



Sulopenem: An Intravenous and Oral Penem for the Treatment of Urinary Tract Infections Due to Multidrug-Resistant Bacteria

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Abstract

Sulopenem (formerly known as CP-70,429, and CP-65,207 when a component of a racemic mixture with its *R* isomer) is an intravenous and oral penem that possesses in vitro activity against fluoroquinolone-resistant, extended spectrum β -lactamases (ESBL)-producing, multidrug-resistant (MDR) *Enterobacterales*. Sulopenem is being developed to treat patients with uncomplicated and complicated urinary tract infections (UTIs) as well as intra-abdominal infections. This review will focus mainly on its use in UTIs. The chemical structure of sulopenem shares properties of penicillins, cephalosporins, and carbapenems. Sulopenem is available as an oral prodrug formulation, sulopenem etzadroxil, which is hydrolyzed by intestinal esterases, resulting in active sulopenem. In early studies, the *S* isomer of CP-65,207, later developed as sulopenem, demonstrated greater absorption, higher drug concentrations in the urine, and increased stability against the renal enzyme dehydropeptidase-1 compared with the *R* isomer, which set the stage for its further development as a UTI antimicrobial. Sulopenem is active against both Gram-negative and Gram-positive microorganisms. Sulopenem's β -lactam ring alkylates the serine residues of penicillin-binding protein (PBP), which inhibits peptidoglycan cross-linking. Due to its ionization and low molecular weight, sulopenem passes through outer membrane proteins to reach PBPs of Gram-negative bacteria. While sulopenem activity is unaffected by many β -lactamases, resistance arises from alterations in PBPs (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]), expression of carbapenemases (e.g., carbapenemase-producing *Enterobacterales* and in *Stenotrophomonas maltophilia*), reduction in the expression of outer membrane proteins (e.g., some *Klebsiella* spp.), and the presence of efflux pumps (e.g., MexAB-OprM in *Pseudomonas aeruginosa*), or a combination of these mechanisms. In vitro studies have reported that sulopenem demonstrates greater activity than meropenem and ertapenem against *Enterococcus faecalis*, *Listeria monocytogenes*, methicillin-susceptible *S. aureus* (MSSA), and *Staphylococcus epidermidis*, as well as similar activity to carbapenems against *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*. With some exceptions, sulopenem activity against Gram-negative aerobes was less than ertapenem and meropenem but greater than imipenem. Sulopenem activity against *Escherichia coli* carrying ESBL, CTX-M, or Amp-C enzymes, or demonstrating MDR phenotypes, as well as against ESBL-producing *Klebsiella pneumoniae*, was nearly identical to ertapenem and meropenem and greater than imipenem. Sulopenem exhibited identical or slightly greater activity than imipenem against many Gram-positive and Gram-negative anaerobes, including *Bacteroides fragilis*. The pharmacokinetics of intravenous sulopenem appear similar to carbapenems such as imipenem-cilastatin, meropenem, and doripenem. In healthy subjects, reported volumes of distribution (V_d) ranged from 15.8 to 27.6 L, total drug clearances (CL_T) of 18.9–24.9 L/h, protein binding of approximately 10%, and elimination half-lives ($t_{1/2}$) of 0.88–1.03 h. The estimated renal clearance (CL_R) of sulopenem is 8.0–10.6 L/h, with $35.5\% \pm 6.7\%$ of a 1000 mg dose recovered unchanged in the urine. An ester prodrug, sulopenem etzadroxil, has been developed for oral administration. Initial investigations reported a variable oral bioavailability of 20–34% under fasted conditions, however subsequent work showed that bioavailability is significantly improved by administering sulopenem with food to increase its oral absorption or with probenecid to reduce its renal tubular secretion. Food consumption increases the area under the curve (AUC) of oral sulopenem (500 mg twice daily) by 23.6% when administered alone and 62% when administered with 500 mg of probenecid. Like carbapenems, sulopenem demonstrates bactericidal activity that is associated with the percentage of time that free concentrations exceed the MIC ($\%fT > MIC$). In animal models,

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bacteriostasis was associated with %fT > MICs ranging from 8.6 to 17%, whereas 2-log₁₀ kill was seen at values ranging from 12 to 28%. No pharmacodynamic targets have been documented for suppression of resistance. Sulopenem concentrations in urine are variable, ranging from 21.8 to 420.0 mg/L (median 84.4 mg/L) in fasted subjects and 28.8 to 609.0 mg/L (median 87.3 mg/L) in those who were fed. Sulopenem has been compared with carbapenems and cephalosporins in guinea pig and murine systemic and lung infection animal models. Studied pathogens included *Acinetobacter calcoaceticus*, *B. fragilis*, *Citrobacter freundii*, *Enterobacter cloacae*, *E. coli*, *K. pneumoniae*, *Proteus vulgaris*, and *Serratia marcescens*. These studies reported that overall, sulopenem was non-inferior to carbapenems but appeared to be superior to cephalosporins. A phase III clinical trial (SURE-1) reported that sulopenem was not non-inferior to ciprofloxacin in women infected with fluoroquinolone-susceptible pathogens, due to a higher rate of asymptomatic bacteriuria in sulopenem-treated patients at the test-of-cure visit. However, the researchers reported superiority of sulopenem etzadroxil/probenecid over ciprofloxacin for the treatment of uncomplicated UTIs in women infected with fluoroquinolone/non-susceptible pathogens, and non-inferiority in all patients with a positive urine culture. A phase III clinical trial (SURE-2) compared intravenous sulopenem followed by oral sulopenem etzadroxil/probenecid with ertapenem in the treatment of complicated UTIs. No difference in overall success was noted at the end of therapy. However, intravenous sulopenem followed by oral sulopenem etzadroxil was not non-inferior to ertapenem followed by oral stepdown therapy in overall success at test-of-cure due to a higher rate of asymptomatic bacteriuria in the sulopenem arm. After a meeting with the US FDA, Iterum stated that they are currently evaluating the optimal design for an additional phase III uncomplicated UTI study to be conducted prior to the potential resubmission of the New Drug Application (NDA). It is unclear at this time whether Iterum intends to apply for EMA or Japanese regulatory approval. The safety and tolerability of sulopenem has been reported in various phase I pharmacokinetic studies and phase III clinical trials. Sulopenem (intravenous and oral) appears to be well tolerated in healthy subjects, with and without the coadministration of probenecid, with few serious drug-related treatment-emergent adverse events (TEAEs) reported to date. Reported TEAEs affecting ≥1% of patients were (from most to least common) diarrhea, nausea, headache, vomiting and dizziness. Discontinuation rates were low and were not different than comparator agents. Sulopenem administered orally and/or intravenously represents a potentially well tolerated and effective option for treating uncomplicated and complicated UTIs, especially in patients with documented or highly suspected antimicrobial pathogens to commonly used agents (e.g. fluoroquinolone-resistant *E. coli*), and in patients with documented microbiological or clinical failure or patients who demonstrate intolerance/adverse effects to first-line agents. This agent will likely be used orally in the outpatient setting, and intravenously followed by oral stepdown in the hospital setting. Sulopenem also allows for oral stepdown therapy in the hospital setting from intravenous non-sulopenem therapy. More clinical data are required to fully assess the clinical efficacy and safety of sulopenem, especially in patients with complicated UTIs caused by resistant pathogens such as ESBL-producing, Amp-C, MDR *E. coli*. Antimicrobial stewardship programs will need to create guidelines for when this oral and intravenous penem should be used.

1 Introduction

With approximately 150 million cases annually worldwide, urinary tract infections (UTIs) account for the greatest proportion of outpatient bacterial infections, including in the US, EU and Asia, and remain the most frequent type of bacterial infection in women [1, 2]. In the US alone, UTIs result in over 15 million medical visits and 21 million prescriptions per year [1, 3]. UTIs may be classified as uncomplicated (uUTI) if the patient is a healthy, non-pregnant, premenopausal female without any structural or functional abnormalities of the urinary tract [4]. If the patient does not meet one of the above criteria or possesses other risk factors, such as recurrent infection or failure of previous therapy, the infection is considered complicated (cUTI) [4]. UTIs may be further specified by their location (upper urinary tract or lower urinary tract) as well as their precise site, i.e. cystitis (urinary bladder infection) or kidney (pyelonephritis) [4].

UTIs are caused primarily by *Enterobacterales*, including *Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis*, *Enterobacter* spp., *Citrobacter freundii*, and *Morganella morganii* [1, 4–7]. Of these, *E. coli* is the most common etiological agent, being responsible for 75–95% of uUTIs and approximately 50% of cUTIs [8]. cUTIs are more likely to be caused by multidrug-resistant (MDR) organisms [1, 4–7].

Given *E. coli*'s significant role in such a common infection, it is concerning that it continues to demonstrate increasing resistance to standard UTI treatments across the world, including in the US, EU and Asia [1–4, 6, 8–10]. A recent US *in vitro* study reported 33% of *E. coli* isolates were resistant to fluoroquinolones, 20% to trimethoprim-sulfamethoxazole (TMP-SMX), 13% to β-lactams, and 7% were MDR (resistant to three or more antimicrobial classes) [3]. Furthermore, the prevalence of clinical isolates of *E. coli* and *Klebsiella* spp. carrying extended spectrum β-lactamases (ESBLs), which frequently confer resistance

Key Points

Sulopenem is an intravenous and oral penem that is active against fluoroquinolone-resistant, extended spectrum β -lactamases-producing, multidrug-resistant *Enterobacterales*.

An ester prodrug, sulopenem etzadroxil, developed for oral administration when administered with probenecid, increases the absorption of sulopenem by 62%.

In clinical trials treating patients with both uncomplicated (comparator was oral ciprofloxacin) and complicated (comparator was intravenous ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate) urinary tract infections (UTIs), sulopenem has demonstrated to be an efficacious and well-tolerated agent.

Sulopenem administered orally and/or intravenously represents a potentially well tolerated and effective option for treating uncomplicated and complicated UTIs due to documented or highly suspected antimicrobial resistant pathogens to first-line agents, and in patients with microbiological or clinical failure or intolerance/adverse effects to first-line agents.

to cephalosporins and are often associated with concurrent resistance to fluoroquinolones, TMP-SMX, and aminoglycosides, are proliferating worldwide [11]. Over a 10-year span, Canada has seen ESBL-producing *E. coli* escalate from 3.4 to 11.1% and ESBL-producing *K. pneumoniae* increase from 1.3 to 9.7%, while the US has seen rates of ESBL-producing *E. coli* and *K. pneumoniae* as high as 24% in some regions [9, 11]. These data are consistent with additional data from the Centers for Disease Control and Prevention (CDC) [5, 12]. Globally, similar trends are seen in fluoroquinolone-resistant and ESBL-producing *Enterobacterales* in both outpatient and inpatient settings [10]. This rising resistance corresponds to worsening patient outcomes, including treatment failure, repeated antimicrobial prescriptions, a doubling likelihood of hospitalization, and extended hospital stays [1, 3, 5, 6, 9]. It has been documented that in the US, each instance of UTI treatment failure burdens the patient and healthcare system with additional costs of approximately US\$200 [3]. Furthermore, the patients most at risk of receiving inappropriate antimicrobial therapy resulting in treatment failure are more likely to be from vulnerable populations, such as those with diabetes mellitus, renal failure, paralysis, older age, obesity, or other comorbidities that further complicate care [2, 3, 7, 9, 13].

Some first- and second-line antimicrobials (e.g., TMP-SMX, fluoroquinolones) are no longer effective therapy for

many UTIs. Growing resistance among UTI pathogens and worsening outcomes in patients with UTI establish a need for new oral antimicrobials that are active against TMP-SMX-resistant, nitrofurantoin-resistant, fluoroquinolone-resistant, ESBL-producing, and MDR organisms. Carbapenems are often indicated for cUTIs, especially when ESBL-producing bacteria are involved [4]. Although *E. coli* and *Klebsiella* spp. resistance to carbapenems is also a concern, carbapenem resistance rates are much lower than the prevalence of ESBL-producing organisms [6, 12]. As Table 1 shows, carbapenems and penems currently approved by the US FDA are available only in parenteral formulations, meaning patients must either be hospitalized or have access to outpatient intravenous antimicrobial services to receive treatment; thus, oral options would be particularly advantageous for improving access to treatment, preventing hospitalizations, and allowing for earlier discharges [8, 14, 15]. Two antimicrobials in development could fill this gap in infectious disease management—sulopenem and tebipenem. Sulopenem (formerly known as CP-70,429, and CP-65,207 when a component of a racemic mixture with its *R* isomer) is an intravenous and oral penem with activity against fluoroquinolone-resistant, ESBL-producing, MDR *Enterobacterales* [1, 4, 6, 8, 10, 16–21]. Sulopenem has been studied extensively *in vitro*, in animal models, and in clinical trials [1, 3–6, 8–10, 13–50]. This article reviews sulopenem's chemistry, mechanisms of action, mechanisms of resistance, microbiology, pharmacokinetics, pharmacodynamics, animal studies, clinical trials, adverse effects, drug interactions, and place in therapy. To conduct this review, we executed a comprehensive literature search via PubMed, subsequently augmented with publications from scientific meetings and relevant references from select articles. It should be mentioned that a significant amount of data currently were only available from preliminary data obtained from conference proceedings and ClinicalTrials.gov reports. This review focuses on sulopenem and its oral prodrug, sulopenem etzadroxil. Sulopenem is being developed for the treatment of uUTIs, cUTIs and intra-abdominal infections [13–15, 19–21, 37, 45]. This review will focus mainly on its use in the treatment of UTIs.

