility to colonisation by carbapenem-resistant *Klebsiella pneumoniae*. Although this is not a formal warning in the prescribing information, these findings are relevant to antimicrobial stewardship and should be considered when selecting therapy.<sup>22,23</sup>

#### *Drug interactions*

Concomitant use of OAT1/OAT3 inhibitors like probenecid increases tebipenem plasma concentrations, necessitating more frequent monitoring for adverse reactions such as diarrhea and headache if unavoidable. It's generally discouraged to use tebipenem with valproic acid, divalproex sodium, or other pivalate-generating drugs due to risks of reduced anticonvulsant efficacy or carnitine

depletion. Studies show that antacids and proton pump inhibitors do not significantly affect tebipenem exposure, so no dose adjustments are needed for acid-suppressive therapy.<sup>7,19</sup>

#### *Use in specific populations*

Available human data on tebipenem pivoxil use during pregnancy are limited, although animal reproduction studies have not demonstrated any developmental toxicity. Tebipenem and/or its metabolites are detected in animal milk. Tebipenem and/or its metabolites are detected in the milk of lactating rats, and the developmental and health benefits of breastfeeding should be weighed against maternal need for therapy. Safety and efficacy in patients less than 18 years have not been established for cUTI. In older adults, no major differences in safety or efficacy were observed, but dose adjustment based on renal function is recommended.<sup>7</sup>

#### *Investigational and emerging uses*

Beyond its approved cUTI indication, tebipenem pivoxil is being investigated as an oral alternative to intravenous antibiotics for other infections. Studies have evaluated its potential use in children with treatment-resistant shigellosis, supported by pharmacokinetic and dose-modelling studies. Preclinical studies have also shown activity against *Shigella* species. Additionally, tebipenem pivoxil combined with avibactam has demonstrated activity against *Mycobacterium abscessus* in animal models. However, these applications remain investigational and are not currently approved.<sup>24-28</sup>

#### *Position among newer oral agents for urinary tract infection*

Tebipenem pivoxil occupies a distinct role among newer oral antibiotics for urinary tract infections. Gepotidacin, sulopenem etzadroxil/probenecid, and pivmecillinam are primarily approved for uncomplicated UTI (uUTI), whereas tebipenem is indicated for complicated UTI (cUTI) requiring broader-spectrum therapy. In cUTI, its main comparators are intravenous  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations such as cefepime-enmetazobactam. Tebipenem offers the advantage of an oral carbapenem option, potentially facilitating outpatient treatment or intravenous-to-oral step-down therapy. However, its activity is limited against carbapenemase-producing organisms, and its pivalate moiety is associated with carnitine depletion. Thus, tebipenem may complement rather than replace intravenous agents in appropriately selected patients.<sup>29-34</sup>

#### *Relevance to India and other high-burden antimicrobial resistance settings*

Tebipenem pivoxil is currently a US-approved drug, with limited availability in India, and its potential role in India requires consideration of the local resistance pattern.

Carbapenem resistance is high in India, particularly among *Klebsiella pneumoniae* and *E. coli*, with NDM and OXA-48-like carbapenemases being important mechanisms. Since tebipenem, like other carbapenems, is ineffective against metallo- $\beta$ -lactamase-producing organisms, its usefulness may be limited in settings with high NDM prevalence. If introduced in India, its use should therefore be guided by culture and susceptibility testing, local antibiograms, and antimicrobial stewardship programmes. Tebipenem may have value as an oral step-down or hospital-discharge option for culture-confirmed, carbapenem-susceptible cUTI, rather than as an empirical first-line agent.<sup>35-37</sup>

### Limitations of current evidence and future research directions

The PIVOT-PO and ADAPT-PO trials mainly included hospitalised, haemodynamically stable adults with confirmed *Enterobacterales* infections and did not focus on patients with severe sepsis, septic shock, or intensive-care needs. The lower response observed in bacteraemic patients also limits conclusions regarding bacteraemic cUTI. Additionally, tebipenem has not been directly compared with newer cUTI therapies such as cefepime-enmetazobactam, so comparative efficacy is currently based on indirect evidence.<sup>29,30,37</sup> Data are limited in patients with eGFR less than 15 ml/min, those receiving haemodialysis, and children/adolescents with cUTI.

Available paediatric data are derived from studies of shigellosis in children, rather than cUTI.<sup>24-26</sup> No cost-effectiveness or health-economic studies and limited real-world data on effectiveness, resistance, or microbiome effects are currently available. Published evidence is mainly from the United States and Japan, with no clinical, pharmacokinetic, or susceptibility data from India or South Asia. Future research should focus on local susceptibility testing, real-world clinical outcomes, cost-effectiveness, and antimicrobial-stewardship impact in these populations.

### DISCUSSION

Tebipenem pivoxil provides an oral carbapenem option for selected adults with cUTI or pyelonephritis who have limited oral treatment options. PIVOT-PO and ADAPT-PO demonstrated non-inferiority to intravenous imipenem-cilastatin and ertapenem, respectively. However, tebipenem should not routinely replace intravenous carbapenems or narrower-spectrum agents when effective alternatives are available.<sup>29,30</sup> Tebipenem is most appropriate for clinically stable patients with susceptible *Enterobacterales* cUTI who require carbapenem-level activity but lack suitable oral alternatives due to resistance, intolerance, or contraindications. It should not be used solely for convenience in severe sepsis, urinary obstruction, inadequate source control, or clinical instability. Caution is also warranted in bacteraemic cUTI, given the lower response observed in PIVOT-PO. Its broad

spectrum also highlights the need for careful antimicrobial stewardship.

Recent cUTI literature emphasises individualised treatment based on local resistance patterns, illness severity, source control and pharmacokinetic/pharmacodynamic considerations. Tebipenem should be reserved for patients who derive clear benefit from its broad-spectrum activity, given the potential for gut microbiome disruption and selection of resistant organisms. Its value lies primarily in reducing or avoiding prolonged intravenous therapy while maintaining carbapenem-level activity in carefully selected, culture-confirmed patients. In high-resistance settings such as India, its use should be guided by local susceptibility patterns and antimicrobial stewardship principles.<sup>31-36</sup>

### CONCLUSION

Tebipenem pivoxil, the first oral carbapenem approved by the US FDA, provides a new option for selected adults with cUTI and pyelonephritis who have limited oral treatment choices. Evidence from ADAPT-PO and PIVOT-PO supports its efficacy against susceptible pathogens. However, its use should be limited to patients who require carbapenem-level activity but are suitable for oral therapy, rather than replacing carbapenem-sparing intravenous options. Concerns regarding antimicrobial resistance, microbiome disruption, carnitine depletion, and drug interactions support careful stewardship. In India and other settings with high metallo- $\beta$ -lactamase-mediated resistance, its use should be guided by culture-confirmed susceptibility and local resistance patterns. Further real-world, comparative, pharmacoeconomic, and regional data are needed to define its long-term role.

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