Faropenem: review of a new oral penem

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Faropenem medoxomil is a new orally administered penem antibiotic. Its chiral tetrahydrofuran substituent at position C2 is responsible for its improved chemical stability and reduced CNS effects, compared with imipenem. Faropenem demonstrates broad-spectrum *in vitro* antimicrobial activity against many Gram-positive and -negative aerobes and anaerobes, and is resistant to hydrolysis by nearly all β-lactamases, including extended-spectrum β-lactamases and AmpC β-lactamases. However, faropenem is not active against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia*. Prospective, multicenter, randomized, double-blind, comparative (not vs placebo) clinical trials of acute bacterial sinusitis (ABS), acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP) and uncomplicated skin and skin structure infections (uSSSIs) have demonstrated that faropenem medoxomil has equivalent efficacy and safety compared with cefuroxime, clarithromycin, azithromycin, amoxicillin, cefpodoxime and amoxicillin–clavulanate. The evidence supports faropenem medoxomil as a promising new oral β-lactam with proven efficacy and safety for the treatment of a variety of community-acquired infections. However, the US FDA recently rejected faropenem for all four indications stating that the clinical trials in ABS and AECB should have been performed versus a placebo. In the CAP studies, the FDA stated that they could not be certain of the validity of the study population actually having the disease and for uSSSI, the FDA stated that only a single trial was not adequate evidence of efficacy for this indication.

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Faropenem is a new, orally administered, β-lactam antibiotic. Although faropenem is structurally similar to the carbapenems, which include the clinically available agents imipenem, meropenem and ertapenem, it is distinguished by a sulfur atom at position 1. The Clinical and Laboratory Standards Institute (CLSI) M100 glossary divides the antimicrobial class of 'penems' into two distinct subclasses, namely 'carbapenems' and 'penems' [1]. Faropenem is currently the only member of the subclass of penems. The differences in faropenem's chemical structure from both the carbapenems and other β-lactam antibiotics provide it with a unique profile in terms of microbiological spectrum of activity, pharmacology, clinical utility and safety [2].

In Japan, faropenem is currently available as an orally administered sodium salt, Farom®; while in the USA, faropenem is in Phase III clinical trials as the ester prodrug, faropenem medoxomil (faropenem daloxate was previously used) [3]. The aim of this article is to provide an in-depth literature review of the chemistry, mechanisms of action and resistance, *in vitro* activity, pharmacokinetics, pharmacodynamics, clinical trials and adverse effects of faropenem medoxomil.

Chemistry

The penem structural core of faropenem is an entirely synthetic molecule representing a combination of penam and cephem nuclei, as seen in FIGURE 1 [2]. It consists of a 4-membered β-lactam ring fused to a 5-membered

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sulfur-containing ring with a double bond between C2 and C3. As with all β-lactam antibiotics, the inherent strain in the β-lactam ring provides a high degree of reactivity, which is responsible for antibacterial activity and is affected by the nature of the ring to which it is conjugated [3]. The double bond between C2 and C3, like that of the cephalosporins, increases reactivity of the β-lactam ring to nucleophiles, including the active site serine of penicillin-binding proteins (PBPs), amines and water [3]. Similar to the carbapenems, the hydrogen atoms at C5 and C6 of faropenem are in the *trans* orientation with S stereochemistry at C6, thus distinguishing the penem class from other β-lactams, which have *cis* orientation with R stereochemistry at the position corresponding to C6. This configuration places the C6 hydroxyethyl side chain on the opposite side of the β-lactam ring resulting in the high degree of stability to degradation by most β-lactamases [3]. Being a hybrid compound, faropenem exhibits similarities to both the penicillins and cephalosporins; however, there are several key structural features that set faropenem apart from all other β-lactams, including penicillins, cephalosporins and the closely related carbapenems.

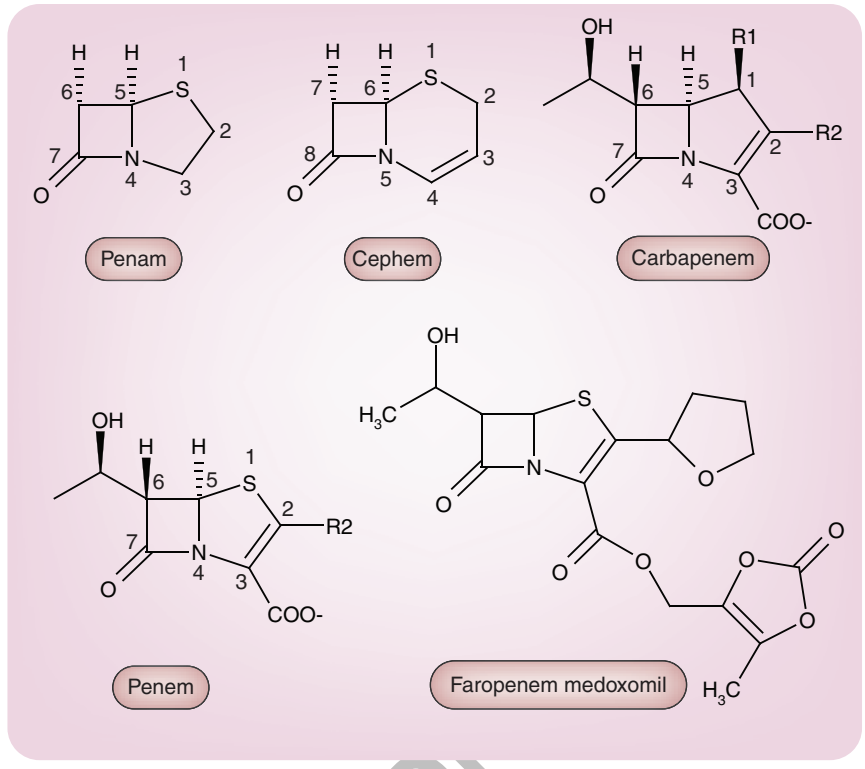

Figure 1. Basic chemical structure of penam, cephem, carbapenem, penem nuclei and faropenem medoxomil.