2 Chemistry

Penems, such as sulopenem or faropenem, fuse properties of both penicillins (i.e., penam) and cephalosporins (i.e., cephem) [40, 51]. Like all β -lactams, penems contain a β -lactam ring responsible for inhibition of penicillin-binding proteins (PBPs) and consequent bactericidal activity (Fig. 1). Penems also share the high β -lactam ring strain of penicillins, generated by the attached five-membered sulphur-containing ring, in contrast to cephalosporins' six-membered

Table 1 Current status of carbapenems and penems

Compound name	US FDA approval or current status	Route of administration
Imipenem	1985	Intravenous
Meropenem	1996	Intravenous
Ertapenem	2001	Intravenous
Doripenem	2007	Intravenous
Panipenem	Marketed in Japan, China and Korea	Intravenous
Biapenem	Marketed in Japan and China	Intravenous
Faropenem	Marketed in Japan	Oral ^a
Sulopenem	Phase III clinical trials	Intravenous, oral ^b
Tebipenem	Phase III clinical trials ^d	Intravenous, oral ^c

^aThe oral formulation of faropenem is faropenem sodium

^bThe oral formulation of sulopenem is the prodrug, sulopenem etzadroxil

^cThe oral formulation of tebipenem is the prodrug, tebipenem pivoxil

^dNew drug application (FDA) submitted to the FDA

ring that allows increased molecular flexibility [52]. Penems also possess valuable attributes of cephalosporins. Similar to the C3=C4 double bond in cephalosporins, the double bond between C2 and C3 in penems makes their β -lactam ring more reactive to nucleophiles, such as the serine in PBP active sites [51, 52].

Although penems contain characteristics of both penicillins and cephalosporins, they have some structural components not present in either (Fig. 1). Their C6 *trans*- α -hydroxyethyl chain confers resistance to a variety of β -lactamases, and its orientation (*trans* orientation of C5 and C6 hydrogen atoms) ensures the chain is positioned opposite the β -lactam ring, which confers considerable stability against degradation by β -lactamases in both penems and carbapenems [52, 53]. While penicillins and cephalosporins demonstrate intraclass variation according to differences in side chains attached to C6 or C7, respectively, penems exhibit more variability in side chains attached to C2, as their C6 side chain must remain a hydroxyethyl chain [40]. Accordingly, penems are not as cross-immunogenic with penicillins and cephalosporins, which have more variation around the β -lactam ring and are more likely to form antigens [40].

The C2 side chain of sulopenem improves its penetration into *E. coli*, as studies have discovered pores in the outer membrane of *E. coli* preferentially select for molecules with two negative charges and one positive charge (Fig. 1) [33]. The sulphoxide forms a positive and negative charge (net neutral) due to resonance, which, in addition to the negative charge on sulopenem's carboxylic acid, gives the molecule the two negative charges and one positive charge necessary for easier access through *E. coli* outer membrane proteins [33]. Neutral side chains, like the C2 side chain of sulopenem, are also associated with lower excitatory potential and lower risk of CNS effects, in contrast to imipenem, which

has a basic side chain thought to be related to its increased risk of seizures (Fig. 2) [51, 53]. A neutral C2 side chain also provides additional stability in aqueous and solid formulations [51]. Unlike meropenem, which has activity against *Pseudomonas aeruginosa* due to its pyrrolidinyl side chain at C2, sulopenem does not possess this side chain and thus lacks activity against *P. aeruginosa* (Fig. 2) [54].

Penems are commonly mistaken for carbapenems [40]. As depicted in Figs. 1 and 2, they share meaningful similarities, but penems have an unsaturated five-membered thiazoline ring (sulphur in first position), while carbapenems have an unsaturated five-membered pyrroline ring (carbon in first position) [40]. The sulphur in penems' thiazoline ring contributes to a smaller bond angle that reduces intra-ring stress, protecting it against enzymatic degradation, such as digestion by dehydropeptidase-1 (DHP-1) [40, 51, 52]. To avoid degradation by DHP-1 in mammalian renal tubules, carbapenems require either a methyl substituent on the C1 carbon or coadministration with a DHP-1 inhibitor (e.g. cilastatin); due to the discussed structural differences, penems have inherent stability against this enzyme [40, 51].

As noted in Fig. 1, sulopenem is in its *S* isomer form. Early studies of the drug reported that the more polar *R* isomer exhibited tighter binding to DHP-1, making it 1.6-fold less stable against DHP-1 hydrolysis [39, 42]. The *R* isomer also produced a sulphurous odor-causing metabolite [42]. Oral administration of the *S* isomer prodrug was associated with better absorption, and intravenous administration of the *S* isomer was associated with higher active drug concentrations in the urine, compared with the *R* isomer [39, 42]. These findings established the potential of the *S* isomer as an antimicrobial for UTIs. Unique to sulopenem is its availability in an oral prodrug formulation, sulopenem etzadroxil. Once sulopenem etzadroxil is orally absorbed, it

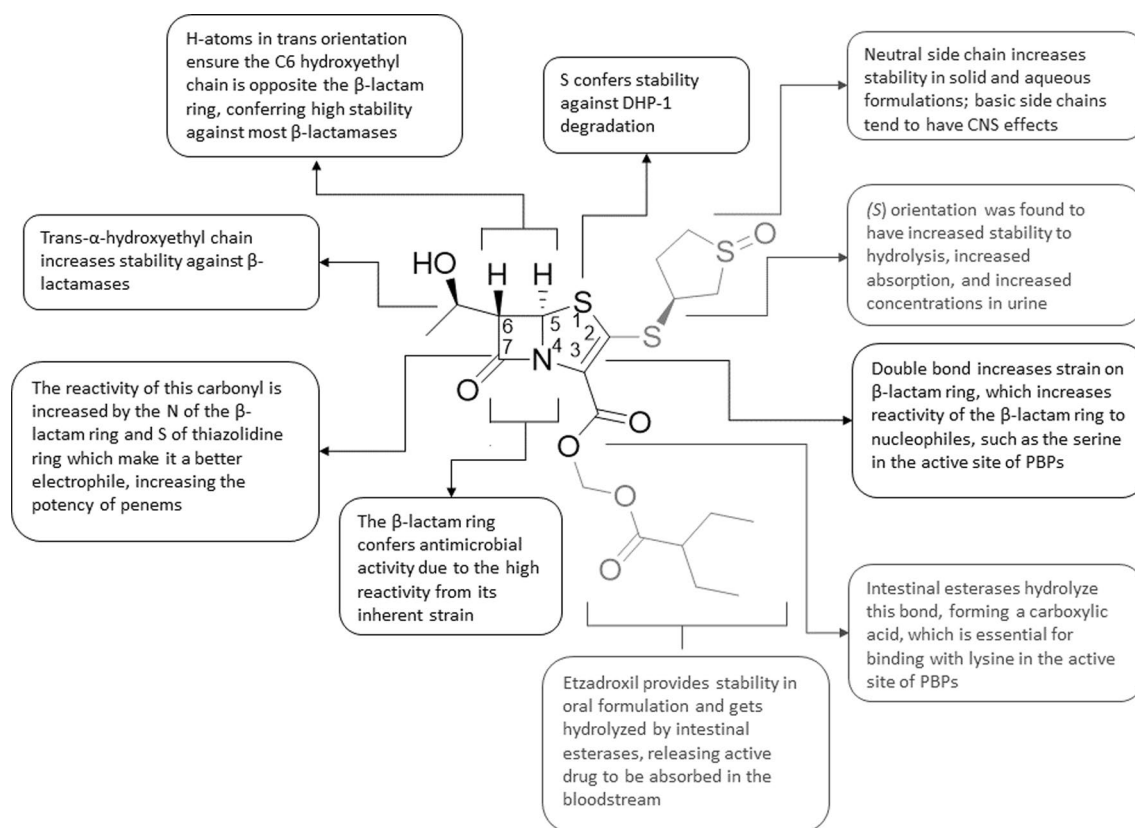


Fig. 1 General structure activity relationships for penems, including sulopenem-specific relationships shown in grey. CNS central nervous system, PBPs penicillin-binding proteins

is hydrolyzed by intestinal esterases, converting it into active sulopenem [15].

3 Mechanisms of Action

As with all β -lactam antimicrobials, the bactericidal activity of sulopenem is the result of its β -lactam ring alkylating PBP serine residues, inhibiting these transpeptidase enzymes from cross-linking peptidoglycan [40, 51, 52]. Hence, sulopenem induces cell lysis as a result of cell wall synthesis inhibition [5, 40]. Compared with Gram-positive bacteria, PBPs of Gram-negative bacteria are more difficult for β -lactams to access as they are located in the periplasmic space which is protected by an outer membrane. However, the ionization and low molecular weight (approximately 300 Da) of penems, including sulopenem, allows them to easily diffuse through outer membrane proteins, such as OmpK in *K. pneumoniae* and OmpF in *E. coli* [33, 40, 43]. The spectrum of sulopenem activity includes both Gram-negative and Gram-positive bacteria.

Sulopenem preferentially binds to PBPs in the following order, starting with greatest to least binding affinity: PBP 2, PBP 1A, PBP 1B, PBP 4, PBP 3, and, finally, PBP 5 or

PBP 6 [23, 43]. Affinity to *Staphylococcus aureus* PBP 2 as well as PBP 1 and PBP 3 of *E. coli* is greater for sulopenem than imipenem [25]. Table 2 provides a comparison of sulopenem and imipenem binding affinities to *E. coli* PBPs. Sulopenem is not active against methicillin-resistant *S. aureus* (MRSA) as it does not bind to PBP 2' (PBP 2a) [25]. The PBP binding pattern of sulopenem may also influence host endotoxin release in Gram-negative species. Generally, when Gram-negative bacteria are lysed, they release endotoxins; however, it has been observed that when *E. coli* are lysed with sulopenem or imipenem, they release fewer endotoxins, compared with *E. coli* lysed by cephalosporins, such as ceftazidime [24]. Aminopenicillins and cephalosporins primarily bind PBP 3 and both compounds can cause *E. coli* to grow as elongated filaments. In contrast, sulopenem preferentially binds PBP 2, similar to imipenem and meropenem; these compounds are associated with *E. coli* adopting a spherical shape and undergoing slower cell lysis, which limits the release of endotoxins [53–55]. Hence, the preferential PBP binding affinity of sulopenem may have larger ramifications and impacts on not only antimicrobial resistance mechanism specificity but also for endotoxin release and host inflammation.

Fig. 2 Chemical structures of (a) imipenem, (b) meropenem, (c) ertapenem, (d) sulopenem, and (e) tebipenem

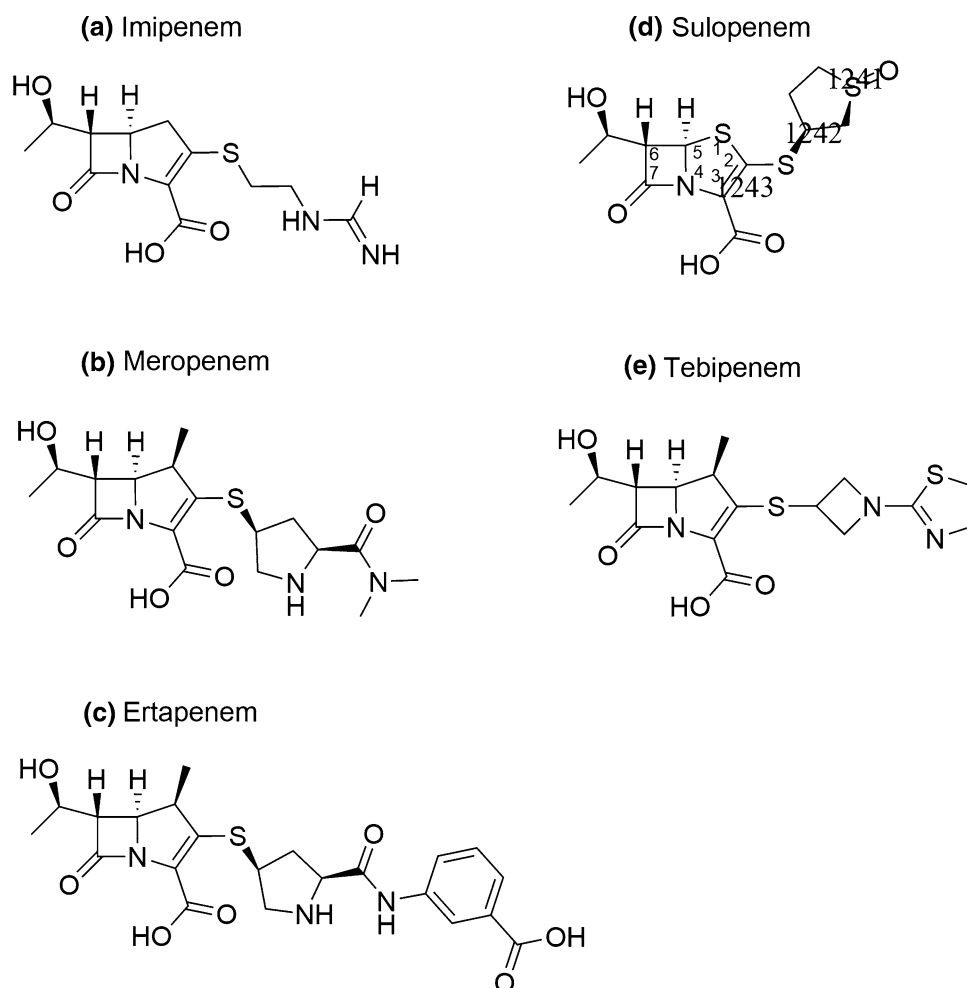


Table 2 Binding of sulopenem and imipenem to PBPs of *Escherichia coli*

PBP	Concentration (mg/L) required to inhibit PBP binding	
	Sulopenem	Imipenem
1A	≤0.1	≤0.1
1B	0.5	2.5
2	≤0.1	≤0.1
3	0.5	2.5
4	≤0.1	≤0.1
5	12.5	2.5
6	12.5	2.5

