Tebipenem, the first oral carbapenem antibiotic


To cite this article: Michael J. Pucci, Akash Jain, Luke Utley, Thomas Zabawa & Thomas R. Parr (2018): Tebipenem, the first oral carbapenem antibiotic, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2018.1496821

To link to this article: https://doi.org/10.1080/14787210.2018.1496821

Accepted author version posted online: 17 Jul 2018.

Submit your article to this journal

View Crossmark data
Drug profile

Tebipenem, the first oral carbapenem antibiotic


Spero Therapeutics, 675 Massachusetts Avenue
Cambridge, MA 02139

*Corresponding author:

Michael J. Pucci
Spero Therapeutics
675 Massachusetts Avenue
Cambridge, MA 02139
Tel: +1-857-242-1600
E-mail: mpucci@sperotherapeutics.com
ABSTRACT

Introduction: Infections caused by antibiotic-resistant pathogens, particularly Gram-negative bacteria, have become increasingly challenging to successfully treat. The beta-lactam antibiotic subclass, the carbapenems, have proven valuable for the treatment of such Gram-negative bacterial infections due to their spectrum and β-lactamase stability properties. However, all marketed carbapenems to date are parenterally administered to adult patients.

Areas covered: One carbapenem, tebipenem-pivoxil (TBPM-PI), is an oral prodrug that was approved in Japan for pediatric use only in 2009. This review summarizes preclinical and clinical data for TBPM-PI, which is now in clinical development again this time for use as the first oral carbapenem available for treatment of bacterial infections in adult patients.

Expert commentary: There is an urgent unmet need with an increasing prevalence of fluoroquinolone-resistant and ESBL-producing Gram-negative pathogens in the hospital and community setting. Carbapenems have traditionally been considered the drugs of choice for infections caused by enterobacteria producing ESBL and AmpC enzymes because they are not affected by these resistance mechanisms. The carbapenem, TBPM-PI, offers an oral option, particularly as step-down therapy, for use of this class in the treatment of serious Gram-negative infections.

Keywords. antibiotic resistance, beta-lactam, beta-lactamase, carbapenem, extended-spectrum beta-lactamase (ESBL), oral, penicillin-binding protein
1. Introduction

For more than 70 years, the β-lactam antibiotics have been a mainstay for the treatment of bacterial infections [1]. These drugs have demonstrated good clinical efficacy and safety and have been tolerated well by patients. However, soon after their introduction, resistance to these compounds appeared, primarily through the emergence of β-lactamase enzymes that hydrolyzed the β-lactam ring rendering the drugs inactive [2]. The effectiveness of this antibiotic class has been maintained primarily using two approaches: by modifying the β-lactam scaffold to identify improved analogs and by the development of β-lactamase inhibitors that protect the partner β-lactam [3-5]. Using the first approach, one of the more important subclasses of β-lactam antibiotics discovered was the carbapenems, the first of which, the natural product thienamycin, was reported by scientists at Merck Sharp & Dohme Research Laboratories in 1976 [6]. The carbapenems possess the broadest spectrum of activity and better β-lactamase stability compared to other β-lactams. Because of these properties, they have often been used as antibiotics of last resort, particularly against multi-drug resistant Gram-negative pathogens [7,8].

Despite the important clinical utility of the carbapenem antibiotics over the past 30 years, the currently marketed products (Figure 1, compounds 1-4) are almost exclusively parenterally administered. Attempts were made to identify an oral carbapenem, but the issues of chemical stability, suitable bioavailability, and cost of chemical synthesis provided serious challenges [9]. One exception is tebipenem pivoxil (TBPM-PI; Figure 1, compound 5), an orally administered carbapenem prodrug that is marketed only in Japan by Meiji Seika Pharma Co.,
Ltd. as a fine granule formulation (Orapenem®) for pediatric otitis media, sinusitis, and pneumonia. The drug was not marketed for adult patients. TBPM-PI (L-084; ME1211) was originally developed by Wyeth Co., Ltd. (currently Pfizer Japan Inc.) in 1994 [10] up to early Phase 2 studies before Meiji received exclusive rights in 2003 [11]. The drug was approved in Japan in April 2009 and launched in August 2009.

A new oral formulation is currently under clinical development to optimize the pharmacokinetic-pharmacodynamic (PKPD) profile of TBPM-PI for adult complicated urinary tract infections (cUTIs) by Spero Therapeutics [12]. Patients with severe infections due to extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and fluoroquinolone resistance often require hospitalization and treatment with parenteral carbapenems (ertapenem, imipenem, meropenem, doripenem) [13]. Current oral antibiotics that are active against *E. coli* ESBL isolates include nitrofurantoin and fosfomycin trometamol. However, these antibiotics are usually effective for therapy of uncomplicated lower urinary tract infection (UTI), such as acute cystitis, but they do not achieve high plasma levels and are not indicated for therapy of upper UTI including acute pyelonephritis. Therefore, more effective oral antibiotics against UTI infections due to ESBL-producing Enterobacteriaceae are needed. TBPM-PI could potentially provide physicians with an oral alternative to cover the increasing number of fluoroquinolone-resistant and ESBL isolates seen in these infections [14]. An oral option would also allow for step-down therapy for patients which could minimize hospitalization stays and reduce both cost and potential complications.
2. Market overview