The sulfur at position 1 differentiates the thiazolidine ring of faropenem from the carbon-containing pyrrolidine ring of the carbapenems. The presence of sulfur alters the 3D shape of the 5-membered ring creating a smaller C–S–C bond angle and a longer bond length between the C and S, thus reducing intra-ring stress [3]. Dramatic differences in both the stability and activity of faropenem, compared with the carbapenems, are attributed to the addition of a chiral tetrahydrofuran ring side chain at C2 of faropenem (FIGURE 1). The C2 side chain of the carbapenems is highly protonated at physiological pH. By contrast, faropenem's side chain remains neutral making it stable in both the solid and aqueous media. Stability to hydrolysis by the renal enzyme dehydropeptidase I (DHP-I) has eliminated the need for coadministration with DHP inhibitors, such as cilastatin, which must be administered with imipenem [2,4]. In addition, the protonated state impacts both the *in vitro* activity of the compounds as well potential CNS effects, which will be discussed later.

Faropenem is synthesized in three forms based on the C3 side chain: the free acid, the sodium salt and the ester prodrug form [5]. The medoxomil portion of faropenem medoxomil is attached via an ester linkage to position C3 of the 5-membered ring. This moiety is hydrolyzed *in vivo* to release the active free-acid form. It is also responsible for the increased bioavailability of faropenem medoxomil compared with the C3 side chain of the faropenem sodium compound presently available in Japan [5].

Mechanism of action

All β-lactam antibiotics, including faropenem, are bactericidal by way of their interactions with various PBPs. The PBPs are a group of enzymes known to play an important role in maintaining the structural integrity of the cell wall during growth and replication. Each organism has a variety of PBPs, including both high- and low-molecular-weight PBPs. β-lactam antibiotics produce their antibacterial effect by binding to and inactivating the high-molecular-weight PBPs that are involved in the transpeptidation reaction, which occurs during the synthesis of peptidoglycan. In Gram-negative bacilli harboring chromosomal AmpC β-lactamases, the concomitant inhibition of both the low- and the high-molecular-weight PBPs results in the accumulation of anhydromuramyl peptides, which interact with regulators of β-lactamase expression, ultimately resulting in the induction of β-lactamases [6]. Ideally, an antibiotic would have a high affinity for the high-molecular-weight PBPs so as to effectively interfere with peptidoglycan synthesis and a low affinity for the low-molecular-weight PBPs in order to reduce AmpC β-lactamase induction. Unlike the strong AmpC β-lactamase inducer imipenem, the PBP-binding profile of faropenem approaches this ideal.

Studies of antibiotic target affinity in Gram-negative organisms revealed that faropenem preferentially targets PBP2 but also has a high affinity for PBP1A, PBP1B and PBP3 [7]. The comparative binding affinity of faropenem to PBP1, PBP2 and PBP3 of methicillin-susceptible *Staphylococcus aureus* (MSSA)

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was found to be higher than that of imipenem; however, faropenem exhibited low affinity for the modified PBP2a (PBP2′) of methicillin-resistant *S. aureus* (MRSA). For *Streptococcus pneumoniae*, the binding affinity of faropenem was higher for all PBPs compared with cefuroxime and the order of faropenem target preference was PBP1 > PBP2 > PBP3 [7].

Morphological changes resulting from faropenem exposure have been observed in *S. aureus* and *Escherichia coli*. Faropenem exposure at concentrations below the minimum inhibitory concentration (MIC) (1/8–1/4 MIC) for *S. aureus* affected septum formation with the number of viable cells decreasing with increasing concentrations of antibiotic. Exposure to concentrations equivalent to the MIC or greater resulted in cell lysis. Cell shape in *E. coli* was affected by exposure to concentrations below the MIC (1/4–1/8 MIC). Upon exposure to concentrations equal to the MIC, bulging was observed followed by lysis after a 4-h period. At four-times the MIC, spheroplasts were formed and cell lysis occurred [7].

Mechanisms of resistance

The two main mechanisms of resistance affecting β-lactam antibiotics are the alteration of PBPs leading to decreased target binding affinity and the production of β-lactamases, which hydrolyze the β-lactam ring, thereby inactivating the drug. β-lactamases can be either chromosomally encoded or carried on a plasmid; as such, they are readily transferred among organisms and present a growing concern in the clinical setting. Owing to the *trans* configuration of its C6 side chain, faropenem demonstrates intrinsic stability to β-lactamases in classes A, C and D (similar to carbapenems and other investigational penems), including extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamses [8]. Class B β-lactamases are zinc-dependent enzymes, also known as metallo β-lactamases or carbapenemases, that completely hydrolyze the β-lactam ring of carbapenems [3]. Regardless of the finding that the rate of faropenem hydrolysis by a metallo β-lactamase derived from an imipenem-resistant strain of *Bacteroides fragilis* was five-times lower than that of imipenem and only 23.6% hydrolysis occurred, the production of metallo β-lactamases results in resistance to faropenem [8]. Despite the diversity of this group and their worldwide distribution, the class B β-lactamases are currently rare.

Pseudomonas aeruginosa is intrinsically resistant to faropenem due to poor outer membrane penetration, despite having a higher binding affinity for the high-molecular-weight PBPs than imipenem [7,9]. Being an uncharged (or neutral) molecule, faropenem is not taken up through the OprD porin, which is responsible for the uptake of the positively charged carbapenems [9]. Furthermore, faropenem is effluxed by the multidrug efflux pump, MexAB-OprM [9]. Interestingly, although faropenem is effluxed via the same pump as many other substrates, including other β-lactams, β-lactam inhibitors, quinolones, chloramphenicol and carbapenems, it appears to have a unique binding site and thus is not likely to select for efflux-mediated carbapenem resistance [9].