Adapted from Yoshida et al. [25]

PBP penicillin-binding protein

Another important sulopenem property is its activity against β -lactamase-producing bacteria. Recently, sulopenem was reported to resist hydrolysis by Ambler class A ESBLs (minimum inhibitory concentration inhibiting growth of 50% of isolates [MIC_{50}] = 0.12 mg/L) but not

class A carbapenemases (KPCs; MIC_{50} = 32 mg/L) [41]. Sulopenem also demonstrated stability against class C cephalosporinases from a variety of strains (MIC_{50} = 0.06 mg/L); however, it was not stable against most class D oxacillinases (MIC_{50} = 8 mg/L) [41]. As noted in Table 3, sulopenem has demonstrated stability to a wide range of *E. coli* β -lactamases that can hydrolyze amoxicillin-clavulanic acid [41]. Generally speaking, an MIC fold increase of 2–8 indicates good to relatively good stability, an MIC fold increase of 16–64 corresponds to moderate stability, and a 64-fold MIC increase or higher denotes poor to no stability [41].

4 Mechanisms of Resistance

Resistance to β -lactams is generally conferred by one of four main well-described mechanisms and in some cases a combination of these mechanisms. Bacteria may alter PBPs such that the antimicrobial can no longer effectively bind to them [36, 40, 53]. Bacteria may also possess and express a wide range of β -lactamases (Table 3) that facilitate hydrolysis of the β -lactam ring, preventing antimicrobial activity [33, 40,

41, 53]. Gram-negative bacteria may modify outer membrane proteins, limiting or preventing access to the periplasmic space and its PBPs [33, 40, 53]. Finally, organisms may express efflux pumps that actively expel the antimicrobial as they enter the cell, preventing and limiting access to the target site [33, 40, 53].

Sulopenem was found to be largely unaffected by PBP alterations that conferred reduced susceptibility or resistance to other β -lactams in *Streptococcus pneumoniae* [36]. In *S. pneumoniae*, mutations in PBP 2B resulted in reduced susceptibility or resistance to penicillin G, whereas mutations in PBP 2X resulted in reduced susceptibility or resistance to cephalosporins. Additionally, mutations in PBP 1A conferred reduced susceptibility or resistance to penicillin G and cefotaxime [36]. Sulopenem demonstrates potent antimicrobial activity against *S. pneumoniae* with PBP 1 and PBP 2 modifications [36]. Similarly, PBP alterations were also responsible for MRSA and *E. faecium* resistance to β -lactams, including sulopenem [53]. MRSA possesses

PBP 2' (PBP 2a) when other PBPs are inhibited, permitting an alternative mechanism for maintaining its cell wall in the presence of sulopenem [53]. Moreover, sulopenem is not active against *E. faecium*, which uses PBP 5 for cell wall synthesis, and sulopenem is known to bind poorly to PBP 5 [53].

Sulopenem activity is unaffected by many β -lactamases, including cephalosporinases, TEM-1, SHV-1, and PSE-2 [40]. In general, penems maintain activity against β -lactamase-producing bacteria, except in bacteria that produce carbapenemases, including Ambler class B metallo- β -lactamases [33]. *Stenotrophomonas maltophilia* and *Aeromonas* spp. carry such metallo- β -lactamases and are consequently resistant to sulopenem [53].

Reducing penem outer membrane permeance can also contribute to resistance. A *K. pneumoniae* study reported that its β -lactam resistance was not associated with β -lactamases but instead was due to the downregulation of outer membrane proteins OmpK35 and OmpK36 [44].

Table 3 Activity of sulopenem and amoxicillin-clavulanic acid against β -lactamases expressed in *Escherichia coli*

β -lactamase	Sulopenem		Amoxicillin-clavulanic acid	
	MIC (mg/L)	Fold increase in MIC compared with vector control	MIC (mg/L)	Fold increase in MIC compared with vector control
<i>Class A</i>				
CTX-M-15	0.25	4	32	4
GES-5	16	256	≥ 1024	≥ 128
KPC-2	128	2048	≥ 1024	≥ 128
KPC-3	128	2048	≥ 1024	≥ 128
KPC-3 D179Y	1	16	32	4
PER-1	0.5	8	8	1
SHV-5	0.5	8	64	8
SHV-12	0.25	4	64	8
TEM-10	0.12	2	64	8
VEB-9	0.25	4	8	1
<i>Class B</i>				
NDM-1	64	1024	≥ 1024	≥ 128
<i>Class C</i>				
ACT-17	0.5	8	≥ 1024	≥ 128
CMY-2	0.5	8	≥ 1024	≥ 128
CMY-42	1	16	≥ 1024	≥ 128
P99/Amp-C	1	16	≥ 1024	≥ 128
<i>Class D</i>				
OXA-23	4	64	≥ 1024	≥ 128
OXA-48	32	512	≥ 1024	≥ 128
OXA-163	0.5	8	≥ 1024	≥ 128
OXA-181	64	1024	≥ 1024	≥ 128
Wild-type (vector control)	0.06	NA	8	NA

Adapted from Chatwin et al. [41]

MIC minimum inhibitory concentration, NA not available

Interestingly, the loss of these outer membrane proteins resulted in some *K. pneumoniae* compensating by over-expressing *phoE*, a phosphate-regulated porin, that allows negatively charged molecules to enter the periplasmic space [44]. Upregulation of *phoE* allowed negatively charged sulopenem diffusion, as well as zwitterionic carbapenems, granting them to access PBPs and resulting in bactericidal activity [44]. However, other *K. pneumoniae* did not demonstrate such *phoE* upregulation, and thus were sulopenem-resistant [44]. The lack of *phoE* upregulation in this second group of *K. pneumoniae* may be the result of *phoE* gene repression in response to antimicrobial pressure [44].

Lastly, microorganisms may develop resistance by combining a few of these aforementioned resistance mechanisms together. An example of this is *P. aeruginosa*, where its resistance to sulopenem is conferred by a combination of three resistance mechanisms [33]. Firstly, *P. aeruginosa* possesses chromosomal β -lactamase Amp-C, which can hydrolyze sulopenem to a limited extent [33]. Secondly, *P. aeruginosa* can alter OmpF expression, reducing sulopenem permeability across the outer membrane [33]. Thirdly, *P. aeruginosa* can express the MexAB-OprM efflux pump system, which effectively reduces or eliminates sulopenem access to the periplasmic targets by expelling the compound [33]. These combined *P. aeruginosa* mechanisms are also congruent with *P. aeruginosa* resistance mechanisms for ertapenem [53]. It is important to note that alterations in PBP binding are not responsible for *P. aeruginosa* resistance to carbapenems or penems, such as sulopenem [33].

Currently, no data are available regarding *in vitro* development of reduced susceptibility or resistance to sulopenem from single exposure or multi-exposure studies. In addition, no data are available assessing the potential impact of sulopenem exposure on the normal microbiota. Thus, whether patients exposed to sulopenem will become colonized with carbapenem-resistant *Enterobacterales* or whether sulopenem-resistant *E. coli* will occur in clinical practice is unknown.

5 Microbiology

Tables 4, 5, 6 and 7 show the *in vitro* activity of sulopenem and its carbapenem comparators (ertapenem, meropenem, and imipenem) against Gram-positive and Gram-negative aerobes and anaerobes, as well as resistant phenotypes of *E. coli* and *K. pneumoniae*, key bacteria involved in UTIs. The tables display MIC values that were reported most frequently for each microorganism. Whenever a modal MIC was not available (e.g., too few isolates), a median MIC was given. Comparator MICs were derived from sulopenem-related literature to ensure the same MIC methodology was used, allowing for accurate comparison. It should be recognized

that, at this time, neither FDA, CLSI, nor EUCAST breakpoints for sulopenem have been established [16].

Table 4 compares the activity of sulopenem against Gram-positive microorganisms versus ertapenem, meropenem, and imipenem [2, 22, 23, 25, 30, 38, 40, 43, 48, 51–53, 56, 57]. Sulopenem activity was either superior (2- to 4-fold reduction in MIC₅₀) or equal to the activity of carbapenems against all phenotypes of *S. pneumoniae* [23, 25, 26, 36, 38, 43, 51, 53, 57]. Of the three comparators, only imipenem demonstrated greater activity than sulopenem (two- to four-fold lower MIC₅₀) against *Enterococcus faecalis*, *Listeria monocytogenes*, methicillin-susceptible *S. aureus* (MSSA), and *Staphylococcus epidermidis* [7, 8, 23, 25, 26, 30, 38, 40, 43, 51–53, 56, 57]. Sulopenem activity against *Streptococcus agalactiae* was reported as identical to meropenem but slightly lower than ertapenem and imipenem (two- to four-fold increase in MIC₅₀) [26, 43, 51, 53, 56, 57]. Sulopenem and all carbapenems demonstrated poor activity against MRSA [7, 40]. While the MIC₅₀ and MIC₉₀ of sulopenem against *Streptococcus pyogenes* remained low at 0.03 mg/L, they were two- to four-fold higher than ertapenem, meropenem, and imipenem MIC₅₀ and MIC₉₀ [25, 26, 38, 43, 51–53, 56, 57].

Table 5 provides activities of sulopenem, ertapenem, meropenem, and imipenem against Gram-negative aerobes and anaerobes [2, 7, 8, 17–22, 25, 26, 30, 37, 38, 40, 43, 48, 51–53, 56, 57]. Generally, sulopenem activity against Gram-negative microorganisms was found to be lower than ertapenem and meropenem (4- to 32-fold increased MIC₅₀) but greater than imipenem (2- to 4-fold reduction in MIC₅₀) [2, 7, 8, 17–22, 25, 26, 30, 37, 38, 40, 43, 48, 51–53, 56, 57]. Exceptions exist for *Acinetobacter* spp., against which sulopenem had greater activity over ertapenem (eight-fold reduction in MIC₅₀) but poorer activity compared with meropenem and imipenem (two-fold increase in MIC₅₀) [51, 53, 57]. Against *Bordetella pertussis* and *Enterobacter* spp., sulopenem demonstrated similar or slightly greater (two-fold reduction in MIC₅₀) activity versus comparators [21, 26, 37]. Sulopenem demonstrated equivalent or slightly better activity against *E. coli* and *K. pneumoniae* compared with meropenem (identical MIC₅₀) and imipenem (8-fold reduction in MIC₅₀) but not ertapenem [2, 7, 8, 17–22, 25, 26, 30, 37, 38, 40, 43, 48, 51–53, 56, 57]. Sulopenem activity against *Proteus vulgaris* was found to be similar to ertapenem and meropenem but greater (16-fold reduction in MIC₅₀ and MIC₉₀) than imipenem [25]. As expected, due to resistance mechanisms described earlier, sulopenem, similar to ertapenem, is not active against *P. aeruginosa*, unlike meropenem and imipenem [2, 8, 23, 25, 26, 30, 38, 40, 43, 51–53, 56, 57].