No oral carbapenems are currently marketed for use in adult patients. Two oral penems, faropenem and sulopenem (Figure 1, compounds 6 and 7), reached advanced stages of clinical development, but neither has gained FDA approval to date [15]. Faropenem [16] is marketed in Japan by Daiichi Sankyo, but after FDA review, it was determined in 2006 that more clinical data would be necessary for US approval and there is no indication that those studies are ongoing or planned. Sulopenem is currently being developed by Iterum Therapeutics. Phase 2 clinical studies of sulopenem are complete and it is reportedly undergoing formulation development to improve prior oral pharmacokinetic challenges [17]. The lead prodrug of sulopenem (Compound 1 or PF-03709270) resulted in significantly lower oral exposure of sulopenem in healthy human volunteers (AUC$_{0-12}$ = 4.55 µg·hr/ml at 500 mg dose; fed patients) [18] as compared to the oral exposure of tebipenem after administration of the TBPM-PI prodrug (AUC$_{0-last}$ = 21.4 µg·hr/ml at 600 mg dose) [19]. Exposure to sulopenem can be improved by combining it with probenecid (AUC$_{0-12}$ = 6.4 µg·hr/ml). Recent clinical data from study IT001-102 reported AUC$_{0-∞}$ = 3.87 µg·hr/ml for 500 mg sulopenem etzadroxil prodrug and AUC$_{0-∞}$ = 4.96 µg·hr/ml for 500 mg sulopenem etzadroxil plus 500 mg probenecid [58]. It was also reported that results from clinical study IT001-101 showed that food increased the mean AUC and mean time above MIC for 500 mg sulopenem etzadroxil dosed with 500 mg probenecid on Day 1 by 62% and 68%, respectively [20]. Another oral treatment in development by Achaogen is a ceftibuten/clavulanate combination designated as C-scape [21]. A potential gap
in bacterial spectrum compared with penems and carbapenems is lack of coverage of AmpC-producing isolates [22].

3. Chemistry

The carbapenems, members of the β-lactam class of antibiotics, are specifically characterized by an all-carbon fused five-membered ring system (as compared to the presence of a sulfur atom in the penam class of molecules), as well as unsaturation in the ring between C2 and C3 (Figure 1). Efficient synthesis of the carbapenem core has proven essential for the development of novel compounds, resulting in a number of new analogs that address significant deficiencies in early carbapenems. Development of a streamlined synthesis of β-methylazetidine-2-one allows for the rapid assembly of carbapenem analogs with methyl-substitution at the 1-position, a key structural feature in carbapenems such as tebipenem as shown compared with other marketed carbapenems in Figure 2. Tebipenem is structurally characterized by a traditional β-methyl carbapenem core, a unique bicyclic azetidine, thiazole moiety at the 2-position, and a prodrug pivoxil ester at the 3-position. The addition of this ester group was determined to greatly improve oral bioavailability [23]. An inexpensive and rapid isocratic LC method has recently been reported for the quantitative determination of tebipenem [24,25].
4. Mechanism of action

Carbapenems penetrate the outer membranes of Gram-negative bacteria through porin channels as they do not readily diffuse through the intact outer membrane [26]. It has been suggested that the translocation kinetics of tebipenem through the *E. coli* OmpC porin are governed mainly by the R2 group of the penem ring and that the compound exhibits lower occupancy due to the (pyrrolidin-3-yl) thio moiety [26]. As with other β-lactam antibiotics, after passing through the outer membrane into the periplasmic space, tebipenem acylates and inhibits the penicillin-binding proteins (PBPs) that catalyze the formation of cell wall peptidoglycan [27]. The end result is weakening of the peptidoglycan followed by lysis of the bacterial cell. Analysis of crystal structures of tebipenem complexed with PBPs 2X and 1A from *S. pneumoniae* revealed that the C-2 side chain formed key hydrophobic interactions with key conserved residues in these PBPs [28]. Tebipenem also displayed good binding to *H. influenzae* PBPs with IC$_{50}$ values for *H. influenzae* LJ5 PBP1B, -2, -3A, and -3B reported as 0.09, 0.01, 0.12, and 0.10 µg/ml, respectively, and showed high binding affinities for PBP1A, -1B, -2A/2X, -2B, and -3 of PRSP [29]. PBP assays for tebipenem have not yet been published for other bacterial pathogens.

5. Microbiology
5.1 In vitro characterization

Tebipenem was reported to have potent and broad-spectrum antibacterial activity, similar to other carbapenems such as ertapenem, against a variety of both Gram-negative and Gram-positive pathogens. MIC$_{90}$s ≤1 µg/ml were
observed against Gram-negative organisms including *E. coli*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Proteus vulgaris*, and *Haemophilus influenzae* including ampicillin-resistant isolates (Table 1). The MIC$_{90}$ reported for *Acinetobacter baumannii* was 2 µg/ml, *Serratia marcescens* was 25 µg/ml, and *Pseudomonas aeruginosa* generally was not susceptible with an MIC$_{90}$ of 32 µg/ml. For Gram-negative pathogens, tebipenem exhibited MIC$_{90}$s ≤1 µg/ml against methicillin-susceptible *Staphylococcus aureus* and *Staphylococcus epidermidis*, *Streptococcus pneumoniae* including penicillin-resistant (PRSP) isolates, and *Streptococcus pyogenes* (Table 1) [29-31]. A nationwide survey of 459 clinical isolates of *S. pneumoniae* including 124 PRSP strains between 2007-2010 in Japan showed that the MIC$_{90}$ for tebipenem was ≤0.063 µg/ml [32]. *Enterococcus faecalis* showed an MIC$_{90}$ of 2 µg/ml while *Enterococcus faecium* was not susceptible with an MIC$_{90}$ of 128 µg/ml. The MIC$_{90}$ against methicillin-resistant staphylococcal isolates was reported as 8 µg/ml [30]. As methicillin-resistant staphylococci are not considered clinically susceptible to carbapenems [33], these isolates will probably not be susceptible to tebipenem as well. A recent publication that listed higher MICs against some of the above organisms directly tested the TBPM-PI prodrug [11], which has reduced antibacterial activity compared with the tebipenem parent compound. A number of Susceptible anaerobes (MIC$_{90}$ ≤1 µg/ml) were reported including *Peptostreptococcus* spp., *Bacteroides fragilis*, and *Clostridium difficile* (MIC$_{90}$ = 1 µg/ml) [34]. A recent study from Thailand reported that all 102 clinical isolates of *Burkholderia pseudomallei*, a Gram-negative pathogen that causes melioidosis and is classified by the CDC as a category B bioterrorism concern, were inhibited by tebipenem with MICs of 1-2 µg/ml [35].
Tebipenem has also been found to possess potent \textit{in vitro} activity against \textit{Mycobacterium tuberculosis} clinical isolates including drug-resistant strains with an MIC range of 0.125 to 8 µg/ml \cite{36,37}. In the presence of either of the β-lactamase inhibitors, clavulanic acid and avibactam, MIC values of tebipenem decreased to 1 µg/ml against a panel of 21 multidrug- and extensively drug-resistant clinical isolates of \textit{M. tuberculosis} \cite{36}. Tebipenem was also reported to exhibit \textit{in vitro} antibacterial activity against \textit{Mycobacterium avium}, an important non-tuberculous mycobacterium (NTM), with MIC$_{90}$ values of 4-8 µg/ml \cite{38}.