In vitro activity

In vitro studies have demonstrated faropenem to be a highly potent, broad-spectrum antimicrobial with excellent activity against a wide range of Gram-positive (TABLE 1), Gram-negative (TABLE 2) and some anaerobic bacteria [10–25; ZHANEL GG & DILAY L, UNPUBLISHED DATA]. The data presented in TABLES 1 & 2 have been compiled from a number of studies including several large-scale investigations of clinical isolates from both Europe and the USA, and thus represents data from thousands of isolates. Faropenem is as much as four- to eightfold more active against penicillin-resistant isolates of *S. pneumoniae* than amoxicillin–clavulanate and cefuroxime, and maintains *in vitro* activity against multidrug-resistant strains of *S. pneumoniae*, including strains that are resistant to macrolides, tetracycline, trimethoprim–sulfamethoxazole (TMP–SMX) and fluoroquinolones (TABLE 1) [ZHANEL GG & WIEBE R, UNPUBLISHED DATA]. Faropenem exhibits *in vitro* activity against β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* (TABLE 2), including the BRO-1 and BRO-2 producing *M. catarrhalis* [26]. In addition, it remains active against the rare β-lactamase-negative ampicillin-resistant *H. influenzae* (BLNAR) [27]. Both group A and group B β-hemolytic streptococci, including macrolide-resistant isolates, are susceptible to faropenem with MICs of 0.12 μg/ml or lower. Antistaphylococcal activity has also been of primary interest in investigations of new compounds, such as faropenem. For MSSA, the faropenem MIC_{50} and MIC_{90} were eight- and 16-times lower, respectively, than for both amoxicillin–clavulanate and cefuroxime [18,23]. Reports on the activity against MRSA vary considerably with studies reporting faropenem MICs ranging from 0.12 to over 32 μg/ml [18,20,23]; however, large-scale investigations have reported MIC_{50} and MIC_{90} to be over 32 μg/ml, indicating that faropenem will have little clinical value in the treatment of infections due to MRSA. Similar data have been reported for methicillin-susceptible and methicillin-resistant *Staphylococcus epidermidis* [20]. Faropenem has also demonstrated limited *in vitro* activity against *E. faecium* and *Staphylococcus haemolyticus* [18].

Rising resistance rates to penicillins, tetracyclines and fluoroquinolones in *Neisseria gonorrhoeae* and the decreasing availability of cefixime, a commonly used treatment, have rendered infections caused by resistance phenotypes progressively more difficult to treat. Thus, finding new oral agents with potent antigonococcal activity has become increasingly important. A recent study of 265 clinical isolates of various phenotypes revealed that faropenem exhibited an MIC_{90} of 0.25 μg/ml against *N. gonorrhoeae* slightly higher than the ceftriaxone MIC_{90} of 0.06 μg/ml [16]. Reducing agents, such as cysteine, found in IsoVitaleX, commonly used for *in vitro* MIC determination of *N. gonorrhoeae*, result in degradation of faropenem, and thus it should be noted that susceptibility testing should be performed on L-cysteine-free media.

Faropenem is active against some members of the Enterobacteriaceae, namely *E. coli*, *Klebsiella* spp., including ESBL-producing strains, and *Proteus mirabilis* [18]. It has limited activity against *Serratia* and *Enterobacter* spp. (unknown

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Table 1. *In vitro* activity of faropenem and comparators against Gram-positive aerobes.

Bacteria	Faropenem			Amox–clav		Cefuroxime		Imipenem	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Staphylococcus aureus (MS)	0.12	0.12	0.03–0.5	1	2	1	2	≤0.5	≤0.5
S. aureus (MR)	>32	>32	0.12–>32	8	16	>32	>32	32	32
Staphylococcus epidermidis (All)	0.12	0.5	0.06–>128	1	8	0.5	16	0.016	16
S. epidermidis (MS)	0.12	0.5	0.06–4	1	2	0.5	1	0.016	0.016
S. epidermidis (MR)	2	>128	0.06–>128	8	16	2	32	32	32
Streptococcus pyogenes	0.03	0.03	≤0.015–0.06	0.03	0.03	≤0.015	≤0.015	≤0.008	≤0.008
Streptococcus agalactiae	0.06	0.06	0.03–0.12	0.06	0.12	0.06	0.06	0.016	0.016
Streptococcus pneumoniae	0.008	0.25	≤0.004–2	0.03	0.5	≤0.12	4	≤0.5	≤0.5
S. pneumoniae (PS)	≤0.004	0.008	≤0.004–0.12	0.03	0.03	0.03	0.06	≤0.008	≤0.008
S. pneumoniae (PI)	0.12	0.25	≤0.004–1	0.25	1	2	4	0.06	0.12
S. pneumoniae (PR)	0.5	1	≤0.004–2	2	8	8	16	0.5	1
Enterococcus faecalis	1	4	0.25–16	1	1	16	>128	1	4
Enterococcus faecium	>128	>128	4–>128	32	128	>128	>128	>8	>8

Adapted from [11–14,17–21,23,24,66].

Amox–clav: Amoxicillin–clavulanic acid; MIC_{50}: Minimum inhibitory concentration (mg/l) of 50% of isolates; MIC_{90}: Minimum inhibitory concentration of 90% of isolates; MR: Methicillin resistant; MS: Methicillin sensitive; PI: Penicillin intermediate (penicillin MIC 0.12–1 mg/l); PR: Penicillin resistant (penicillin MIC ≥ 2.0 mg/l); PS: Penicillin susceptible (penicillin MIC ≤ 0.06 mg/l).

Clinical and Laboratory Standards Institute approved and tentative breakpoints [1]:

1. *Staphylococcus* spp.: amox–clav ≥ 8/4 mg/l is resistant, cefuroxime axetil ≥ 32 mg/l is resistant, imipenem ≥ 16 mg/l is resistant, faropenem data not available.
2. *S. pneumoniae*: amox–clav ≥ 8/4 mg/l is resistant, cefuroxime axetil ≥ 4 mg/l is resistant, imipenem ≥ 1 mg/l is resistant, faropenem data not available.

mechanism) and is not active against the nonfermenting Gram-negative bacilli, including *P. aeruginosa*, *Stenotrophomonas maltophilia* and *Acinetobacter* spp. [18].

A number of smaller studies have been performed to evaluate the *in vitro* activity of faropenem against anaerobes and have shown faropenem to have similar activity to the carbapenems, imipenem and meropenem. MICs for the *B. fragilis* group range from 0.03 to 4 µg/ml [14,22,23,28]. A study of anaerobic pathogens found in animal bite wound infections revealed that faropenem was active against members of the *B. fragilis* group, *Fusobacterium*, *Porphyromonas*, *Prevotella* and *Eubacterium* spp. (MIC_{90} ≤ 2 µg/ml) [14]. A study assessing the activity of faropenem against 106 anaerobic pathogens involved in periodontal infections reported that faropenem was highly active with a MIC_{90} of 0.25 µg/ml or lower [28]. Faropenem susceptibility was not affected by the presence of β-lactamase production. No data are currently available regarding faropenem's activity against atypical pathogens, but it would be expected to be similar to other β-lactam antibiotics.

Pharmacokinetics

The pharmacokinetics of faropenem medoxomil have been evaluated in numerous clinical trials. The pharmacokinetic parameters of faropenem medoxomil following oral administration of a single 300-mg dose in healthy volunteers are listed in TABLE 3. In single-dose range studies the area under the curve (AUC) and maximum concentration (C_{max}) demonstrated linear pharmacokinetics from 50 to 2000 mg and 50 to 500 mg, respectively [29]. For C_{max} dose increases above 500 mg, the results were slightly less than linear kinetics. Similar pharmacokinetics were observed upon administration of repeat doses. No accumulation of faropenem was observed [29].