Table 6 compares the anti-anaerobic activity of sulopenem and imipenem and shows that for many Gram-positive and Gram-negative anaerobes, including *Clostridium*

Table 4 In vitro activity (MIC, mg/L) of sulopenem and comparators against Gram-positive microorganisms [2, 22, 23, 25, 30, 38, 40, 43, 48, 51–53, 56, 57]

Organism	Sulopenem			Ertapenem		Meropenem		Imipenem	
	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)
<i>Enterococcus faecalis</i>	4	8	0.25 to ≥32	8	16	8	8	1	2
<i>Listeria monocytogenes</i>	0.06	0.12	0.06–0.12	0.25	0.5	0.12	0.12	0.03	0.12
<i>Streptococcus agalactiae</i>	0.06	0.06	0.03–0.25	0.03	0.06	0.06	0.06	0.016	0.03
<i>Staphylococcus aureus</i> (MSSA)	0.06	0.12	0.03–0.25	0.12	0.25	0.12	0.25	0.03	0.06
<i>Staphylococcus aureus</i> (MRSA)	16	64	0.25 to >128	4	32	8	16	8	32
<i>Staphylococcus epidermidis</i>	0.12	2	0.12 to >128	0.25	0.25	0.12	8	0.03	0.5
<i>Streptococcus pneumoniae</i> (PEN-S)	0.008	0.06	0.003–0.125	0.016	0.016	≤0.016	0.016	0.008	0.008
<i>Streptococcus pneumoniae</i> (PEN-I)	0.06	0.25	0.03–0.25	0.25	1	0.12	0.5	0.06	0.12
<i>Streptococcus pneumoniae</i> (PEN-R)	0.25	0.5	0.12–1	1	2	0.5	1	0.5	1
<i>Streptococcus pyogenes</i>	0.03	0.03	0.016–0.25	≤0.016	≤0.016	≤0.016	≤0.016	≤0.008	0.016

MIC minimum inhibitory concentration, MIC₅₀ MIC inhibiting growth of 50% of isolates, MIC₉₀ MIC inhibiting growth of 90% of isolates, MSSA methicillin-susceptible *Staphylococcus aureus*, MRSA methicillin-resistant *S. aureus*, PEN-S penicillin-susceptible (MIC ≤0.06 mg/L), PEN-I penicillin-intermediate (MIC 0.12–1 mg/L), PEN-R penicillin-resistant (MIC ≥2 mg/L).

difficile, *Clostridium perfringens*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Fusobacterium mortiferum*, *Gardnerella vaginalis*, and *Porphyromonas gingivalis*, sulopenem exhibited identical or two- to four-fold greater activity than imipenem, while versus others, such as *Anaerococcus* spp., *Bifidobacterium* spp., *Eggerthella lenta*, *Finegoldia magna*, *Micromonas micros*, *Peptostreptococcus anaerobius*, *Propionibacterium acnes*, and *Prevotella* spp., sulopenem demonstrated two- to eight-fold higher MICs [16, 22, 25, 26, 43, 52, 53, 57]. Of note, activity against *Lactobacillus* spp. was the most variable in terms of MIC differences, with sulopenem MIC₅₀ >8 mg/L (generally considered as resistant), while for imipenem, the MIC₅₀ was 0.06 mg/L (generally considered as susceptible) [16, 53]. Researchers reported no evidence that sulopenem selects for *C. difficile* or that using sulopenem increases *C. difficile* colony-forming units (CFUs) following administration [22].

Table 7 shows the activity of sulopenem and its comparators ertapenem, meropenem, and imipenem against resistant *E. coli* and *K. pneumoniae* [8, 11, 17, 20, 37, 48, 52]. Sulopenem activity against *E. coli* non-susceptible to TMP-SMX, ciprofloxacin, or both, or those exhibiting ESBL, CTX-M, Amp-C, or multidrug resistance, as well as *K. pneumoniae* producing ESBL or KPC, was found nearly identical (one- to two-fold difference in MIC₅₀) to ertapenem and meropenem

and improved (eight-fold reduction in MIC₅₀) over imipenem [2, 7, 8, 20, 37, 52, 53, 56]. Sulopenem, like carbapenems, was not active against carbapenemase-producing *Enterobacteriales* containing KPC, NDM and OXA enzymes (Tables 3 and 7) [8, 11, 17, 20, 37, 41, 48, 52].

Researchers have tested sulopenem MICs in various types of media, including horse serum, and reported little to no significant impact on MIC [26]. A potential exception exists for *P. aeruginosa* where increasing concentrations of horse serum was found to lower sulopenem MICs [26]. The effect of human serum on sulopenem activity was unremarkable except for *E. coli* ML4707, where results showed a four-fold increase in MICs from 0.016 mg/L to 0.06 mg/L as human serum concentration increased from 0 to 50% [24]. Given sulopenem is being developed for UTIs, the influence of pH is of interest. Changes in pH ranging from 5.5 to 8.5 resulted in no notable differences in MICs for *E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *S. aureus*, or *Serratia marcescens* [26]. The inoculum effect was also minimal for *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *S. aureus*, and *S. marcescens*, but may exist for *E. coli*, as increasing the inoculum from 10⁴ to 10⁸ CFU/mL demonstrated two- to four-fold MIC increases [26]. As expected, MICs for sulopenem matched minimum bactericidal concentrations (MBCs), confirming its bactericidal activity [26].

Table 5 *In vitro* activity (MIC, mg/L) of sulopenem and comparators against Gram-negative microorganisms [2, 7, 8, 17–22, 25, 26, 30, 37, 38, 40, 43, 48, 51–53, 56, 57]

Organism	Sulopenem		Ertapenem		Meropenem		Imipenem	
	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)
<i>Acinetobacter</i> spp.	0.5	1	4	>8	0.25	1	0.25	0.25
<i>Bordetella pertussis</i>	1	2	ND	ND	ND	ND	1	2
<i>Moraxella catarrhalis</i>	0.03	0.12	0.008	0.008–0.25	0.008	0.008	0.06	0.12
<i>Neisseria gonorrhoeae</i>	0.06	0.12	0.008	≤0.008–0.25	ND	0.03	0.06	0.12
<i>Stenotrophomonas maltophilia</i>	128	>128	>8	4 to >128	>16	>16	>8	>128
<i>Citrobacter freundii</i>	0.12	0.5	≤0.06	≤0.016–4	0.12	0.12	0.25	1
<i>Citrobacter</i> spp.	0.06	0.06	0.008	0.016 to >8	0.03	0.03	0.25	0.25
<i>Enterobacter aerogenes</i>	0.25	0.5	≤0.016	0.03–1	0.03	0.06	1	1
<i>Enterobacter cloacae</i>	0.12	0.5	≤0.06	≤0.016–8	0.06	0.12	0.5	1
<i>Enterobacter</i> spp.	0.06	0.25	0.06	0.016–8	0.03	0.12	ND	ND
<i>Escherichia coli</i>	0.03	0.06	0.008	≤0.008–4	0.03	0.03	0.25	0.25
<i>Haemophilus influenzae</i>	0.25	0.25	0.06	0.03–1	0.06	0.12	1	2
<i>Klebsiella oxytoca</i>	0.06	0.12	≤0.06	0.03–0.25	≤0.03	0.03	0.25	0.5
<i>Klebsiella pneumoniae</i>	0.03	0.12	0.008	≤0.008 to >8	0.03	0.03	0.25	0.5
<i>Klebsiella</i> spp.	0.06	0.12	0.008	0.03 to >8	0.03	0.06	0.12	0.12
<i>Morganella morganii</i>	0.5	1	≤0.016	0.03–4	0.06	0.12	4	4
<i>Proteus mirabilis</i>	0.25	0.5	0.016	≤0.008–1	0.06	0.12	1	2
<i>Proteus vulgaris</i>	0.12	0.5	0.12	0.03–1	0.12	0.25	2	4
<i>Providencia rettgeri</i>	0.25	0.5	ND	≤0.008 to >8	0.06	0.12	1	2
<i>Providencia stuartii</i>	0.25	0.5	ND	0.03–1	ND	0.25	1	2
<i>Pseudomonas aeruginosa</i>	32	>64	8	≤8 to >128	0.5	4	1	4
<i>Salmonella</i> spp.	0.06	0.12	≤0.06	0.06–0.12	0.03	0.03	0.25	0.5
<i>Serratia marcescens</i>	1	16	0.03	0.06 to >128	0.12	0.25	1	2
<i>Shigella</i> spp.	≤0.03	0.06	≤0.06	≤0.03–0.06	0.03	0.03	0.12	0.25
<i>Yersinia enterocolitica</i>	0.06	0.12	ND	0.06–0.12	ND	0.03	0.25	0.25

MIC minimum inhibitory concentration, MIC₅₀ MIC inhibiting growth of 50% of isolates, MIC₉₀ MIC inhibiting growth of 90% of isolates, ND no data

Table 6 In vitro activity (MIC, mg/L) of sulopenem and imipenem against anaerobes [16, 22, 25, 26, 43, 52, 53, 57]

Organism	Sulopenem			Imipenem	
	MIC ₅₀ (mg/L) ¹	MIC ₉₀ (mg/L) ²	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)
Gram-positive					
<i>Anaerococcus</i> spp.	0.12	0.25	0.03–1	0.03	0.06
<i>Bifidobacterium</i> spp.	0.25	1	0.06–1	0.03	0.12
<i>Clostridium difficile</i>	2	4	1–4	4	4
<i>Clostridium perfringens</i>	≤0.03	0.06	≤0.03–0.5	0.06	0.12
<i>Clostridium</i> spp.	2	4	0.06–4	1	1
<i>Eggerthella lenta</i>	1	1	1	0.5	0.5
<i>Finnegoldia magna</i>	0.12	0.25	≤0.03–0.5	0.06	0.12
<i>Lactobacillus</i> spp.	>8	>8	0.5 to >8	0.12	2
<i>Micromonas micros</i>	0.12	0.12	0.12–0.25	0.03	0.06
<i>Peptostreptococcus anaerobius</i>	0.5	2	0.12–4	0.06	1
<i>Peptostreptococcus asaccharolyticus</i>	≤0.03	0.12	≤0.03–0.12	≤0.03	0.06
<i>Propionibacterium acnes</i>	0.12	0.25	0.12–0.25	0.03	0.03
Gram-negative					
<i>Bacteroides distasonis</i>	0.5	1	0.25–1	0.5	1
<i>Bacteroides fragilis</i>	0.06	0.5	≤0.016–8	0.25	0.5
<i>Bacteroides ovatus</i>	0.25	0.5	0.25 to >1	0.25	0.25
<i>Bacteroides thetaiotaomicron</i>	0.25	0.5	0.06 to >4	0.5	1
<i>Bacteroides</i> spp.	0.5	1	0.25–1	0.5	0.5
<i>Fusobacterium mortiferum</i>	0.5	0.5	0.12–1	0.5	1
<i>Fusobacterium nucleatum</i>	≤0.016	0.03	≤0.016–0.06	0.03	0.06
<i>Fusobacterium varium</i>	0.5	0.5	0.12–0.5	0.5	1
<i>Fusobacterium</i> spp.	≤0.03	≤0.03	≤0.016–0.03	0.12	0.5
<i>Gardnerella vaginalis</i>	0.25	0.25	≤0.03–0.5	0.25	0.5
<i>Mobiluncus</i> spp.	0.25	0.5	≤0.025–0.5	0.25	1
<i>Porphyromonas gingivalis</i>	≤0.03	0.12	≤0.03–0.12	0.06	0.12
<i>Prevotella bivia</i>	0.12	0.25	≤0.03 to >1	0.03	0.25
<i>Prevotella buccae</i>	0.12	0.25	0.06–0.25	0.03	0.12
<i>Prevotella intermedia</i>	0.06	0.12	≤0.025–0.12	0.03	0.12
<i>Prevotella melaninogenica/Prevotella denticola</i>	0.12	0.25	0.03–0.25	0.03	0.12
<i>Prevotella</i> spp.	0.06	0.12	0.03–0.12	0.03	0.06

MIC minimum inhibitory concentration, MIC₅₀ MIC inhibiting growth of 50% of isolates, MIC₉₀ MIC inhibiting growth of 90% of isolates

6 Pharmacokinetics and Pharmacodynamics

To our knowledge, only one pharmacokinetic study of sulopenem in humans [42] has been published to date and no pharmacodynamic studies. The information in this section is largely based on preliminary data obtained from conference proceedings and ClinicalTrials.gov reports. Sulopenem was initially studied as an SR-stereoisomeric mixture, however subsequent research and development has been with the S-isomer [42].