Although prior reports on tebipenem \textit{in vitro} antibacterial activity focused on respiratory pathogens and did not always include parenteral carbapenem comparators, where other carbapenems were included MICs often tracked closely \cite{30,34}. One exception is that tebipenem, unlike meropenem and doripenem, is not active against \textit{P. aeruginosa}. The reported MIC$_{90}$ of 2 µg/ml against \textit{A. baumannii} is also questionable and should be confirmed against recent clinical isolates. Breakpoints were reported in Japan for \textit{S. aureus} and \textit{H. influenzae} of 1 µg/ml for susceptible, 2 µg/ml for intermediate and 4 µg/ml for resistant \cite{39}.

Further studies for stability against β-lactamases showed that tebipenem retained potent antibacterial activity with MICs ≤0.05 µg/ml against methicillin-susceptible \textit{S. aureus}, \textit{E. coli}, and \textit{K. pneumoniae} strains expressing either penicillinases or ESBLs. Enterobacteriaceae strains expressing cephalosporinases all had MICs ≤0.78 µg/ml \cite{29-34}. Slightly higher MIC values (1.56-6.25 µg/ml) were observed in three \textit{P. aeruginosa} strains producing cephalosporinases. As would be expected, MICs were 50 to >100
µg/ml against *Stenotrophomonas maltophilia* and *P. aeruginosa* strains expressing carbapenemases.

Bacterial culture medium with pH values between 5 and 8 was found to have minimal effects of 2- to 4-fold on tebipenem MICs against *S. aureus*, *E. coli*, and *P. aeruginosa*. Similar effects were observed with the addition of 50% human serum [34]. As expected for a β-lactam antibiotic, tebipenem was found to be rapidly bactericidal at concentrations above the MIC with a 3-log decrease in colony-forming units (CFUs) within 4 hours of addition of drug against *S. aureus*, *E. coli*, *S. pneumoniae*, and *H. influenzae* [34]. There was also a post-antibiotic effect (PAE) against both *S. aureus* and *E. coli* of approximately 0.8 hours after a 1-hour exposure of 4X MIC [34].

### 5.2 Animal efficacy studies

Several *in vivo* animal efficacy studies have been reported. The efficacy of tebipenem was compared with that of amoxicillin in the treatment of acute otitis media caused by penicillin-resistant *S. pneumoniae* (PRSP) in chinchillas [40]. A total of 36 animals were inoculated with 40 to 60 CFU of PRSP and oral treatment was initiated 21 hours after infection with 25 mg/kg BID of tebipenem, amoxicillin, or vehicle. Treatment continued for 5 days and animals were monitored for an additional 4 days. TBPM-PI showed superior animal survival (>80%) compared with amoxicillin (30% animal survival) and a greater reduction of bacterial burden. In the chinchilla model, tebipenem treatment also led to better improvement of otitis media symptoms, some of which resemble those of human children [41].
Efficacy was demonstrated in mouse lung infection models for both penicillin-susceptible and penicillin-resistant *S. pneumoniae* strains. For the former, an ED$_{50}$ was obtained and, for the latter, log$_{10}$ CFU/lung was 2.53 at 10 mg/kg and below the limits of detection at a 50 mg/kg dose compared with 7.36 log$_{10}$ for the untreated control. Treatment was three times per day for three days. Similarly, efficacy was also observed for *H. influenzae*, log$_{10}$ CFU/lung at a 4 mg/kg dose was 2.57 compared with 6.91 for the control [30].

### 5.3 Bacterial resistance

Tebipenem shares susceptibility to resistance mechanisms that affect other carbapenems. These include production of carbapenem hydrolyzing β-lactamases, porin mutations, efflux pumps, and mutations in the PBP targets [4,42]. These mechanisms in combination can lead to high levels of resistance as often seen in organisms such as *P. aeruginosa* and *E. coli* [43]. Some bacterial species are intrinsically resistant to tebipenem and other carbapenems with examples including methicillin-resistant staphylococci, *E. faecium*, *Stenotrophomonas maltophilia*, and many *P. aeruginosa* isolates [36]. Probably the most important mechanism of resistance to carbapenem antibiotics is enzymatic inactivation of the drug via acquisition of β-lactam-inactivating enzymes. Although impervious to many of the earlier penicillinase and cephalosporinase β-lactam-hydrolyzing enzymes, carbapenem usage has selected for carbapenemases that can inactivate carbapenem antibiotics, particularly among the Enterobacteriaceae leading to the emergence of CRE (carbapenemase-resistant Enterobacteriaceae) isolates that are CPE.
(carbapenemase-producing Enterobacteriaceae) [44]. Examples of current important carbapenemases include KPCs (members of the class A Ambler), some OXA enzymes, particularly OXA-48 (class D), and NDM-1 and other metallo-β-lactamases (class B). Since KPC was first identified in the United States in 1996, these enzymes have spread worldwide to varying degrees in different locations [45,46]. Recent data from a study in a large US clinical database from 2009-2013, revealed that 3.1% of >40,000 Enterobacteriaceae isolates were CRE [47]. The proliferation and increasing prevalence of these β-lactam-inactivating enzymes has made successful treatment of infections caused by Gram-negative pathogens significantly more challenging in recent years.