Following oral administration, faropenem medoxomil is readily absorbed [30]. The addition of the medoxomil ester to the active faropenem moiety improves bioavailability following oral administration compared with orally administered faropenem sodium (72–84% vs 20–30%, respectively) [5,31]. Subsequent to absorption, faropenem medoxomil is rapidly hydrolyzed to faropenem, diacetyl (2,3-butanedione) and CO_2 by

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Table 2. *In vitro* activity of faropenem and comparators against Gram-negative aerobes

Bacteria	Faropenem			Amox–clav		Cefuroxime		Imipenem	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Acinetobacter spp.	32	>32	0.12–>32	4	32	>32	>32	0.25	0.25
Citrobacter freundii	1	8	0.25–32	32	>32	8	>32	1	1
Enterobacter aerogenes	4	16	0.25–>32	>32	>32	>32	>32	2	2
Enterobacter cloacae	4	8	0.5–32	>16	>16	32	>32	0.5	2
Escherichia coli	0.5	1	0.12–32	4	16	4	8	≤0.5	≤0.5
Haemophilus influenzae	0.25	1	≤0.004–4	0.5	1	0.5	2	1	4
H. influenzae (BLN)	0.25	1	≤0.004–4	0.5	1	0.5	2	1	2
H. influenzae (BLP)	0.25	0.5	≤0.004–4	0.5	1	0.5	2	1	2
Klebsiella pneumoniae	0.5	2	0.25–>32	2	8	4	>32	0.25	1
Klebsiella oxytoca	0.5	2	0.25–8	2	16	4	>32	0.25	0.5
Klebsiella spp.	0.5	2	0.06–8	2	8	2	32	0.12	0.12
Moraxella catarrhalis	0.25	0.5	0.008–2	0.12	0.25	1	2	0.06	0.125
M. catarrhalis (BLN)	0.03	0.12	0.015–1	0.25	0.5	0.5	0.5	0.5	1
M. catarrhalis (BLP)	0.25	0.5	0.008–2	0.25	0.5	1	2	0.5	1
Morganella morganii	4	8	1–16	>32	>32	32	>32	4	4
Neisseria gonorrhoeae	0.06	0.25	≤0.008–0.5	na	na	0.25	1	1	4
Proteus mirabilis	4	4	0.25–16	1	2	2	>32	1	2
Proteus vulgaris	4	4	0.5–16	8	8	>32	>32	2	4
Pseudomonas aeruginosa	>32	>32	2–>32	>16	>16	>32	>32	1	>8
Burkholderia cepacia	16	>32	2–>32	na	na	>32	>32	na	na
Serratia marcescens	8	32	1–>128	>32	>32	>32	>32	1	2
Stenotrophomonas maltophilia	>32	>32	>32	32	>32	>32	>32	>8	>8

Adapted from [11,13,15–19,21,23,66].

Amox–clav: Amoxicillin–clavulanic acid; BLN: β-lactamase negative; BLP: β-lactamase positive; MIC_{50}: Minimum inhibitory concentration (mg/l) of 50% of isolates; MIC_{90}: Minimum inhibitory concentration of 90% of isolates; na: Information not available.

Clinical and Laboratory Standards Institute approved and tentative breakpoints [1]:

1. *Enterobacteriaceae*: amox–clav ≥ 32/16 mg/l is resistant, cefuroxime ≥ 32mg/l is resistant, imipenem ≥ 16 mg/l is resistant, faropenem data not currently available.
2. *Pseudomonas aeruginosa* and other non-*Enterobacteriaceae*: imipenem ≥ 16 mg/l is resistant, no data available for amox–clav, cefuroxime and faropenem.

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serum esterases. Despite the increased stability to DHP-I compared with the carbapenems, some hydrolysis occurs [2]. Renal DHP-I hydrolyzes faropenem to the inactive metabolites, M-1 and M-2. Concentrations of these metabolites in plasma were found to be significantly lower than faropenem [32]. The activity of faropenem is affected by its high degree of protein binding. Various studies, including arithmetic MIC determinations conducted in 100% serum and broth, as well as ultrafiltration studies using radiolabelled faropenem and accounting for non-specific protein binding, have determined protein binding of

Table 3. Pharmacokinetics parameters of faropenem medoxomil.

Dosage	C_{max} (mg/l)	AUC_{0-24} (mg*h/l)	Half-life (h)	T_{max} (h)	% bioavailability	% protein binding	% excreted unchanged
300 mg twice daily	13.8	25.7	1.31	0.88	72–84	88–90	8–26

Adapted from [35,63].
AUC: Area under the curve; C_{max}: Maximum concentration; T_{max}: Time of maximum concentration.

faropenem to be in the range of 88–90% [33]. Faropenem binding was found to be saturable, with maximal binding at a serum protein concentration of 50 mg/l [33]. The primary component involved in faropenem binding was found to be human serum albumin [34]. Faropenem, M-1 and M-2 are eliminated primarily through renal excretion with 8–26% of unchanged faropenem being recovered in urine [35]. Urinary concentrations 8–12 h after faropenem administration were less than 1–2.3 mg/l. No data are currently available regarding faropenem pharmacokinetics in patients with impaired renal function or the elderly or regarding impact of food administration on faropenem pharmacokinetics or tissue penetration.

Pharmacodynamics

In contrast to the penicillins and cephalosporins that exhibit only time-dependent killing, the pharmacodynamic activity of faropenem is both time and concentration dependent [36,37]. Faropenem bacterial killing is time dependent while persistent effects, such as the postantibiotic effect (PAE), are concentration dependent [28]. Using the mouse neutropenic thigh infection model, the primary pharmacodynamic parameter was determined to be time of the antimicrobial above the MIC ($T_{>MIC}$) [38]. Similar to the carbapenems, faropenem requires the $T_{>MIC}$ to be less than 40% of the dosing interval (to achieve stasis of growth) compared with the penicillins and cephalosporins, which require $T_{>MIC}$ to be 40% or greater. The free time above the MIC ($fT_{>MIC}$), which represents the free or nonprotein bound fraction of faropenem as determined in the mouse neutropenic thigh infection model for *S. pneumoniae* was 13.9% [38]. *In vivo*, the immune system further impacts faropenem activity. Studies using non-neutropenic mice demonstrated that the presence of neutrophils enhanced the activity of the drug three- to fourfold [38]. *In vitro* studies have shown that faropenem enhances the production of superoxide anion by neutrophils, thus contributing to their oxygen-dependent bactericidal effects [39].