The PKs of intravenous sulopenem appear similar to carbapenems such as imipenem-cilastatin, meropenem, and doripenem (Table 8) [53]. Investigations in healthy subjects

reported volumes of distribution (V_d) ranging from 15.8 to 27.6 L, with total drug clearances (CL_T) of 18.9–24.9 L/h and elimination half-lives ($t_{1/2}$) of 0.88–1.03 h [42, 58]. The estimated renal clearance (CL_R) of sulopenem was 8.0–10.6 L/h [42, 58], and in one study, 35.5% ± 6.7% of a 1000 mg dose was recovered unchanged in the urine [42]. In the abstract by Hazra-Raybon et al., the $t_{1/2}$ of sulopenem increased from 1.0 h in subjects with creatinine clearances (CrCL) >80 mL/min to 2.3 h in those with CrCL <30 mL/min [58]. In subjects with normal renal function, the maximum plasma concentration at the end of the infusion (C_{max}) and area under the plasma concentration versus time curve (AUC) following a 1000 mg dose of sulopenem infused over

Table 7 *In vitro* activity (MIC, mg/L) of sulopenem and comparators against *Escherichia coli* and *Klebsiella pneumoniae* with various phenotypes [8, 11, 17, 20, 37, 48, 52]

Phenotype	Sulopenem			Ertapenem		Meropenem		Imipenem	
	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)
<i>Escherichia coli</i>									
TMP-SMX non-susceptible	0.03	0.06	0.016–0.12	0.03	0.03	≤0.03	≤0.03	0.25	0.25
Ciprofloxacin non-susceptible	0.03	0.06	0.016–0.12	0.03	0.03	≤0.03	≤0.03	0.25	0.25
TMP-SMX and ciprofloxacin non-susceptible	0.03	0.06	0.016–0.12	0.03	0.03	≤0.03	≤0.03	0.25	0.25
MDR ^a	0.03	0.06	0.016–4	0.03	0.03	≤0.03	≤0.03	0.25	0.25
ESBL producers	0.03	0.06	0.016–0.25	0.03	0.25	0.03	0.06	0.25	0.5
CTX-M producers	0.06	0.125	0.016–0.125	0.03	0.25	0.03	0.06	0.25	0.5
Amp-C-positive	0.06	0.25	0.016–4	0.03	0.25	≤0.06	0.06	0.25	0.5
<i>Klebsiella pneumoniae</i>									
ESBL producers	0.06	0.25	0.03 to >8	0.06	0.5	0.06	0.12	0.5	1
KPC producers	32	32	4 to >64	32	64	32	64	32	64

MIC₅₀ minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates, MIC₉₀ minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates, MDR multidrug-resistant, TMP-SMX trimethoprim-sulfamethoxazole, ESBL extended spectrum β-lactamases, KPC *Klebsiella pneumoniae* carbapenemase

^aDefined as non-susceptible to three or more antibiotics from separate classes

10 min were 69.8 ± 4.3 mg/L and 54.1 ± 7.9 mg × h/L, respectively [42]. In another study, the mean $C_{\max}$ was 17.7 mg/L and AUC was 32.3 mg × h/L with an 800 mg dose infused over 90 min [58]. In the report by Gootz et al., the protein binding of sulopenem in pooled human serum was 10% at a concentration of 20 mg/L [39].

An ester prodrug, sulopenem etzadroxil, was developed for oral administration. Initial investigations estimated an oral bioavailability of 20–34% under fasted conditions [15], however subsequent work showed that bioavailability could be improved by administering sulopenem with food to increase its oral absorption, or with probenecid to reduce its renal tubular secretion (Table 9). Dunne et al. reported that food consumption increased the AUC of oral sulopenem (500 mg twice daily) by 23.6% when administered alone and 62% when administered with 500 mg of probenecid [32]. In the study by Chandra et al., the AUC following an oral dose of sulopenem (600 mg, fasted) was 34% higher when administered with 500 mg of probenecid and 66.9% higher when administered with 1000 mg of probenecid [15]. Dunne et al. reported similar results where coadministering sulopenem and probenecid (500 mg each, fasted) increased the AUC of sulopenem by 28% [31]. Another study by the same authors showed that probenecid (500 mg) had a greater effect under fed conditions, where the AUC with an oral dose of sulopenem (500 mg) was only 7.3% higher when fasted compared with 40.7% higher when fed [32]. Currently, there is no published information on the bioavailability of specific formulations intended for clinical use.

Finally, Forrest et al. used plasma concentrations from 24 healthy subjects to develop population pharmacokinetic models for intravenous and oral sulopenem [50]. Intravenous doses ranged from 400 to 2800 mg infused over 60 min, whereas oral doses ranged from 600 to 1200 mg under fasted conditions, with and without probenecid (1000 mg). Intravenous sulopenem was best described by a two-compartment model with a central volume of 16.1 L (3.1% residual standard error [RSE]), peripheral volume of 3.9 L (8.1% RSE), and intercompartmental clearance of 2.71 L/h (12% RSE). The central clearance was described by (intercept – slope × dose), where the intercept was 26.8 L/h (5.5% RSE) and slope was 0.00252 L/h/mg (22% RSE). Oral sulopenem was characterized by a one-compartment model with first-order absorption and elimination. The pharmacokinetic estimates included an absorption rate constant of 0.78 h⁻¹ (6.8% RSE), central volume/*F* of 90.7 L (15% RSE), and CL_T/*F* of 122 L/h (7.4% RSE) without probenecid and 71.4 L/h (7.6% RSE) with probenecid.

Like carbapenems, sulopenem demonstrates bactericidal activity [48] that is associated with the percentage of time that free concentrations exceed the MIC (%*f*T > MIC). The activity of sulopenem in urine was also studied in healthy subjects who received a 500 mg oral dose followed by 2 h of urine collection [35]. The urine samples were inoculated with a reference *E. coli* isolate (MIC = 0.015 mg/L), ESBL-producing *E. coli* (MIC = 0.03 mg/L), Amp-C-positive *E. coli* (MIC = 0.12 mg/L), or OXA-48-positive *S. pneumoniae* (MIC = 16 mg/L) and incubated for 24 h. Sulopenem

concentrations in urine were highly variable, ranging from 21.8 mg/L to 420.0 mg/L (median 84.4 mg/L) in fasted subjects and 28.8 mg/L to 609.0 mg/L (median 87.3 mg/L) in those who were fed. Bactericidal activity was observed against all isolates that were tested.

There are limited pharmacodynamic data and no published studies on the optimal %f T > MIC thresholds for sulopenem activity. Girard et al. tested sulopenem against single isolates of penicillin-resistant *S. pneumoniae* and ESBL-producing *K. pneumoniae* in an immunosuppressed murine thigh infection model [49]. The reduction in CFUs per thigh at 24 h best correlated with %f T > MIC ($R^2 = 0.84$), compared with f AUC/MIC ($R^2 = 0.45$) or f $C_{\max}$ /MIC ($R^2 = 0.45$). For *S. pneumoniae*, bacteriostasis and 3-log₁₀ bacterial kill were associated with %f T > MICs of 11.6% and 14.6%, respectively, while for *K. pneumoniae*, bacteriostasis and 2-log₁₀ kill was observed at %f T > MICs of 16.4% and 20.2%, respectively. The investigators studied the same isolates in an immunocompetent murine thigh infection model [50]. Overall, bacteriostasis was associated with %f T > MICs ranging from 8.6 to 17%, whereas 2-log₁₀ kill was seen at values ranging from 12 to 28% [50].

7 Animal Models

The in vivo efficacy of sulopenem has been assessed in a variety of animal models, including guinea pig and murine systemic and lung infections [22, 23, 26]. Pathogens studied in these animal models included *Acinetobacter calcoaceticus*, *B. fragilis*, *C. freundii*, *E. cloacae*, *E. coli*, *K. pneumoniae*, *P. vulgaris*, *S. marcescens*, *S. aureus*, and *S. pneumoniae*, as well as mixed infections combining *B. fragilis* and *E. coli* [22, 23, 26, 40]. Comparator agents included carbapenems (imipenem, meropenem) and cephalosporins (cefotiam, ceftazidime, cefuzonam, flomoxef) [22, 23, 26, 40]. It should be noted that the available animal studies were primarily published in the 1990s, available in Japanese, and typically did not include robust statistical analysis; therefore, confidence intervals (CIs) were commonly used in this section to evaluate antimicrobial comparisons of efficacy. Whenever there was overlap in the 95% CIs in the 50% effective dose (ED₅₀) values, we depicted the efficacy as similar, however where there was no overlap, a conclusion of higher or lower ED₅₀ was made.

In a study of intraperitoneal *S. aureus* infections, sulopenem demonstrated a lower ED₅₀ than either meropenem or ceftazidime, but a higher ED₅₀ compared with imipenem [26]. In the same study, sulopenem and imipenem displayed similar ED₅₀ values for *S. pneumoniae* intraperitoneal infections, while meropenem and ceftazidime displayed significantly increased ED₅₀ values [26]. No statistically significant difference was reported when treating *C. freundii*, *E.*

cloacae, *E. coli*, *K. pneumoniae*, *P. vulgaris*, or *S. marcescens* intraperitoneal infections with sulopenem versus imipenem [26]. Sulopenem ED₅₀ values were higher than imipenem, similar to meropenem, and lower than ceftazidime in treating *A. calcoaceticus* systemic infections [23, 26].

Sulopenem ED₅₀ values were statistically similar to imipenem in treating mixed intraperitoneal infections combining *E. coli* and *B. fragilis*; in such infections, both sulopenem and imipenem reduced the abscess formation rate by 50% [22, 26]. No statistical difference was reported between sulopenem and imipenem in the therapeutic effect, defined as bacterial inoculum reduction in the lung, using a *K. pneumoniae* guinea pig lung infection model [26]. However, sulopenem achieved a significantly ($p < 0.01$) greater reduction of the inoculum in the lung compared with second-generation cephalosporins [26]. In summary, *in vivo* animal studies have reported that sulopenem is well tolerated and effective in treating lung and intraperitoneal infections, including mixed microbial infections involving abscess formation. These studies reported that overall, sulopenem was non-inferior to carbapenems but appeared to be superior to cephalosporins.

8 Clinical Trials

Clinical trials for sulopenem are summarized in Table 10 [13, 14, 45], including three completed phase III trials for the treatment of uUTI in adult women (NCT03354598) and cUTI in adults (NCT03357614). Although the focus of this paper is UTIs, we have added the data on sulopenem treatment of adults with complicated intra-abdominal infection (cIAI) for completeness (NCT03358576).

8.1 SURE-1

The efficacy and safety of oral sulopenem etzadroxil/probenecid has been studied for the treatment of uUTI in adult women in a multicenter, double-blind, randomized, active-controlled phase III trial (SURE-1, NCT03354598). A total of 1671 patients were randomly assigned (1:1) to receive sulopenem etzadroxil/probenecid (500/500 mg) orally twice daily for 5 days with 3 days of placebo, or ciprofloxacin (250 mg) orally twice daily for 3 days with 5 days of placebo. Patients enrolled were consenting women ≥18 years of age with 24–96 h of symptoms attributable to a UTI (with at least two of urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain) and a mid-stream urine specimen with a dipstick analysis positive for nitrite and evidence of pyuria. Patients were excluded from the study if they had signs or symptoms of acute pyelonephritis; had a urine culture with more than two microorganisms or a confirmed fungal UTI; had an indwelling urinary catheter in the previous 30 days; had ileal loops,

Table 8 Pharmacokinetics of intravenous sulopenem

Study, year	Subjects	n	IV dose × 1 (t')	C _{max} (mg/L)	AUC (mg × h/L)	V _{ss}	CL _T (L/h)	CL _R (L/h) ^d	k _e (h ⁻¹)	t _{1/2} (h)
Foulds et al., 1991 [42]	Healthy adults 25.7 years (19–43), 74.8 kg (57–85)	12	463 mg (10 min) ^a	36.0 ± 9.4	21.0 ± 4.8 ^b	0.22 ± 0.04 L/kg	21.2 ± 4.0	10.6 ± 3.1	NA	0.88 ± 0.17
	Healthy adults 28.5 years (19–45), 75.6 kg (64–96)	6	472 mg (10 min) ^a 1000 mg (10 min)	36.4 ± 3.4 69.8 ± 4.3	23.4 ± 2.1 ^b 54.1 ± 7.9 ^b	27.6 ± 6.7 L 24.0 ± 4.7 L	20.3 ± 2.0 18.9 ± 3.2	NA	0.77 ± 0.17 0.80 ± 0.16	NA
	Healthy adults 28.5 years (19–450), 74.6 kg (64–95)	10	226.5 mg (10 min) ^a	16.1 ± 6.3	7.2 ± 2.3 ^b	NA	NA	NA	0.89 ± 0.23	NA
Hazra-Raybon et al., 2011 (abstract) [58]	60.4 ± 3.2 years, CrCL >80 60.6 ± 7.3 years, CrCL >50 to ≤80	8	800 mg (90 min)	17.7 ± 1.9	32.2 ± 4.8 ^c	NA	24.9 ± 3.9	8.0 ± 5.6	NA	1.03 ± 0.22
Clinicaltrials.gov ID: NCT00759564 [62]	64.3 ± 15.7 years, CrCL 30 to ≤50 69 ± 9.4 years, CrCL <30	8 8 4	800 mg (90 min) 800 mg (90 min) 200 mg (90 min)	22.1 ± 3.4 28.9 ± 6.9 10.3 ± 2.8	54.1 ± 10.6 ^c 79.9 ± 24.6 ^c 35.4 ± 9.6 ^c		14.8 ± 2.7 10.0 ± 3.7 5.6 ± 1.3	6.9 ± 2.5 3.0 ± 3.3 2.3 ± 0.6	NA 1.82 ± 0.27 2.31 ± 0.58	

Adapted from Foulds et al. [42], Hazra-Raybon et al. [58] and ClinicalTrials.gov [62]