6. Pharmacokinetics (PK)/ADME

Many β-lactam antibiotics are highly hydrophilic which leads to reduced oral absorption due to poor membrane permeability. Prodrug strategies have been successfully used to improve oral bioavailability, however, it is generally still less than 50% [48]. When TBPM-PI is orally administered, the cumulative amount that is urinary excreted in humans is 54-73% of the dose and, if metabolites (main metabolite observed was the open-ring form of tebipenem) are included, is about 80% of the dose [23]. This level of absorption is higher than other β-lactam prodrugs and it has been reported that TBPM-PI has high intestinal apical membrane permeability due to multiple intestinal transport routes, including uptake transporters such as OATP1A2 and OATP2B1 as well as simple diffusion [23]. Surprisingly, it was also reported that the ester prodrug, TBPM-PI, but not the active form, tebipenem, was a substrate of the
influx transporters, since typically this type of ester prodrug is expected to have higher membrane permeability due to increased simple diffusion. Human serum protein binding was relatively low, approximately 60-70% in vitro. Both in vitro drug metabolism and drug-drug interaction studies suggested that cytochrome P450 (CYP) interactions would be unlikely in patients. At concentrations of 3, 30, and 300 μmol/L, tebipenem demonstrated no inhibitory action in relation to the hERG channel.

6.1 Clinical PK/ADME

A comprehensive clinical development program was performed in Japan, including assessment of biopharmaceutical properties, clinical PK and PD, efficacy, and safety of TBPM-PI These included one biopharmaceutical, eleven clinical PK, one clinical PD, and eleven efficacy and safety studies. A listing of studies including more details is found in Table 2 with many of the results unpublished to date. Brief summaries of selected studies are found below.

A biopharmaceutical study (Meiji study ME1211-18) in twelve adult subjects provided a comprehensive evaluation of coated immediate-release tablets and fine granules (final market formulation). The results indicated that the PK of fine granules and tablets were similar [19], and that absorption of fine granules in adults is slowed in the presence of food (delayed $T_{\text{max}}$ and lower $C_{\text{max}}$) while exposure (AUC) remained similar between fed and fasted states.

Twelve clinical pharmacokinetic studies yielded valuable data in regard to exposures, safety, and tolerability that aided in final clinical dose selections. Administration of fine granules in healthy adult males showed dose-proportional
PK at single doses of 100, 200, and 400 mg with cumulative urinary excretion of tebipenem at 24 hours of 60-70% (80% if the open-ring form included) [49]. In comparison to other carbapenems, tebipenem possesses higher stability to human renal dehydropeptidase-I (DHP-I) than meropenem and does not require the co-administration of a DHP-I inhibitor such as cilastatin similar to what is necessary for imipenem [50].

The pharmacokinetics, safety, and tolerability of TBPM-PI tablets were assessed in healthy male volunteers after single and repeat dosing. Tebipenem was mainly detected in plasma and urine after oral TBPM-PI administration. After a single oral administration, $C_{\text{max}}$ and $AUC_{0-\infty}$ increased in proportion to dosage from 25 to 500 mg (Figure 3). Cumulative urinary excretion of TBPM-PI from 0 to 24 hours after administration was 50-70% [41]. After multiple oral doses of tablets, $C_{\text{max}}$ and $AUC_{0-\infty}$ increased in proportion to dose from 100 to 500 mg. $C_{\text{max}}$ of tebipenem was linear from 100 to 200 mg and $AUC_{0-\infty}$ of tebipenem was linear from 100 to 500 mg. Terminal half-life ($t_{1/2}$) and urinary excretion of tebipenem were almost constant regardless of the day of administration and tebipenem did not accumulate with multiple dosing as shown in Figure 4 [19].

The pharmacokinetics of TBPM-PI and tebipenem were evaluated in a Phase 2 clinical study in adults with otolaryngologic infection (ME-1211-3) [51]. TBPM-PI was administered in both as 150 mg TID, 250 mg BID or 300 mg TID. The mean pharmacokinetic parameters of the 3 treatment groups were similar between the two studies; absorption rate constant ($k_a$) ranged from 2.51 to 5.64 hr$^{-1}$. and mean $C_{\text{max}}$ and $AUC_{0-8}$ or $AUC_{0-12}$ of tebipenem in plasma were shown
to increase in proportion to dose. The $t_{\text{max}}$ and $t_{1/2}$ did not change in proportion to dose.

Some general observations reported from clinical pharmacology studies included that serum protein binding was relatively low, approximately 60-70% in vitro [52]. Both in vitro drug metabolism and drug interaction studies suggested that cytochrome P450 (CYP) interactions would be unlikely in patients. The main metabolite observed was the open-ring form of tebipenem [52]. The PK of tablets in healthy adult males was also found to be dose-proportional and accumulation upon repeated dosing was not observed [19]. Older pneumonia patients displayed a longer half-life, lower clearance, higher AUC than otolaryngology patients. Tissue distribution showed transfer to otolaryngological sites and to sputum.

Renal function was considered in human subjects and clearance was found to be reduced in renally-impaired individuals with concomitant increase in AUC and $C_{\text{max}}$, reduced half-life, and reduced urinary excretion. However, no dose adjustment was proposed in the Japanese Orapenem pediatric label, but rather that “renal function should be considered in administering TBPM-PI, especially in patients with severely impaired renal function” (ME1211-13). To assess effects in combination with drugs that increase gastric pH, famotidine or an antacid were tested. Results indicated that $C_{\text{max}}$, AUC, and urinary excretion were decreased approximately 40-60%, 70-80%, and 80%, respectively. Use in combination with probenecid showed an increase in $C_{\text{max}}$, AUC, prolongation of half-life, and decreased renal clearance.