Like the carbapenems, faropenem exerts a PAE against both Gram-positive and -negative organisms. An *in vitro* PAE has been demonstrated against *E. coli*, *S. aureus*, *S. pneumoniae*, as well as certain periodontal anaerobes and β-lactamase-positive isolates of *H. influenzae* [28,36]. The PAE for the periodontal anaerobes was not affected by β-lactamase production [28]. For *H. influenzae* the PAE at four- and ten-times the MIC was observed to be more than 4 h [40]. Although a PAE was observed for all strains of *S. pneumoniae* at four- and ten-times the MIC, penicillin-resistant strains exhibited an effect even at one-times the MIC. The PAE for penicillin-resistant isolates was also prolonged in comparison to the penicillin-susceptible *S. pneumoniae* isolates [40]. It is presently unclear why the faropenem PAE is longer for penicillin-resistant isolates compared with penicillin-susceptible *S. pneumoniae*.

Clinical trials

Indications sought from the US FDA for faropenem medoxomil include: acute bacterial sinusitis (ABS), acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP) and uncomplicated skin and skin structure infections (uSSSIs). A total of 11 Phase III clinical studies have been conducted to evaluate the efficacy of faropenem medoxomil for these indications and the data are summarized in TABLE 4. In addition, its efficacy in the treatment of urinary tract infections (UTIs) and tonsillitis/pharyngitis has been evaluated in clinical trials and these data are included in TABLE 5.

Unless otherwise indicated, the trials outlined here were all prospective, multicenter, randomized, double-blind comparative Phase III clinical trials designed to show statistical equivalence (noninferiority) between faropenem medoxomil and a comparator. No placebo trials were performed with faropenem. Statistical equivalence was defined by the 95% confidence interval (CI) for the difference in clinical success rates (faropenem medoxomil minus the comparator). A lower CI limit of greater than -10% indicated noninferiority and a result of greater than 0 indicated clinical superiority of faropenem medoxomil over its comparator. The primary end point for determining clinical cure was established at the test-of-cure (TOC) visit for the clinically evaluable population, which included only those subjects deemed valid per protocol (vPP). Microbiological eradication and clinical cure rates are also presented for those patients that were microbiologically evaluable (MBE).

Acute bacterial sinusitis

Study 100288 was conducted in Canada and the USA to compare the efficacy and the safety of both 7- and 10-day course treatments of 300 mg twice-daily faropenem medoxomil to a 10-day course of 250 mg twice-daily cefuroxime axetil [41,42]. A total of 1106 patients of 12 years of age or older were enrolled, 77.8% of whom were clinically evaluable. The criteria for inclusion in the study were as follows: more than 7 but less than 28 days for duration of symptoms, evidence of air fluid levels, opacification or mucosal thickening of the sinuses on sinus x-ray, presence of at least one major symptom of sinusitis

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Table 4. Summary of faropenem Phase III clinical trials for indications currently under review for FDA approval.

Study number	Regimen	ITT	vPP	Duration of treatment (days)	TOC (days post therapy)	% of patients (number of patients)		
						Clinical cure (vPP)	*Microbiological eradication (MBE)*	*Clinical cure (MBE)*
Acute bacterial sinusitis								
10186	FM – 300 mg BID	275	228	7	7–16	89.0 (203)	90.1 (64)	91.5 (65)
	CEF – 250 mg BID	273	224	7	7–16	88.4 (198)	90.8 (59)	90.8 (59)
100288	FM – 300 mg BID	370	295	7	7–21	80.3 (237)	nd	nd
	FM – 300 mg BID	365	280	10	7–21	81.8 (229)	nd	nd
	CEF – 250 mg BID	371	286	10	7–21	74.5 (213)	nd	nd
100287	FM – 300 mg BID	354	300	7	7–18	82.0 (246)	83.2 (119)	83.9 (120)
Acute exacerbations of chronic bronchitis								
10187	FM – 300 mg BID	369	299	5	7–14	87.6 (262)	68.6 (48)	78.6 (55)
	CLR – 500 mg BID	379	318	7	7–14	90.6 (288)	77.1 (64)	89.2 (74)
100291	FM – 300 mg BID	414	278	5	14–18	80.9 (225)	80.0 (96)	nd
	AZI – 500 mg QD (day 1), 250 mg QD (days 2–5)	410	279	5	14–18	84.6 (236)	78.9 (90)	nd
Community-acquired pneumonia								
10188	FM – 300 mg BID	329	284	10	7–14	91.5 (260)	80.6 (54)	85.1 (57)
	AMOX – 1000 mg TID	321	268	10	7–14	88.4 (237)	91.5 (43)	91.5 (43)
100290	FM – 300 mg BID	306	229	10	7–14	89.5 (205)	82.9 (29)	91.4 (32)
	CPD – 200 mg BID	301	229	14	7–14	88.6 (203)	86.2 (25)	90.0 (27)
10189	FM – 300 mg BID	305	257	10	7–14	86.4 (222)	85.7 (24)	85.7 (24)
	A/C – 625 mg TID	312	253	10	7–14	88.1 (223)	93.3 (28)	93.3 (28)
100289	FM – 300 mg BID	393	294	10	7–14	85.7 (252)	85.9 (55)	89.1 (57)
Uncomplicated skin and skin structure infections								
100292	FM – 300 mg BID	290	246	7	7–14	85.4 (210)	86.4 (130)	nd
	CPL – 500 mg BID	283	246	7	7–14	91.9 (226)	92.5 (139)	nd
10190	FM – 300 mg BID	298	246	7	7–14	91.1 (224)	91.6 (141)	nd
	A/C – 625 mg TID	295	227	7	7–14	91.2 (207)	90.6 (126)	nd

Adapted from [41,42,44,45,47,48,50,51,55,56].
A/C: Amoxicillin–clavulanate; AMOX: Amoxicillin; AZI: Azithromycin; BID: Twice daily; CEF: Cefuroxime axetil; CLR: Clarithromycin; CPD: Cefpodoxime proxetil; CPL: Cephalexin; FM: Faropenem medoxomil; ITT: Intent to treat; MBE: Microbiologically evaluable; nd: Not determined; QD: Per day; TID: Three-times daily; TOC: Test of cure; vPP: Valid per protocol.