Non-compartment pharmacokinetic analysis

Data are expressed as mean (range) or mean ± standard deviation

AUC area under the plasma concentration versus time curve, CrCL creatinine clearance (mL/min), CL_R renal drug clearance, CL_T total drug clearance, C_{max} maximum plasma concentration at the end of the infusion, IV intravenous, k_e elimination rate constant, NA data not available, t' infusion time, t_{1/2} half-life, V_{ss} volume of distribution at steady state^aDose calculated based on the percentage of S-isomer^bAUC from time zero to 8 h^cAUC from time zero to infinity^dAmount of unchanged drug in urine divided by the plasma AUC during the same time interval

Table 9 Pharmacokinetics of oral sulopenem

Study, year	Subjects	n	PO dose(s)	Concurrent probene- cid	Fasted/fed	C _{max} (mg/L)	AUC (mg × h/L)	F (%)	CL/F (L/h)	CL _R (L/h) ^e	t _{1/2} (h)
Chandra et al., 2008 (poster) [15]	Healthy adults	9	400 mg × 1	No	Fasted	1.46 ± 0.44	3.45 ± 0.67 ^b	33.6 ± 6.5	NA	NA	0.84 ± 0.16
		4	1000 mg × 1	No	Fasted	2.86 ± 0.57	6.42 ± 1.21 ^b	23.8 ± 4.5			1.00 ± 0.17
			2000 mg × 1	No	Fasted	4.67 ± 1.18	13.13 ± 2.10 ^b	20.1 ± 3.2			1.10 ± 0.62
			600 mg × 1	No	Fasted	2.21 ± 0.41	5.83 ± 1.00 ^b				0.82 ± 0.06
			600 mg × 1	500 mg × 1	Fasted	2.38 ± 0.41	7.81 ± 3.20 ^b				0.99 ± 0.15
			600 mg × 1	1000 mg × 1	Fasted	3.67 ± 1.61	9.73 ± 2.73 ^b				1.41 ± 0.18
Hazra-Raybon et al., 2011 (abstract) [58]	60.4 ± 3.2 years, CrCL >80	8	1000 mg tab × 1	No	NA	2.75 ± 0.42	6.52 ± 1.33 ^c	NA	153.5 ± 31.5	15.47 ± 1.89	0.84 ± 0.12
		8	1000 mg tab × 1	No		3.70 ± 1.05	13.67 ± 5.09 ^c		73.2 ± 24.1	7.95 ± 2.54	1.45 ± 0.34
		8	1000 mg tab × 1	No		6.22 ± 1.84	23.04 ± 9.40 ^c		43.4 ± 19.7	4.24 ± 2.65	1.81 ± 0.57
		4	1000 mg tab × 1	No		7.83 ± 0.74	47.99 ± 16.19 ^c		20.9 ± 6.9	3.29 ± 4.40	2.75 ± 0.83
Dunne et al., 2017 (poster) [32]	Healthy adults	16	500 mg bid × 13	No	Fasted	1.77 ± 0.53	3.68 ± 0.73 ^d	NA	NA	NA	NA
		16	500 mg bid × 13	No	Fed ^a	1.87 ± 0.74	4.55 ± 1.13 ^d				
		16	500 mg bid × 13	500 mg bid × 13	Fasted	1.77 ± 0.47	3.95 ± 0.89 ^d				
		16	500 mg bid × 13	500 mg bid × 13	Fed ^a	1.69 ± 0.58	6.40 ± 1.42 ^d				
Dunne et al., 2018 (poster) [31]	Healthy adults	10	500 mg susp × 1	No	Fasted	1.93	3.89 ^c	NA	136.3	NA	NA
		11	500 mg susp × 1	500 mg × 1	Fasted	1.93	4.98 ^c		108.4		

Adapted from Chandra et al. [15], Dunne et al. [31, 32], Hazra-Raybon et al. [58] and ClinicalTrials.gov [62]

Non-compartment pharmacokinetic analysis, except Dunne et al. [32], where the methods are not reported

Data are expressed as mean ± standard deviation

AUC area under the plasma concentration versus time curve, *bid* twice daily, *CrCL* creatinine clearance (mL/min), *CL/F* clearance divided by bioavailability, *CL_R* renal drug clearance, *C_{max}* maximum plasma concentration, *F* estimated bioavailability, *NA* data not available, *PO* oral, *susp* suspension, *tab* tablet, *t_{1/2}* half-life^a30 min prior to the sulopenem dose^bAUC from time zero to 8 h^cAUC from time zero to infinity^dAUC during the dosing interval (steady state)^eAmount of unchanged sulopenem in urine divided by plasma AUC during the same time interval

Table 10 Completed clinical trials of sulopenem

Trial description	<i>n</i>	Treatment regimen	Primary outcome(s)	Primary outcome results [<i>n</i> / <i>N</i> (%)]	Secondary outcome(s)	Secondary outcome results [<i>n</i> / <i>N</i> (%)]
SURE-1: Phase III treatment of uUTI in adult women	1671	Experimental: Sulopenem etzadroxil/probenecid, 500/500 mg PO bid × 5 days, plus placebo × 3 days	Overall success ^a at TOC (micro-MITT R ^b)	Sulopenem: 92/147 (62.6) Ciprofloxacin: 50/139 (36.0)	Microbiologic success ^d at TOC (micro-MITT R ^b)	Sulopenem: 109/147 (74.1) Ciprofloxacin: 69/139 (49.6)
ClinicalTrials.gov ID: NCT03354598		Comparator: Ciprofloxacin 250 mg PO bid × 3 days, plus placebo × 5 days	Overall success ^a at TOC (micro-MITT S ^c)	Sulopenem: 247/370 (66.8) Ciprofloxacin: 326/415 (78.6)	Overall success ^a at TOC (micro-MITT ^c)	Sulopenem: 339/517 (65.6) Ciprofloxacin: 376/554 (67.9)
SURE-2: Phase III treatment of cUTI in adults	1395	Experimental: Sulopenem 1000 mg IV (<i>t</i> 3 h) once daily × 5 days minimum, followed by sulopenem etzadroxil/probenecid, 500/500 mg PO bid to complete 7–10 days	Overall success ^a at TOC (micro-MITT ^f)	Sulopenem: 301/444 (67.8) Ertapenem: 325/440 (73.9)	Microbiologic success ^d at TOC (micro-MITT ^f) Clinical ^g success at TOC (micro-MITT ^f)	Sulopenem: 316/444 (71.2) Ertapenem: 343/440 (78.0) Sulopenem: 397/444 (89.4) Ertapenem: 389/440 (88.4)
ClinicalTrials.gov ID: NCT03357614		Comparator: Ertapenem 1000mg IV (<i>t</i> 30 min) once daily × 5 days minimum, followed by: Ciprofloxacin 500 mg PO bid to complete 7–10 days OR Amoxicillin-clavulanate 500 mg PO bid to complete 7–10 days if the causative pathogen was ciprofloxacin-resistant				
SURE-3: Phase III treatment of cIAI in adults	674	Experimental: Sulopenem 1000 mg IV (<i>t</i> 3 h) once daily × 5 days minimum, followed by sulopenem etzadroxil/probenecid, 500/500 mg PO bid to complete 7–10 days	Clinical success ^g at TOC (micro-MITT ^h)	Sulopenem: 213/349 (85.5) Ertapenem: 240/266 (90.2)	Clinical success ^g at EOT (micro-MITT ^h)	Sulopenem: 208/249 (83.5) Ertapenem: 227/266 (85.3)
ClinicalTrials.gov ID: NCT03358576		Comparator: Ertapenem 1000 mg IV (<i>t</i> 30 min) once daily × 5 days minimum, followed by: Ciprofloxacin 500 mg PO bid plus metronidazole 500 mg PO qid to complete 7–10 days OR Amoxicillin-clavulanate 875 mg PO bid to complete 7–10 days if the causative pathogen was ciprofloxacin-resistant				

Table 10 (continued)

Adapted from Dunne et al. [13, 14] and Iterum Therapeutics [45]

bid twice daily, *cIAI* complicated intra-abdominal infection, *cUTI* complicated urinary tract infection, *EOT* end of treatment (last day of study treatment, day 11–14 for the SURE-3 trial), *IV* intravenous, *micro-MITT* modified microbiological intent to treat, *PO* by mouth, *qid* four times daily, *R* resistant, *S* susceptible, *TOC* test of cure (12, 21 and 28 days following treatment initiation for the SURE-1, SURE-2 and SURE-3 trials, respectively), *t'* infusion time, *uUTI* uncomplicated urinary tract infection

^aOverall success was defined as clinical success (resolution of symptoms present at study entry and no new symptoms) AND microbiologic success (eradication of baseline pathogen)

^bSURE-1 Micro-MITT R population = all randomized patients who received at least one dose of study drug and had a baseline uropathogen that was non-susceptible to ciprofloxacin

^cSURE-1 Micro-MITT S population = all randomized patients who received at least one dose of study drug and had a baseline uropathogen that was susceptible to ciprofloxacin

^dMicrobiological success was defined as eradication of the baseline pathogen (<1000 CFU/mL at TOC)

^eSURE-1 Micro-MITT = all randomized patients who received at least one dose of study drug and had a baseline uropathogen

^fSURE-2 micro-MITT population = all randomized patients who received at least one dose of study drug and had a positive urine culture (> 100,000 CFU/mL of a uropathogen, no more than two species of a uropathogen > 100,000 CFU/mL) within 48 h prior to the first dose of study drug, and patients who had one of the uropathogens isolated from baseline blood culture, regardless of the baseline urine culture result

^gClinical success was defined as resolution of symptoms present at study entry and no new symptoms (and without the need for additional antimicrobials or interventions for the SURE-3 trial)

^hSURE-3 micro-MITT population = all randomized patients who received at least one dose of study drug and had at least one Gram-negative study pathogen identified at study entry within 48 h prior to first dose and up to 24 h after the first dose, regardless of isolate susceptibilities and regardless of other organisms identified in the culture

urinary stoma, paraplegia, liver disease, uncontrolled diabetes mellitus or acute gouty attack; were pregnant or unable to take adequate contraceptive precautions; had a history of seizures, myasthenia gravis, uric acid kidney stones, blood dyscrasias, trauma to the pelvis or urinary tract, CrCl <50 mL/min or allergy to the studied antimicrobial classes or probenecid; were immunocompromised, receiving hemodialysis or peritoneal dialysis or had a renal transplant, receiving chronic methotrexate therapy or considered unlikely to survive the 4-week study period, or had a rapidly progressive or terminal illness associated with a high risk of mortality. Patients were also excluded if they received effective antimicrobial therapy in the past 7 days for uUTI, used concurrent non-study treatments that could affect outcome evaluations, were likely to receive ongoing antibacterial prophylaxis following uUTI treatment, required concomitant administration of tizanidine or valproic acid, or had used any other investigational drug in the 30 days prior to the study.

The primary outcomes of the SURE-1 trial were overall success (composite of clinical and microbiologic success) at the test-of-cure assessment (TOC, 12 days following initiation of treatment) in the microbiologic modified intent-to-treat resistant (micro-MITT R) and microbiologic modified intent-to-treat susceptible (micro-MITT S) populations. Overall success was defined as resolution of uUTI symptoms present at trial entry (with no new symptoms) and eradication of the pathogen identified at baseline (<1000 CFU/mL at TOC). The micro-MITT R population included all randomized patients who received at least one dose of study drug and had a baseline uropathogen that was non-susceptible (MIC ≥2 mg/L) to the comparator antimicrobial, ciprofloxacin; this population comprised 286 patients, including 147 in the sulopenem arm and 139 in the ciprofloxacin arm. Sulopenem was superior to ciprofloxacin in the micro-MITT R population, where overall success at TOC was 62.6% for sulopenem and 36.0% for ciprofloxacin, a difference of 26.6% (95% CI 15.1, 37.4) (Table 10). The overall response for sulopenem was consistent at end of treatment (EOT, day 5), final visit (day 28) and among MDR pathogens.

The micro-MITT S population included all randomized patients who received at least one dose of study drug and had a baseline uropathogen that was susceptible to ciprofloxacin; this population comprised 785 patients, including 370 in the sulopenem arm and 415 in the ciprofloxacin arm. Sulopenem was not non-inferior to ciprofloxacin in the micro-MITT S population, where overall success at TOC was 66.8% for sulopenem and 78.6% for ciprofloxacin, a difference of −11.8% (95% CI −18.0, −5.6). The difference in outcome was the result of a lower rate of asymptomatic bacteriuria (resulting in microbiologic failure) at TOC in the ciprofloxacin arm ($n = 16$, 3.9%) in comparison with the sulopenem arm ($n = 47$, 12.7%).

A secondary endpoint in the SURE-1 trial was microbiologic success in the micro-MITT R population at TOC. Sulopenem was superior to ciprofloxacin in the micro-MITT R population, where microbiologic success at TOC was 74.1% for sulopenem and 49.6% for ciprofloxacin, a difference of 24.5% (95% CI 13.4, 35.1). An additional endpoint was overall success in the micro-MITT population at TOC. The complete micro-MITT population included all randomized patients who received at least one dose of study drug with a baseline uropathogen, regardless of fluoroquinolone susceptibility; this population comprised 1071 patients, including 517 in the sulopenem arm and 554 in the ciprofloxacin arm. Sulopenem was non-inferior to ciprofloxacin in the micro-MITT population, where overall success at TOC was 65.6% for sulopenem and 67.9% for ciprofloxacin, a difference of -2.3% (95% CI -7.9, 3.3). Adverse events observed in the SURE-1 study will be discussed in Sect. 9.