Pivoxil prodrugs are sometimes associated with hypocarnitinemia and associated hypoglycemia. A pharmacodynamic trial (L-084-02) was performed
to study the effect of TBPM-PI on carnitine. The results showed that serum free carnitine was decreased on repeat dosing (100, 200 mg TID for 7 days or 500 mg BID for 7 days) in 16 healthy adult males, however, levels returned to normal by 7 days after completion of administration. It should be noted that the lowest serum carnitine levels noted in this study were ~20μM which is near the lower end of normal serum carnitine range (25-50 μM). There were no adverse events attributable to reduced serum carnitine reported in the study. In children, serum free carnitine showed a trend toward lower values during dosing with recovery 7 days after completion of administration.

A clinical pharmacology study was performed in 12 healthy adult males by placebo-controlled, double-blind comparison to examine the effect of TBPM-PI on the QT interval and pharmacokinetics of the drug (ME1211-17). Consistent with the lack of hERG channel activity, TBPM-PI was found to have no effect on the QT interval. Conclusions from the study were that the drug carried a low risk of clinically prolonging the QT interval and had an acceptable safety profile.

7. Clinical efficacy

Three controlled and eight uncontrolled studies in either adult or pediatric patients were performed. Results from a Phase 2 double-blind, randomized, comparative study in 212 adult patients (ME1211-3) with otitis media, pharyngolaryngitis or sinusitis were evaluated where TBPM-PI was administered either at 150 mg TID, 250 mg BID or 300 mg TID for seven days [44]. The clinical efficacy of treatment was 80% and higher in patients receiving 250 mg BID or 300 mg TID and bacterial clearance was 90% or higher in all dose groups. For specific pathogens, eradication was 100% for S. pneumoniae,
S. pyogenes and M. catarrhalis. The eradication rate for Haemophilus influenzae varied among the administration groups and was 76.9% in the 150 mg TID group, 100% in the 250 mg BID group, and 66.7% in the 300 mg TID group, resulting in 78.6% eradication across all groups. There were no serious adverse events, however, diarrhea and loose stools, mostly mild in severity, were noted at adverse drug-related incidences of 13.2% and 14.2%, respectively. There were no differences observed in the eradication rates between bacterial strains that were designated susceptible or non-susceptible to antibiotics available at the time of the study. Based on these results, the clinically recommended adult dosage regimen for otorhinolaryngological infections was determined to be 250 mg/dose, twice daily (500 mg/day).

An adult pneumonia Phase 2 study evaluated the effect of TBPM-PI in 150 patients (ME1211-2) [53] for 7 days at three different dosing schedules: 150 mg TID (450 mg group), 250 mg BID (500 mg group), and 300 mg TID (900 mg group). The primary efficacy endpoint was clinical effect at the end of administration or at discontinuation. The secondary clinical endpoints were clinical and bacteriological effects 3 days after start of administration, bacteriological effect after the end of administration or discontinuation, and clinical and bacteriological effects 7 days after final administration. The efficacy rate determined by proportion of subjects for whom the clinical effect was evaluated as “effective”. The final total % effective was reported as 88.5% with the 450 mg group (150 mg TID) determined to be the most effective at 90.9% [53]. Clinical efficacy reported for the 450 mg, 500 mg, and 900 mg groups were 91.3%, 90.0%, and 84.5%, respectively. The major pathogens identified were S. pneumoniae and H. influenzae. The clinical recommended dosage regimen of
TBPM-PI for bacterial pneumonia was determined to be 250 mg per dose, twice daily (500 mg/day).

Two Phase 2 complicated urinary tract infection (cUTI) clinical studies in adults were performed. The first study (L-084-04) included 51 patients, ages 20-74, in three dose arms: 100 mg TID, 150 mg BID, and 150 mg TID with 40 patients treated for seven days included in the efficacy analysis. The major Gram-positive pathogen identified was *E. faecalis* while Gram-negative pathogens included *K. pneumoniae, Serratia marcescens, and E. coli* with the latter organism observed most frequently. The 40 patients included 7 with complicated pyelonephritis and 33 with cystitis. Clinical efficacy at the end of treatment showed 92.9%, 94.1%, and 100% (9/9) for the 100 mg TID, 150 mg BID, and 150 mg TID groups, respectively. The second study (ME1211-1) included 37 patients enrolled into two treatment arms: 250 mg BID for 7 days and 300 mg TID for 7 days with 37 patients included in efficacy analysis. The 37 patients included 5 with complicated pyelonephritis and 27 with complicated cystitis. Clinical efficacy at the end of treatment was reported as 93.8% for both the 250 mg BID and 300 mg TID groups. As in study L-084-04 above, the major pathogens isolated were *E. faecalis* and *E. coli*.

Clinical data were reported for two Phase 2 studies where 50 children with mild-to-moderate acute otitis media, sinusitis, pharyngolaryngitis or bronchitis received TBPM-PI at either 4 or 6 mg/kg BID for 7 days (ME1211-7, ME1211-8) [54,55]. Patients (n = 43) ranged in age from 8 months to 10 years. The primary endpoints were clinical effect in the patients with infections by common pathogens, and safety. It was found that clinical cure was achieved in 100% of patients at both dose levels. Pathogens isolated included *H. influenzae, S.*
pneumoniae, M. catarrhalis, and S. pyogenes. Adverse effects included gastrointestinal disorders, with recovery occurring during the drug administration period. The clinically recommended dose regimen was 4 mg/kg twice daily, with the 6-mg/kg dose available for severe cases of infection.