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and presence of at least two minor symptoms. The clinical cure rates at TOC for the vPP population were 80.3% for the 7-day course and 81.8% for the 10-day course of faropenem medoxomil, and 74.5% for the 10-day course of cefuroxime axetil. The 95% CIs of -0.9, 12.7 and 0.5, 14.1 for the difference between the 7-day and the 10-day faropenem medoxomil regimens and the cefuroxime axetil regimen, respectively, indicated both treatment regimens were statistically superior to the 10-day cefuroxime axetil treatment. Noninferiority of the faropenem medoxomil 7- and 10-day regimens (70.8 and 69.9% clinical cure rates, respectively) to the cefuroxime axetil regimen (67.4% clinical cure rate) was observed in the intent-to-treat (ITT) population [41,42].

Study 10186 was conducted in six European countries and in Israel. The study was designed to evaluate the efficacy and safety of 300 mg faropenem twice daily for 7 days versus 250 mg cefuroxime axetil twice daily for 7 days [43–45]. The inclusion criteria were comparable to study 100288 with the exceptions that only subjects 18 years of age or older were included, no minimum duration of symptoms was specified and subjects with symptoms lasting more than 4 weeks were excluded [41]. Subjects were evaluated upon enrollment, 5–7 days after commencing treatment and 7–16 days after the final dose (TOC). Patients who responded to treatment were also evaluated at a long-term follow-up visit (25–45 days after the last dose). A total of 548 subjects were enrolled (ITT) with 82.5% deemed clinically evaluable. Clinical cure rates in the vPP population were 89.0 and 88.4% for faropenem medoxomil and cefuroxime axetil, respectively. This study demonstrated statistical noninferiority of the 7-day regimen of faropenem medoxomil to the 7-day cefuroxime axetil regimen. The 95% CI for the difference between the faropenem medoxomil and the cefuroxime axetil regimens was -5.2, 6.5. Sinus puncture and aspiration (TAP), as well as endoscopic collection, were used to determine microbiology and assess bacteriological response. Presumed eradication rates at the TOC visit for the three major pathogens *H. influenzae, M. catarrhalis* and *S. pneumoniae* were 85.0, 85.7 and 97.3%, with faropenem, respectively, compared with 90.5, 83.3 and 96.3%, with cefuroxime axetil, respectively, for the MBE population using both TAP and endoscopy [41,44,45].

Study 100287 was an open-label, noncomparative, 'sinus-tap' trial designed to evaluate the microbiological response to a 7-day course of 300 mg faropenem medoxomil twice daily [41,46]. Inclusion criteria matched the criteria listed for study 100288. The study enrolled 354 subjects of which 84.7% were clinically evaluable and 40.4% were MBE. The clinical cure rates for the vPP and the MBE populations were 82.0 and 83.9%, respectively. Presumed eradication of the key pathogens as determined by both TAP and endoscopy were 80.6 % for *H. influenzae*, 100% for *M. catarrhalis* and 92.5% for *S. pneumoniae* [41].

Acute exacerbations of chronic bronchitis

Two comparative Phase III clinical trials assessing the efficacy of faropenem medoxomil as a treatment for AECB have been conducted. Both studies included stringent criteria to ensure that subjects had true acute bacterial exacerbation of chronic bronchitis. Chest x-rays were used to exclude patients with pneumonia [47–49]. Study 10187 included pulmonary function tests at baseline and TOC visits. This study was conducted in Europe, Israel, Mexico and South Africa, and compared a 5-day twice-daily 300-mg faropenem medoxomil regimen to a 7-day twice-daily 500-mg clarithromycin regimen [47]. The ITT population for this study was 748 patients, 82.5% of which were considered vPP. Clinical cure rates for the vPP population at the TOC visit were 87.6 and 90.6%, for the faropenem medoxomil group and the clarithromycin group, respectively. The clinical cure rates for the vPP population, as well as the ITT population (85.6% for faropenem medoxomil and 88.9% for clarithromycin), supported noninferiority of the faropenem medoxomil regimen to the clarithromycin regimen with 95% CI of -8.1, 1.5 for vPP population and -8.2, 1.5 for the ITT population [47]. The microbiological eradication rates in the MBE population of 68.6 and 77.1% for the faropenem medoxomil and the clarithromycin groups, respectively, were significantly lower than the clinical cure rates in this population. The 95% CI of -23.4, 6.3 for the microbiological eradication rates suggested superiority of the clarithromycin regimen; however, these results may reflect the small sample size of the MBE population. The eradication rates (eradicated and presumed eradicated) for the faropenem medoxomil regimen were 63.0% for *H. influenzae*, 54.6% for *M. catarrhalis* and 80% for *S. pneumoniae*. Comparatively, the eradication rates for the clarithromycin group were 70.3, 94.1 and 94.4% for *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, respectively [48]. The differences in eradication between the two regimens is likely due to the small patient numbers evaluable for microbiological response (faropenem n = 70 and clarithromycin n = 83). Whether there was a true difference in *M. catarrhalis* eradication between the two regimens in unclear. It is difficult to evaluate clinical studies where the vast majority of patients evaluated did not demonstrate a bacterial etiology.

Study 100291 was conducted in the USA and in Argentina. Efficacy of faropenem medoxomil 300 mg twice daily for 5 days was compared with the efficacy of azithromycin [48,49]. The azithromycin group received a 500-mg dose on day 1 and a 250-mg dose on each of days 2–5. Enrollment criteria were similar to study 10187. A total of 824 participants were enrolled with only 67.6% being clinically evaluable. The TOC visit occurred 14–21 days after the last dose of medication was administered. Clinical cure rates for the vPP population were 67.1% for the faropenem medoxomil group and 68.0% for the azithromycin group. The 95% CI was -9.9, 2.6, thus indicating noninferiority of the faropenem medoxomil regimen to the azithromycin regimen. The ITT population clinical cure rates of 66.9% for the faropenem medoxomil group and 69.0% for the azithromycin group supported this data with a 95% CI of -8.5, 4.3. Unlike study 10187, the microbiological eradication rates did not favor the comparator over faropenem medoxomil [48,49]. The bacterial eradication rates of faropenem medoxomil for *H. influenzae, M. catarrhalis* and *S. pneumoniae* were 88.9, 87.1 and 82.6%, respectively. The eradication rates for the azithromycin group were 86.7, 83.3 and 82.4% for for *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, respectively [48].