Based on the SURE-1 results, on 23 July 2021 the FDA gave Iterum a Complete Response Letter (CRL) for its New Drug Application (NDA) for sulopenem etzadroxil/probenecid (oral sulopenem) [<https://www.iterumtx.com>, 23 July 2021]. The CRL stated that the FDA has completed its review of the NDA and has determined that it cannot approve the NDA in its present form. In the CRL, the FDA acknowledged that the phase III SURE-1 clinical trial demonstrated statistical significance in difference in the overall response rate of oral sulopenem compared with ciprofloxacin in the ciprofloxacin-resistant population. However, the FDA determined that additional data were necessary to support approval for the treatment of adult women with uncomplicated UTIs caused by designated susceptible microorganisms proven or strongly suspected to be non-susceptible to a fluoroquinolone. The FDA recommended that Iterum conduct at least one additional adequate and well-controlled clinical trial, potentially using a different comparator drug. Additionally, the FDA recommended that Iterum conduct further non-clinical investigations to determine the optimal dosing regimen, although the FDA stated that this recommendation does not raise an approvability issue. After a meeting with the FDA, Iterum stated that they are currently evaluating the optimal design for an additional phase III uncomplicated UTI study to be conducted prior to the potential resubmission of the NDA.

8.2 SURE-2

The efficacy and safety of intravenous sulopenem followed by oral sulopenem etzadroxil/probenecid has been studied for the treatment of cUTI in adults in a multicenter, double-blind, double-dummy, randomized, active-controlled phase III trial (SURE-2, NCT03357614) [14]. A total of 1395 patients were randomly assigned (1:1) to receive sulopenem (1000 mg) administered intravenously once daily (infused

over 3 h) for a minimum of 5 days followed by sulopenem etzadroxil/probenecid (500/500 mg) orally twice daily to complete 7–10 days of treatment, or ertapenem (1000 mg) administered intravenously once daily (infused over 30 min) for a minimum of 5 days followed by ciprofloxacin (500 mg) orally twice daily to complete 7–10 days of treatment (or amoxicillin-clavulanate [500 mg] orally twice daily if the baseline pathogen was non-susceptible to ciprofloxacin) (Table 10). Patients enrolled were consenting adults ≥ 18 years of age with >24 h of urinary symptoms attributable to a UTI (with at least two of the following: rigors, chills or fever/hypothermia; flank or pelvic pain; nausea or vomiting; dysuria, urinary frequency or urinary urgency; costovertebral angle tenderness on physical examination), clinically documented pyelonephritis with normal anatomy or cUTI (as defined by one or more of the following: the presence of an indwelling catheter; >100 mL of residual urine after voiding; neurogenic bladder; obstructive uropathy due to nephrolithiasis, tumor or fibrosis; azotemia due to intrinsic renal disease; urinary retention in men possibly due to benign prostatic hypertrophy; surgically modified or abnormal urinary tract anatomy), and a mid-stream urine specimen with a dipstick analysis positive for nitrite and evidence of pyuria. Patients were excluded from the study if they had uUTI; an ertapenem-resistant organism isolated from the urine culture within the last year; high risk of cUTI caused by *Pseudomonas* spp.; a severe structural or functional urinary tract abnormality responsible for an intractable infection that, in the opinion of the investigator, would require >10 days of therapy or post-treatment prophylaxis; cUTI associated with complete obstruction, emphysematous pyelonephritis, known or suspected renal or perinephric abscess or expected to require surgical intervention to achieve cure; had hypotension with systolic blood pressure [BP] <90 mmHg, chronic indwelling catheters/stents, ileal loops, vesico-urethral reflux, paraplegia/quadriplegia, renal transplantation, prostatitis or acute gouty attack; were pregnant, breastfeeding or unable to take adequate contraceptive precautions, or were unwilling to use effective barrier contraception during the study and 14 days post-treatment if male; had a history of liver disease, kidney disease, neutropenia, seizures, myasthenia gravis, uric acid kidney stones, blood dyscrasias, trauma to the pelvis or urinary tract in the past 30 days or allergy/hypersensitivity to the studied antimicrobial classes or probenecid; were immunocompromised, required dialysis, receiving chronic methotrexate therapy or considered unlikely to survive the 4-week study period, or had a rapidly progressive or terminal illness associated with a high risk of mortality. Patients were also excluded if they received effective antimicrobial therapy for cUTI for a continuous duration >24 h in the prior 72 h, required concomitant administration of tizanidine or valproic acid, were participating in any other clinical study that involved the administration of an

investigational medication, or were unlikely to comply with the study protocol.

The primary outcome of the SURE-2 trial was overall success (composite of clinical and microbiologic success) at the TOC assessment (21 days following initiation of treatment) in the micro-MITT population. Overall success was defined as complete resolution of cUTI symptoms present at trial entry (with no new symptoms) and eradication of the pathogen identified at baseline (<1000 CFU/mL at TOC). The micro-MITT population included all randomized patients who received at least one dose of study drug and had a positive urine culture ($>100,000$ CFU/mL of a uropathogen, no more than two species of a uropathogen $>100,000$ CFU/mL) within 48 h prior to the first dose of study drug, and patients who had one of the uropathogens isolated from baseline blood culture, regardless of the baseline urine culture result. The micro-MITT population comprised 884 patients, including 444 in the sulopenem arm and 440 in the ertapenem arm. Intravenous sulopenem followed by oral sulopenem etzadroxil was not non-inferior to ertapenem followed by oral stepdown therapy; overall success at TOC was 67.8% for sulopenem and 73.9% for ertapenem, a difference of -6.1% (95% CI $-12.0, -0.1$) [Table 10]. This fell short of non-inferiority, which required that the lower limit of the difference in the outcome rates be greater than -10% . The difference in outcome was a result of a lower rate of asymptomatic bacteriuria (microbiologic failure) occurring between EOT and TOC in the ertapenem arm, particularly in those patients with a fluoroquinolone-susceptible isolate receiving oral ciprofloxacin as stepdown therapy. No difference in overall success was noted at EOT (86.7% for sulopenem and 88.9% for ertapenem, a difference of -2.2% [95% CI $-6.5, 2.2$]). Intravenous sulopenem followed by oral sulopenem etzadroxil (or intravenous sulopenem alone) performed well at TOC in comparison with ertapenem followed by oral amoxicillin/clavulanate (or intravenous ertapenem alone) for patients infected with quinolone non-susceptible strains (overall success of 70.4% for sulopenem and 63.2% for ertapenem, a difference of 7.2% [95% CI $-2.7, 16.8$]).

Secondary endpoints in the SURE-2 trial included microbiologic success and clinical success in the micro-MITT population at TOC. Microbiologic success at TOC was 71.2% for sulopenem and 78.0% for ertapenem, a difference of -6.8% (95% CI $-12.5, -1.1$). Clinical response at TOC was similar between both treatment arms (89.4% for sulopenem and 88.4% for ertapenem, a difference of 1.0% [95% CI $-3.1, 5.1$]). Adverse events observed in the SURE-2 study will be discussed in Sect. 9.

From these data, it is clear that clinical data are required to fully assess the clinical efficacy and safety of sulopenem, especially in patients with cUTI caused by resistant pathogens such as ESBL-producing, Amp-C and MDR *E. coli*.

8.3 SURE-3

The efficacy and safety of intravenous sulopenem followed by oral sulopenem etzadroxil/probenecid has been studied for the treatment of cIAI in adults in a multicenter, double-blind, randomized, active-controlled phase III trial (SURE-3, NCT03358576) [45]. A total of 674 patients were randomly assigned (1:1) to receive sulopenem (1000 mg) administered intravenously once daily (infused over 3 h) for a minimum of 5 days followed by sulopenem etzadroxil/probenecid (500/500 mg) orally twice daily to complete 7–10 days of treatment, or ertapenem (1000 mg) administered intravenously once daily (infused over 30 min) for a minimum of 5 days followed by ciprofloxacin (500 mg) orally twice daily plus metronidazole (500 mg) orally four times daily to complete 7–10 days of treatment. If the patient had a causative pathogen non-susceptible to ciprofloxacin, amoxicillin-clavulanate (875 mg) orally twice daily was used instead of ciprofloxacin (Table 10). Patients enrolled were consenting adults ≥ 18 years of age with either intra- or postoperative enrollment with visual confirmation of an IAI associated with peritonitis, including at least one of the following: cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall, diverticular disease with perforation or abscess, appendiceal perforation or peri-appendiceal abscess, traumatic perforation of the intestines, only if operated on >12 h after perforation occurred, secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites) or intra-abdominal abscess (including of liver or spleen provided that there was extension beyond the organ with evidence of intraperitoneal involvement); or preoperative enrollment where one of the following surgical procedures are planned within 24 h prior to the first dose of study drug: open laparotomy, percutaneous drainage of an intra-abdominal abscess or laparoscopic surgery. Patients enrolled also had specimens from the surgical intervention sent for culture, evidence of systemic inflammatory indicators (with at least one of the following: fever [body temperature >38 °C] or hypothermia with a core body temperature <35 °C, elevated white blood cell count [$>12,000$ cells/mm³], drop in BP [systolic BP <90 mmHg without pressor support], increased heart rate [>90 bpm] and respiratory rate [>20 breaths/min], hypoxia [oxygen saturation $\leq 90\%$ on room air]) and physical findings or symptoms consistent with IAI (with one or more of the following: abdominal pain and/or tenderness, with or without rebound; localized or diffuse abdominal wall rigidity; abdominal mass; nausea/vomiting; altered mental status).

Patients were excluded from the study if they were diagnosed with traumatic bowel perforation undergoing surgery within 12 h, perforation of gastroduodenal ulcers undergoing surgery within 24 h, or had surgery including staged

abdominal repair, ‘open abdomen’ technique or marsupialization; had abdominal wall abscess or bowel obstruction without perforation, ischemic bowel without perforation, simple or gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, infected necrotizing pancreatitis, pancreatic abscess, perinephric infections, an indwelling peritoneal dialysis catheter, acute gouty attack, known inflammatory bowel disease, *Clostridioides difficile*-associated diarrhea, a body mass index >45 kg/m² or an APACHE II score >30 ; had a cIAI at study entry due to fungus, parasites, virus or tuberculosis, or caused by pathogens known to be resistant to study antimicrobials, or a concurrent infection that may interfere with the study evaluation; received systemic antimicrobial therapy in the 72 h prior to study entry {unless (1) the patient had a new infection [not a treatment failure] and received ≤ 24 h of total prior therapy and one or fewer doses of a treatment postoperatively administered not more than 6 h following the procedure; or (2) the patient did not respond to the previous treatment, provided the following criteria were met: the regimen had been administered for ≥ 72 h and was judged to have been inadequate, the patient had an operative intervention that was just completed or was intended ≤ 24 h after study entry, findings of infection were documented at surgery, specimens for bacterial cultures and susceptibility testing were taken at surgery, and no further non-study antimicrobials were administered after randomization}; were pregnant, breastfeeding or unable to take adequate contraceptive precautions, or were unwilling to use effective barrier contraception during the study and 14 days post-treatment if male; had a history of acute hepatitis in the recent past (3 months prior to study entry), chronic hepatitis, cirrhosis, acute hepatic failure, acute decompensation of chronic hepatic failure, epilepsy/seizure disorders, uric acid kidney stones, blood dyscrasias or allergy/hypersensitivity to the studied antimicrobial classes or probenecid; were immunocompromised, required hemodialysis or peritoneal dialysis, receiving chronic methotrexate therapy or considered unlikely to survive the 4-week study period or had a rapidly progressive or terminal illness associated with a high risk of mortality; or were known to have any of the following laboratory values: hematocrit $<25\%$ or hemoglobin <8 g/dL, absolute neutrophil count $<1000/\text{mm}^3$, platelet count $<75,000/\text{mm}^3$, bilirubin $>3 \times$ the upper limit of normal (ULN) [unless the value was directly related to the acute infection or known Gilbert’s disease], estimated CrCl <50 mL/min, or alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase $>3 \times$ ULN values at screening (up to $5.0 \times$ ULN were eligible if acute and documented as being directly related to the infection being treated). Patients were also excluded if they required effective concomitant systemic antimicrobials or antifungals in addition to the study compounds (except vancomycin,

linezolid, or daptomycin if started for known or suspected MRSA or *Enterococcus* spp.), were participating in any other clinical study in the 30 days prior to enrollment that involved the administration of an investigational medication, or had previously been treated with sulopenem, were unlikely to comply with the study protocol, were unlikely to respond to 10–14 days of antimicrobial treatment, or were in a situation/had a condition that may interfere with optimal study participation.