An additional clinical study of note investigated the efficacy, safety and pharmacokinetics of TBPM-PI in pediatric patients (n = 66), aged 8 months to 12 years, with bacterial pneumonia (ME1211-11 and ME1211-16) [56]. In Phase 2 study ME1211-11, with twice daily dosing at 4 mg/kg for 7 days, a 100% cure rate was observed while twice daily dosing at 6 mg/kg achieved a clinical efficacy of 87.5%. In Phase 3 study ME-1211-16, the cure rates were 95.7% and 92.3% in the 4 and 6 mg/kg groups dosed for 7 days, respectively. TBPM-PI was determined to be safe and effective. Pathogens evaluated in these studies were H. influenzae, S. pneumoniae, M. catarrhalis, and S. pyogenes.

Meiji Seika ran a double-blind comparative Phase 3 study (ME1211-15) in 204 children with otitis media to assess both the safety and efficacy of TBPM-PI with high-dose cefditoren pivoxil (CDTR-PI) as the comparator antibiotic [57]. Both were dosed orally for seven days with the doses and schedules as follows: TBPM-PI twice daily at 4 mg/kg (≧3.5 mg/kg - <5.0 mg/kg) and CDTR-PI three times daily at ≧4.2 mg/kg - <6.0 mg/kg. TBPM-PI non-inferiority to high-dose CDTR-PI was demonstrated efficacy at 98.2% (108/110 subjects) for TBPM-PI, 92.6% (87/94 subjects) for high-dose CDTR-PI. Causative organisms (S. pneumoniae and H. influenzae 138 strains) were determined in 125/204 subjects. Eradication three days after administration was evaluated to determine bacteriological efficacy and was found to be 98.2% (55/56 subjects) for TBPM-PI and 80.3% (53/66) for high-dose CDTR-PI. Eradication at the end
of treatment was also evaluated to determine bacteriological efficacy and was found to be 100% (69/69 subjects) for TBPM-PI and 98.5% (64/65) for high-dose CDTR-PI. Clinical observations of 212 subjects for safety found the incidence of drug-related reactions to be 15.3% (17/111) for TBPM-PI and 13.9% for high-dose CDTR-PI. Also similar between the two drug treatment groups was the incidence of diarrhea-related adverse drug-related reactions 11/111 subjects (9.9%) in the TBPM-PI group and 11/101 subjects (10.9%) reporting such events. The incidence of adverse drug-related reactions associated with abnormal changes in laboratory data was also tracked with 1.8% (2/109 subjects) for TBPM-PI and 7.4% (7/94 subjects) for high-dose CDTR-PI reporting such events. The results supported the conclusion that a dose of 4 mg/kg of TBPM-PI administered twice daily for seven days is clinically efficacious for the treatment pediatric acute otitis media infections.

To assess the safety and efficacy of a three-day treatment regimen of TBPM-PI for pediatric community-acquired pneumonia, a post-marketing, multi-center prospective clinical study was performed [58]. The efficacy of TBPM-PI was evaluated in 36 patients 2-4 days after initiation of treatment to 49 patients at 12 mg/kg/day twice daily. The results showed that 32 patients were cured 7-15 days after initiation of treatment with only 6/49 patients reporting mild diarrhea. From this small study, it was concluded that a three-day treatment with TBPM-PI was safe and efficacious for treating pediatric community-acquired pneumonia and suggested further study to explore shorter duration dosing regimens for TBPM-PI treatment of bacterial pneumonia.
8. Microflora impact

Due to the fact that tebipenem is a broad-spectrum antibacterial agent, the impact of orally administered tebipenem on intestinal microflora was investigated in rodents [59]. It was found that doses of 30 mg/kg BID for 5 days had little impact on caecal flora in either mice or rats despite strong in vitro activity of the drug against intestinal aerobes and anaerobes [34]. Effects on intestinal flora in humans were examined with total, aerobic, and anaerobic bacterial counts assessed after 7 days of dosing three times daily with 100 and 200 mg TBPM-PI (L-084-02). Reductions in numbers of anaerobes were noted by day 7 in the 100 mg subject group and in both aerobes and anaerobes in the 200 mg group. No fecal *Clostridium difficile* or *C. difficile* toxin was detected in any subject. A four-fold increase in the MIC of *Bacteroides vulgatus*, a normal intestinal organism, was observed in 6/10 subjects in the 100 mg group and were reported to be all β-lactamase producers.

9. Post-marketing surveillance

Post-marketing surveillance of TBPM-PI granules was done 2010-2013 with an estimated number of patients at nearly 4 million. The safety and efficacy were evaluated in patients with pneumonia, otitis media, or sinusitis {60] with 3,331 patients included in the safety analyses, 2,769 in the clinical efficacy analyses, and 461 in the bacteriological efficacy analyses. In regard to efficacy, the overall efficacy rate was 94.0% (2,604/2,769). The investigators looked for changes in drug susceptibility and cross-resistance before and after the administration of tebipenem and found none. Safety analyses showed that the incidence of
adverse drug reactions (ADRs) in the treatment outcome survey was 9.97% (332/3,331), which was lower in comparison to the incidence of ADRs at the time of approval, which was 26.36% (116/440). The frequency of the occurrence of diarrhea, which showed the greatest number of instances that occurred amongst the adverse drug reactions, was 9.4% (313/3,331) with all of these instances considered to be non-serious. The conclusions were that no issues in terms of safety were observed with this drug, and adequate efficacy was demonstrated.

10. Regulatory affairs

Tebipenem is approved in Japan for pediatric pneumonia, otitis media, and sinusitis.