Community-acquired pneumonia

Four Phase III clinical trials, including three comparative studies and one open-label single-arm multicenter study were conducted to evaluate the efficacy of a faropenem medoxomil 300 mg twice-daily 10-day regimen in the treatment of CAP. The three comparative studies, 10188, 10189 and 100290, were designed to show noninferiority to the clinically approved β-lactams, amoxicillin, amoxicillin–clavulanate and cefpodoxime proxetil, respectively. Inclusion in all trials

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Table 5. Summary of faropenem clinical trials for indications not submitted for FDA new drug approval.

Study number	Regimen	ITT	vPP	Duration of treatment (days)	TOC (days post therapy)	% of patients (number of patients)		
						Clinical cure (vPP)	*Microbiological eradication (MBE)*	*Clinical cure (MBE)*
Uncomplicated urinary tract infections								
100286	FM – 300 mg BID	443	214	5	5–11	86.2 (181)	80.8 (173)	nd
	TMP–SMX – 160/800 mg BID	448	212	5	5–11	95.7 (200)	88.7 (188)	nd
Tonsillitis/pharyngitis								
100293	FM – 300 mg BID	337	223*	5	4–12	nd	80.7 (180)	89
	Pen VK – 500 mg TID	336	215*	10	4–12	nd	89.8 (193)	95

Adapted from [35,67].
*Primary efficacy parameter was bacterial eradication vPP represents MBE.
BID: Twice daily; FM: Faropenem medoxomil; ITT: Intent to treat; MBE: Microbiologically evaluable; nd: Not determined; Pen VK: Penicillin VK; TID: Three-times daily; TMP–SMX: Trimethoprim–sulfamethoxazole; TOC: Test of cure; vPP: Valid per protocol.

required a diagnosis of CAP that required two or more predefined signs and symptoms or changes in the white blood cell count, as well as radiographic evidence [50]. The primary efficacy determinant in all studies was clinical response of the vPP population at the TOC visit. Clinical response at long-term follow-up visit (28–35 days post therapy) and microbiological response (atypical pathogens not assessed) at the TOC visit were used as secondary end points.

Studies 10188 and 10189 were conducted in Europe, Latin America and South Africa [50–52]. These studies included outpatients, subjects hospitalized for less than 48 h and subjects residing in long-term care facilities. Study 10188 enrolled 650 participants (ITT) yielding a vPP population of 552 subjects. The clinical cure rates for the vPP population were 91.5 and 88.4% for the faropenem medoxomil and the amoxicillin regimens, respectively. The 95% CI was -1.9, 8.1 indicating noninferiority of faropenem medoxomil compared with amoxicillin [50,52]. Study 10189 enrolled 617 subjects resulting in a clinically evaluable population of 510 subjects. Clinical cure rates in the vPP population were 86.4% for the faropenem medoxomil group and 88.1% for the amoxicillin–clavulanate group. Noninferiority was suggested by the 95% CI of -7.5, 4.0 [51]. Neither study was powered to demonstrate noninferiority of faropenem medoxomil to its comparator based on bacterial eradication [50].

Study 100290 was conducted in the USA and included outpatients only. A total of 607 subjects were enrolled with 458 subjects considered to be clinically evaluable [50]. Clinical cure rates of faropenem medoxomil were 89.5 and 72.9% in the vPP and the ITT populations, respectively. Comparatively, the cefpodoxime proxetil regimen produced clinical cure rates of 88.6 and 74.4%. The 95% CI of -4.8, 6.6 for the vPP population and -8.6, 5.5 for the ITT population supported noninferiority of faropenem medoxomil compared with cefpodoxime proxetil [50,53]. As with the other comparative studies, this study was not powered to assess noninferiority of faropenem based on microbiological response.

The open-label study 100289 was conducted in Canada and the USA. This study included outpatients only. The ITT population consisted of 393 subjects, 294 of which were considered clinically evaluable and 64 of which were microbiologically evaluable. Clinical cure rates in these populations were 72.8, 85.7 and 89.1%, respectively [50,54].

Integrated analysis of the CAP clinical trials calculated bacterial eradication rates of five key pathogens. Faropenem medoxomil eradication rates were 91.1% (82 out of 90) for *S. pneumoniae*, 80.3% (49 out of 61) for *H. influenzae*, 93.0% (13 out of 14) for *S. aureus*, 75.0% (six out of eight) for *Haemophilus parainfluenzae* and 85.7% (six out of seven) for *M. catarrhalis*. The comparator β-lactams reported rates of 96.1% (49 out of 51) for *S. pneumoniae*, 93.8% (30 out of 32) for *H. influenzae*, 80.0% (eight out of ten) for *S. aureus*, 0.0% (zero out of two) for *H. parainfluenzae* and 100% (four out of four) for *M. catarrhalis* [50]. Bacterial eradication rates were similar for comparators compared with faropenem medoxomil. An integrated analysis revealed 13 out of 16 subjects with pneumococcal bacteremic pneumonia receiving faropenem medoxomil demonstrated clinical response to therapy, which was similar to comparators. Faropenem demonstrated similar bacterial eradication rates in patients with CAP for both penicillin-susceptible and multidrug-resistant *S. pneumoniae* (80–90%) [50].

Uncomplicated skin & skin structure infections

Two comparative Phase III clinical trials have evaluated the efficacy of faropenem medoxomil 300 mg twice daily for 7 days. Study 100292 was conducted in the USA and compared the efficacy and safety of faropenem medoxomil to that of cephalexin 500 mg twice daily for 7 days. The primary efficacy

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parameter was clinical cure at TOC in the clinically evaluable population. The ITT population consisted of 573 subjects, 492 of which were clinically evaluable and 301 of which were MBE. Based on the primary efficacy parameter, the faropenem medoxomil regimen was found to be statistically inferior to the cephalexin regimen. This was not supported by the clinical cure rate for the ITT population (faropenem medoxomil: 75.9%; cefuroxime axetil: 80.6%; 95% CI: -11.5, 2.1) or by the eradication rate for the MBE population (faropenem medoxomil: 86.4%; cefuroxime axetil: 92.5%) [55]. Eradication of *S. aureus* occurred in 74 out of 82 (90.2%) and 74 out of 79 (93.7%) of faropenem- and cephalexin-treated patients, respectively.