The primary outcome of the SURE-3 trial was clinical success at the TOC assessment (28 days following initiation of treatment) in the micro-MITT population. Clinical success was defined as resolution of signs and symptoms of the index infection (with no new symptoms), without the need for additional antimicrobials or interventions. The micro-MITT population included all randomized patients who received at least one dose of study drug and had at least one Gram-negative pathogen identified at study entry (irrespective of isolate susceptibilities). Patients with a bacterial species not expected to respond to any of the study antimicrobials were excluded. The micro-MITT population comprised 515 patients, including 249 in the sulopenem arm and 266 in the ertapenem arm. Intravenous sulopenem followed by oral sulopenem etzadroxil was not non-inferior to ertapenem followed by oral stepdown therapy; clinical success at TOC was 85.5% for sulopenem and 90.2% for ertapenem, a difference of -4.7% (95% CI $-10.3, 1.0$). This fell short of non-inferiority, which required that the lower limit of the difference in the outcome rates be greater than -10% . A secondary outcome was clinical success at the EOT assessment (11–14 days following initiation of treatment) in the micro-MITT population. Clinical success at EOT was 83.5% for sulopenem and 85.3% for ertapenem, a difference of -1.8% (95% CI $-8.1, 4.5$). Adverse events observed in the SURE-3 study will be discussed in Sect. 9.

9 Adverse Effects

The safety and tolerability of sulopenem has been reported in three phase I pharmacokinetic studies and three phase III clinical trials [13–15, 31, 32, 45]. Adverse effects reported in comparative phase III clinical trials are shown in Table 11 [13, 14, 45].

An initial pharmacokinetic study assessed the safety of oral sulopenem in two separate groups of subjects [15]. First, the safety of escalating doses of sulopenem (400–2000 mg) was assessed in nine healthy adult subjects in a fasted state. Second, the safety of sulopenem administered in combination with probenecid was assessed. Four healthy adults in a fasted state received sulopenem alone (600 mg), and in combination with probenecid (500 mg, 1000 mg). Treatment-emergent adverse events (TEAEs) were all mild in severity

and included abdominal pain, diarrhea, nausea, dysgeusia and headache. There were no deaths, serious adverse events (SAEs) or discontinuations due to TEAEs reported in either group. The investigators reported no clinically significant changes in vital signs, telemetry, ECGs or clinical laboratory test findings.

A second phase I pharmacokinetic study assessed the effects of food and probenecid on the safety and tolerability of sulopenem etzadroxil [32]. Subjects were administered 500 mg of sulopenem etzadroxil twice daily under either fed or fasted conditions, and with or without the coadministration of 500 mg of probenecid (16 subjects per group). TEAEs occurred in 12, 10, 12 and 13 subjects in the fed with probenecid, fed without probenecid, fasted with probenecid and fasted without probenecid treatment groups, respectively, of which 10, 8, 11 and 13 were drug-related. No SAEs were recorded and only one TEAE (in the fed with probenecid group) resulted in premature discontinuation of the study. The most frequent TEAE was diarrhea, which was mild, self-limited and not associated with discontinuation of treatment. Diarrhea occurred in two subjects each who were fed with probenecid, fed without probenecid and fasted with probenecid, and three subjects who were fasted without probenecid.

A final phase I pharmacokinetic study assessed the safety and tolerability of a single dose of sulopenem etzadroxil with or without probenecid [31]. Twenty-four healthy male and female subjects (12 of each) were randomized to receive a single dose of sulopenem etzadroxil (500 mg oral suspension) with or without probenecid (500 mg). Only two TEAEs occurred, in subjects who did not receive probenecid, although neither was drug-related and both were mild. Specific information on the two events was not available. No severe TEAEs, SAEs or discontinuations of study drug were reported.

In the SURE-1 phase III clinical trial, the safety of oral sulopenem etzadroxil was evaluated against oral ciprofloxacin for the treatment of uUTI in women [13]. Of the subjects receiving sulopenem and ciprofloxacin, 24.8% (207/833) and 13.9% (115/827) experienced a TEAE, respectively, including 142 and 51 drug-related events. TEAEs affecting $\geq 1\%$ of patients were (from most to least common) diarrhea, nausea, headache, vomiting and dizziness. Diarrhea was more common in the sulopenem treatment group in comparison with ciprofloxacin (12.4% [103/833] and 2.5% [21/827], respectively), while the remainder were similar in occurrence between treatment groups (Table 11). SAEs occurred in 0.7% (6/833) and 0.2% (2/827) of patients treated with sulopenem and ciprofloxacin, respectively, including one drug-related event (angioedema) in the sulopenem group. Discontinuation of study therapy occurred due to a TEAE in 1.6% (13/833) and 1.0% (8/827) of patients treated with sulopenem and ciprofloxacin, respectively, however only one

subject (in the ciprofloxacin arm) had an SAE leading to discontinuation of the study. One subject in the sulopenem arm died due to lung cancer, which was unrelated to the study drug. The investigators concluded that sulopenem was well-tolerated with a favorable safety profile [59].

The SURE-2 clinical trial evaluated the safety of intravenous sulopenem followed by oral sulopenem etzadroxil/probenecid stepdown therapy in comparison with intravenous ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate stepdown therapy for the treatment of cUTI in adults [14]. In the sulopenem treatment group, 14.8% of subjects (103/695) experienced a TEAE, including 72 and 42 events due to intravenous and oral therapy, respectively. Forty-two subjects (6.0%) in the sulopenem group had a drug-related TEAE, including 32 and 13 events due to intravenous and oral therapy, respectively. In comparison, 16.1% of subjects in the ertapenem group (112/697) experienced a TEAE, including 94 and 27 events due to intravenous and oral therapy, respectively. Sixty-four subjects (9.2%) in the ertapenem group had a drug-related TEAE, including 52 and 13 events due to intravenous and oral therapy, respectively. Discontinuation of the study drug due to a TEAE occurred for 3 (0.4%) and 4 (0.6%) subjects in the sulopenem and ertapenem groups, respectively. TEAEs affecting $\geq 1\%$ of patients included headache, diarrhea and nausea, and were similar in occurrence between treatment groups (Table 8). SAEs occurred in 2.0% (14/695) and 0.9% (6/697) of patients treated with sulopenem and ertapenem, respectively, including no drug-related events. No SAEs led to discontinuation of the study drug or from the study, however two subjects in the sulopenem arm had an SAE leading to death, although they were unrelated to the study drug. Overall, the investigators concluded that sulopenem, both intravenous and oral, was well tolerated.

In the SURE-3 trial, the safety of intravenous sulopenem followed by oral sulopenem etzadroxil/probenecid stepdown therapy was evaluated in comparison with intravenous ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate stepdown therapy for the treatment of cIAI in adults [45]. TEAEs were observed in 6.0% and 5.1% of patients receiving sulopenem and ertapenem, respectively, with the most reported drug-related adverse event being diarrhea (4.5% and 2.4%, respectively) [Table 11]. SAEs unrelated to study treatment were seen in 7.5% and 3.6% of patients in the sulopenem and ertapenem treatment groups, respectively. Discontinuations of the treatment/study were uncommon, only seen in 1.5% of patients receiving sulopenem and 2.1% of patients receiving ertapenem.

10 Drug Interactions

Limited information is currently available regarding specific drug interactions with sulopenem.

As previously discussed, administering probenecid in combination with sulopenem etzadroxil was found to increase sulopenem plasma concentrations and time over MIC [15, 31, 32]. Although probenecid decreases renal excretion of β -lactams, resulting in an increase in plasma concentration [60], urine concentrations of sulopenem exceeded that of plasma and were sustained above the MIC₉₀ for 8–12 h postdose [32].

Similar to other carbapenem antimicrobials, one would expect that sulopenem would decrease serum concentrations of valproic acid. A retrospective study on the interactions of various carbapenems (ertapenem, meropenem, imipenem/cilastatin) with valproic acid reported a 60% reduction in valproic acid serum concentration within 24 h of initial

carbapenem administration [61]. The authors noted that some compounds had a higher impact (ertapenem, meropenem) on valproic acid concentrations than others (imipenem/cilastatin) [61]. It is unknown at this time whether sulopenem will have a higher or lower impact.

11 Place in Therapy

Sulopenem is an intravenous and oral penem being developed for the treatment of uncomplicated and complicated UTIs. In vitro studies have reported that sulopenem is a broad-spectrum agent with activity versus both gram-positive and gram-negative bacteria. Sulopenem activity against *E. coli* carrying ESBL, CTX-M, or Amp-C enzymes, or demonstrating MDR phenotypes, as well as against ESBL-producing *K. pneumoniae*, is nearly identical to ertapenem and meropenem. Sulopenem has demonstrated to be an efficacious and well-tolerated agent in clinical trials treating patients with

Table 11 Adverse effects of sulopenem in comparative phase III clinical trials

Study	Treatment dose	Adverse effects	Patients with adverse events [n/N (%)]
SURE-1 [13]	Experimental: Sulopenem etzadroxil/probenecid, 500/500 mg PO bid $\times$ 5 days	Diarrhea	103/833 (12.4)
		Clinically significant	60/833 (7.2)
		Mild	47/833 (5.6)
		Nausea	31/833 (3.7)
		Headache	18/833 (2.2)
		Vomiting	13/833 (1.6)
		Dizziness	9/833 (1.1)
	Comparator: Ciprofloxacin 250 mg PO bid $\times$ 3 days, plus placebo $\times$ 5 days	Nausea	30/827 (3.6)
		Diarrhea	21/827 (2.5)
		Clinically significant	10/827 (1.2)
		Mild	9/827 (1.1)
		Headache	18/827 (2.2)
		Vomiting	11/827 (1.3)
		Dizziness	5/827 (0.6)
SURE-2 [14]	Experimental: Sulopenem 1000 mg IV (t' 3 h) once daily $\times$ 5 days minimum, followed by sulopenem etzadroxil/probenecid, 500/500 mg PO bid to complete 7–10 days	Headache	21/695 (3.0)
		Diarrhea	19/695 (2.7)
		Nausea	9/695 (1.3)
	Comparator: Ertapenem 1000 mg IV (t' 30 min) once daily $\times$ 5 days minimum, followed by ciprofloxacin or amoxicillin/clavulanate 500 mg PO bid to complete 7–10 days	Diarrhea	21/697 (3.0)
		Headache	15/697 (2.2)
		Nausea	11/697 (1.6)
SURE-3 [45]	Experimental: Sulopenem 1000 mg IV (t' 3 h) once daily $\times$ 5 days minimum, followed by sulopenem etzadroxil/probenecid, 500/500 mg PO bid to complete 7–10 days	Diarrhea	4.5% ^a
	Comparator: Ertapenem 1000 mg IV (t' 30 min) once daily $\times$ 5 days minimum, followed by ciprofloxacin 500 mg PO bid plus metronidazole 500 mg PO qid, or amoxicillin/clavulanate 875 mg PO bid to complete 7–10 days	Diarrhea	2.4% ^a

Adapted from Dunne et al. [13, 14] and Iterum Therapeutics [45].

bid twice daily, IV intravenous, PO oral, t' infusion time

^a Specific *N* values for each treatment group were not available

both uncomplicated (sulopenem etzadroxil with probenecid in SURE-1) and complicated (intravenous sulopenem, stepping down to sulopenem etzadroxil with probenecid in SURE-2) UTIs. The safety and tolerability of sulopenem has been reported in various phase I pharmacokinetic studies and phase III clinical trials. Sulopenem (intravenous and oral) appears to be well tolerated in healthy subjects, with and without the coadministration of probenecid, with few serious drug-related TEAEs reported to date. Sulopenem orally and/or intravenously represents a potentially well tolerated and effective option for treating uncomplicated and complicated UTIs, especially in patients with documented or highly suspected antimicrobial pathogens to commonly used agents (e.g. fluoroquinolone-resistant *E. coli*), and in patients with documented microbiological or clinical failure, or patients who demonstrate intolerance/adverse effects to first-line agents. This agent will likely be used orally in the outpatient setting and intravenously followed by oral stepdown in the hospital setting. Sulopenem also allows for oral stepdown therapy in the hospital setting from intravenous non-sulopenem therapy. More clinical data are required to fully assess the clinical efficacy and safety of sulopenem, especially in patients with cUTI caused by resistant pathogens such as ESBL-producing, Amp-C and MDR *E. coli*. Antimicrobial stewardship programs will need to create guidelines for when this oral and intravenous penem should be used.

Declarations

Conflicts of interest George G. Zhanel has received research grants from Iterum Pharmaceuticals. Marianna Pozdirca, Alyssa Golden, Courtney K. Lawrence, Sheryl Zelenitsky, Liam Berry, Frank Schweizer, Denice Bay, Heather J. Adam, Michael A. Zhanel, Philippe Lagacé-Wiens, Andrew Walkty, Neal Irfan, Kurt Naber, Joseph P. Lynch III and James A. Karlowksy have declared no conflicts of interest.

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Therapy sections. NI: design and concept of the entire manuscript and drafting the Adverse Effects, Drug Interactions and Place in Therapy sections. KN: design and concept of the entire manuscript and drafting the Clinical Trials section. JPLIII: design and concept of the entire manuscript and drafting the Clinical Trials and Place in Therapy sections. JAK: design and concept of the entire manuscript and drafting all sections.

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