11. Expert commentary

The continual proliferation and increased variety of \( \beta \)-lactam-inactivating enzymes has eroded the utility of penicillins and cephalosporins for the treatment of infections caused by Gram-negative pathogens [61]. The carbapenems are the most potent broad-spectrum \( \beta \)-lactams with activity against these pathogens and are minimally affected by the majority of \( \beta \)-lactam hydrolyzing enzymes that limit the utility of other classes of \( \beta \)-lactams [4,7]. As a result, and due to the prevalence of fluoroquinolone resistance, they have evolved from “antibiotics of last resort” to a standard-of-care role. However, to date, with the exception of tebipenem-pivoxil (TBPM-PI; Orapenem®) approved for pediatric indications in Japan, all other marketed carbapenems are
intravenously administered. TBPM-PI has an established track record of safety and efficacy with relatively few adverse events similar in rate to other oral antibiotics such as amoxicillin/clavulanate (Augmentin). There is an urgent unmet need with an increasing prevalence of fluoroquinolone-resistant and ESBL-producing Gram-negative pathogens in the hospital and community setting, particularly in cUTI disease. Carbapenems have traditionally been considered the drugs of choice for infections caused by enterobacteria producing ESBL and AmpC enzymes because they are not affected by these resistance mechanisms. Furthermore, in the case of ESBL Enterobacteriaceae, they have been associated with lower failure rates than those for other drugs including cephalosporins and fluoroquinolones [13].

TBPM-PI is currently in clinical development for cUTI with the potential to be the first oral carbapenem approved for use in adults. It could address an important unmet medical need to treat serious infections in adults caused by MDR Gram-negative pathogens, allowing step-down therapy for hospitalized patients and an option for use in outpatient settings. This could avoid the need for hospitalization and the use of venous catherization, thereby reducing both cost and the risk of complications. We envision use of oral TBPM-PI for UTIs to be targeted based on risk factors for resistance including anatomical abnormalities, indwelling hardware, male gender, history of frequent UTIs, recent prior antibiotic therapy, etc. Use can also be targeted based on culture results of documented MDR-UTI. Oral tebipenem will be especially valuable in treating Enterobacteriaceae isolates that express ESBLs and are fluoroquinolone non-susceptible, thus providing a key addition to the global portfolio of marketed antibacterial products.
12. Five-year view

It has been thirty years since the discovery of the last novel chemical structure that eventually became a marketed antibiotic and even longer for a novel agent with efficacy for infections caused by key Gram-negative pathogens. Fortunately, we have been able to keep pace with the emergence and spread of antibiotic resistance through improvements in analogs from existing antibiotic classes and through effective combinations, particularly $\beta$-lactam/$\beta$-lactamase pairs. The subject of this work, tebipenem pivoxil, TBPM-PI, offers a carbapenem that can be orally administered that offers a new treatment option, particularly for complicated urinary tract infections (cUTIs), including those caused by ESBL-producer and fluoroquinolone-resistant Enterobacteriaceae. This oral option could prevent or shorten hospital stays for patients while reducing health care costs with the associated economic benefit.

As has been observed throughout the antibiotic era, bacterial pathogens have eventually acquired or developed resistance mechanisms that have eroded the effectiveness of all antibiotic classes used to date. With selective usage and good stewardship of our available antibiotics, serious resistance impacts can often be significantly delayed. For TBPM-PI, overall effectiveness will be likely linked to the levels of carbapenem-resistant Enterobacteriaceae (CRE) found in patient populations. Hopefully, in the near future, incidence of CRE will remain relatively low and should prolong the effectiveness of one of our most valuable antibiotic classes. However, we need to continue to look for novel chemical structures or additional improved analogs to keep ahead of the relentless progression of bacterial resistance to antibiotics.
13. Key issues:

- Carbapenem β-lactam antibiotics have been important therapeutic options for serious Gram-negative infections, however, only parenteral administration is currently available for adult patients.
- Tebipenem pivoxil, TBPM-PI, offers an oral carbapenem option that can have immediate utility in the treatment of cUTIs increasingly caused by fluoroquinolone-resistant and/or ESBL-producing Enterobacteriaceae isolates.
- TBPM-PI has demonstrated both human safety and clinical utility as a pediatric antibiotic that is available in Japan.
- Prior clinical study data suggest that safety and efficacy for TBPM-PI will also be observed in adult patients.
- Use of TBPM-PI for complicated urinary tract infections offers the prospect of preventing/reducing hospital stays and lowering health care costs.
Funding
The manuscript was not funded.

Declaration of Interest
The authors are employees of Spero Therapeutics, Inc., which is developing tebipenem-pivoxil (SPR994) as an oral carbapenem antibiotic for adult patients. Spero has an agreement with Meiji Seika Pharma Co., Ltd. for worldwide market rights except for the following countries: Japan, Bangladesh, Brunei, Cambodia, China, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements
The authors would like to acknowledge Tim Kuetzer, Cristina Larkin, and David Melnick for helpful discussions. The authors also thank Meiji Seika Pharma Co., Ltd. for sharing unpublished data with us and for assistance in ensuring accuracy in this review.
References

Reference annotations
* Of interest
** Of considerable interest


**Historical paper describing the discovery and characterization of the first carbapenem


**Good recent review of the carbapenem subclass of β-lactam antibiotics


18. Dunne M, Dunzo E, Puttagunta S. A Phase 1 study to assess the pharmacokinetics of sulopenem etzadroxil (PF-03709270). IDWeek 2017;Poster 1839.


*Explores the possibility of using tebipenem to treat melioidosis*


*In-depth review of carbapenem resistance providing up-to-date information on the subject*


Table 1. Minimum inhibitory concentrations (MICs) of tebipenem against selected bacterial pathogens.

<table>
<thead>
<tr>
<th>Organism</th>
<th># Strains</th>
<th>MIC$_{90}$ (µg/ml)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive aerobes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (Meth$^S$)</td>
<td>43</td>
<td>≤0.06</td>
<td>30</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (Meth$^R$)</td>
<td>39</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em> (Meth$^S$)</td>
<td>34</td>
<td>0.125</td>
<td>30</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em> (Meth$^R$)</td>
<td>30</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> (PSSP)</td>
<td>34</td>
<td>0.002</td>
<td>31</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> (PRSP)</td>
<td>72</td>
<td>0.063</td>
<td>31</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>19</td>
<td>≤0.06</td>
<td>29</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>35</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>45</td>
<td>128</td>
<td>30</td>
</tr>
<tr>
<td><strong>Gram-negative aerobes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>53</td>
<td>0.05</td>
<td>29</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>53</td>
<td>0.05</td>
<td>29</td>
</tr>
<tr>
<td><em>Enterobacter cloaceae</em></td>
<td>53</td>
<td>0.2</td>
<td>29</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>53</td>
<td>0.39</td>
<td>29</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>54</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>48</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>30</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td><em>Haemophilus influenza</em> (Amp$^S$)</td>
<td>65</td>
<td>0.12</td>
<td>62</td>
</tr>
<tr>
<td><em>Haemophilus influenza</em> (Amp$^R$)</td>
<td>119</td>
<td>1</td>
<td>62</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>34</td>
<td>≤0.06</td>
<td>30</td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> spp.</td>
<td>1</td>
<td>0.06</td>
<td>34</td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em></td>
<td>1</td>
<td>0.06</td>
<td>34</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>1</td>
<td>1</td>
<td>34</td>
</tr>
</tbody>
</table>
**Other**

*Burkholderia pseudomallei*  
102  
2  
35

*Mycobacterium tuberculosis*  
20  
1/4  
36

Abbreviations Meth$: methicillin-susceptible; Meth$^R$: methicillin-resistant; PSSP: penicillin-susceptible *S. pneumoniae*; PRSP: penicillin-resistant *S. pneumoniae*; Amp$: ampicillin-susceptible; Amp$^R$: ampicillin-resistant

---

### Table 2. Selected tebipenem clinical studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study Number/Title/Description</th>
<th>Patients Treated</th>
<th>Clinical Phase</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopharmaceutical</td>
<td><strong>ME1211-18</strong>: Clinical Pharmacology Study of ME1211 in Healthy Adult Males (Fine Granules)</td>
<td>12</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>Clinical PK</td>
<td><strong>L-084-02</strong>: Examination of the tolerability, disposition, and effect on intestinal flora of L-084 (oral antimicrobial agent) administered at 100 or 200 mg on repeated doses 3 times daily for 1 week in healthy adult males</td>
<td>16</td>
<td>1</td>
<td>unpublished</td>
</tr>
<tr>
<td></td>
<td><strong>ME1211-13</strong>: Clinical pharmacology study of ME1211 in adult subjects with impaired renal function and subjects with normal renal function (tablets) - Examination of pharmacokinetics and</td>
<td>17</td>
<td>1</td>
<td>unpublished</td>
</tr>
<tr>
<td>Clinical PD</td>
<td>Study Description</td>
<td>Participants</td>
<td>Completed</td>
<td>Status</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-----------</td>
<td>--------------</td>
</tr>
<tr>
<td>ME1211-17:</td>
<td>Clinical Pharmacology Study of ME1211 by Placebo-Controlled Double-Blind Comparison in Healthy Adult Males (Tablet) – Effect of ME1211 on QT Interval</td>
<td>12</td>
<td>1</td>
<td>Unpublished</td>
</tr>
<tr>
<td>Efficacy</td>
<td>ME1211-2: Exploratory Study of ME1211 in Patients with Bacterial Pneumonia – dose regimen confirmation (adults)</td>
<td>150</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>ME1211-3: Exploratory Study of ME1211 in Patients with Infections in the Field of Otorhinolaryngology – dose regimen confirmation (adults)</td>
<td>121</td>
<td>2</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>ME1211-7: An open clinical trial study of tebipenem pivoxil fine granule for treatment of pediatric patients with otolaryngological infections</td>
<td>43</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>ME1211-8: An open clinical study of tebipenem pivoxil in children with acute otitis media and acute upper respiratory tract infection</td>
<td>43</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>L-084-04: Exploratory Study of ME1211 in Patients with Complicated Urinary Tract Infection (adults)</td>
<td>51</td>
<td>2</td>
<td>Unpublished</td>
</tr>
<tr>
<td></td>
<td>ME1211-1: Early Phase II Clinical Study of L-084 (Complicated Urinary Tract Infections) (adults)</td>
<td>37</td>
<td>2</td>
<td>Unpublished</td>
</tr>
</tbody>
</table>
**ME1211-11 (Phase 2) and ME1211-16 (Phase 3): Open Clinical Study of ME1211 Fine Granules in Pediatric Patients with Bacterial Pneumonia.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Patients</th>
<th>Children</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME1211-11</td>
<td>Open Clinical Study of ME1211 Fine Granules in Pediatric Patients with Bacterial Pneumonia.</td>
<td>66</td>
<td>2/3</td>
<td>56</td>
</tr>
<tr>
<td>ME1211-15</td>
<td>Confirmatory Double-Blind Controlled Study of ME1211 Fine Granules in Comparison with High-Dose CDTR-PI in Pediatric Patients with Acute Otitis Media</td>
<td>111</td>
<td>3</td>
<td>57</td>
</tr>
</tbody>
</table>

**Figure 1.** Chemical structures of carbapenems.

**Figure 2.** Chemical synthesis of tebipenem-pivoxil (TBPM-PI).

**Figure 3.** Pharmacokinetics of TBPM-PI tablets assessed in healthy male volunteers after single dose administration - $C_{\text{max}}$ versus dose [19]. Plasma concentrations are in $\mu$g/ml and doses of TBPM-PI are in mg.

**Figure 4.** Tebipenem cumulative urinary excretion after multiple oral administration of 100 to 500 mg TBPM-PI [19]. Cumulative percent of doses are plotted versus dose and sampling time (hours). Crossed bars are Day 1, white bars are Day 4, and black bars are Day 7.