Study 10190 was conducted in Europe, Israel and South Africa and compared efficacy of faropenem medoxomil with amoxicillin–clavulanate 625 mg twice daily for 7 days. The ITT consisted of 593 subjects, 473 of which were clinically evaluable. Clinical cure rates for the vPP population were 91.1% for faropenem medoxomil and 91.2% for amoxicillin–clavulanate with a 95% CI of 5.1, 5.3 thus supporting noninferiority of faropenem medoxomil to amoxicillin–clavulanate. Subgroups in this study including cellulitis, furunculosis, impetigo and simple abscess all showed similar results [56]. Eradication of *S. pyogenes* occurred in 35 out of 35 (100%) and 34 out of 35 (97.1%) of faropenem- and cephalexin-treated patients, respectively.

It should be restated that faropenem is not active against MRSA, including community-associated MRSA strains, which may cause skin and skin structure infections.

Faropenem has been compared with TMP–SMX for the treatment of females with acute uncomplicated UTIs (TABLE 5). Faropenem demonstrated reduced bacteriological and clinical outcomes compared with TMP–SMX. The reduced bacteriological outcomes with faropenem may be due to the metabolism of faropenem by renal DHP-I leading to inactive metabolites in the urine.

Safety & tolerability

Adverse events reported have been similar to other β-lactams, with the main events reported being gastrointestinal in nature. An integrated safety analysis of 17 Phase II/III clinical trials has been executed comparing the safety of faropenem medoxomil with penicillin, amoxicillin, amoxicillin–clavulanate, cephalexin, cefuroxime axetil, cefpodoxime, clarithromycin, azithromycin and TMP–SMX. The results are summarized in TABLE 6 [31]. The effect of multiple oral doses of faropenem medoxomil on oral and fecal flora was evaluated in healthy male volunteers. Analyses of fecal microflora detected increases in enterococci and decreases in *Clostridium* spp. Only minor changes in oral flora were noted [29,57].

CNS excitability has been noted with other β-lactam antibiotics when administered in high doses. In patients with renal insufficiency, excitability has the potential to result in seizures. The carbapenem's tendency to produce neurotoxicity was found to be associated with the basicity of the C2 side chain. The C2 side chain of faropenem is neutral and thus shows a very low excitatory potential [3]. *In vitro* data were collected using a hippocampus animal model to compare faropenem and faropenem medoxomil with amoxicillin, penicillin and imipenem. These results confirmed the weak excitatory potency of faropenem compared with other β-lactams [58].

In vitro investigations have also been performed to evaluate the potential for allergic reactions in patients who have been previously sensitized to β-lactams. Considering that up to 10% of the population have penicillin allergies, cross-reactivity of the β-lactams is of major concern [59]. The C2 position of faropenem affects its cross-immunogenicity with penicillins and cephalosporins [5]. In the rabbit sera model, cross-reactivity of faropenem antibodies to other β-lactams was found to be low, as was the reactivity of antibodies to other β-lactams with faropenem [60]. A recent study in healthy volunteers administered single oral faropenem doses of 300, 600 or 2400 mg demonstrated a placebo-like effect on QT_C prolongation [61].

Table 6. Percentage of subjects experiencing adverse events in 17 Phase II/III faropenem medoxomil clinical trials.

Event	% subjects experiencing adverse events	
	FM (n = 5023)	*Comparators (n = 3795)*
Any adverse event	38.2	39.2
Gastrointestinal	*14.6*	*15.8*
Diarrhea	4.7	5.4
Nausea	3.8	4.9
Vomiting	1.4	1.5
Abdominal pain	1	1.3
Infections and infestations	*9.3*	*7.7*
Vaginosis fungal	3.2	1.5
Urinary tract infection	0.5	0.6
Nervous system disorders	*6.8*	*7.6*
Headache	4.1	4.8
Dizziness	1.2	1.3

Adapted from [31].
Comparators: penicillin, amoxicillin, amoxicillin–clavulanate, cephalexin, cefuroxime axetil, cefpodoxime, clarithromycin, azithromycin and trimethoprim–sulfamethoxazole.
FM: Faropenem medoxomil.

Drug interactions

Possible drug interactions with faropenem medoxomil have been investigated in human studies. Of primary concern is the potential interaction with other drugs that are also eliminated through the kidneys upon coadministration with faropenem medoxomil.

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Compounds investigated for such interactions included probenecid, furosemide, digoxin and theophylline. With the exception of probenecid, none of the drugs produced any clinically significant interactions upon administration with faropenem [62]. Probenecid has previously been shown to extend the exposure time of other drugs, including penicillin, by inhibiting renal secretion. Doubling of the AUC and terminal half-life was observed upon coadministration of probenecid, as well as a lesser increase in C_{max}. Renal excretion of the original oral dose was reduced by approximately 40% [63]. Coadministration with probenecid extends exposure to faropenem; however, this does not present any safety issues as exposure remains well below the plasma concentration levels previously deemed safe [63].

Other drugs evaluated for potential interactions with faropenem medoxomil included warfarin, cholestyramine, ranitidine, aluminum–magnesium hydroxide and hormonal contraceptives. No significant interactions were observed [62,64,65].

Expert commentary

Faropenem medoxomil's potent broad-spectrum activity, stability against class A, C, and D β-lactamases, favorable pharmacokinetics (including high oral bioavailability) and pharmacodynamics, as well as good bacteriological and clinical outcomes relative to comparators, in ABS, AECB, CAP and uSSSI, and a favorable safety profile make it an excellent candidate for future development as an orally administered penem for community-acquired infections [70].

Five-year view

Faropenem medoxomil is currently under development and commercialization by Replidyne, Inc. and Forest Laboratories Holdings, Ltd. The results of the 11 clinical trials evaluating its efficacy and safety in four indications, ABS, AECB, CAP and uSSSI, were submitted to support the application for new drug approval (NDA) to the FDA in December 2005. Recently, the FDA rejected faropenem for all four indications stating the clinical trials in ABS and AECB should have been performed versus placebo. In the CAP studies, the FDA stated that they could not be certain of the validity of the study population actually having the disease and for uSSSI, the FDA stated that only a single trial was not adequate evidence for efficacy for this indication. Replidyne is presently assessing the next course of action with faropenem. This is an important new agent that needs to be developed to offer an alternative to macrolides and fluoroquinolones for community-acquired infections.

Key issues

- Faropenem medoxomil is a novel, broad-spectrum, penem-type antibiotic with stability against class A, C, and D β-lactamases.
- The key distinguishing feature of faropenem is its chiral tetrahydrofuran substituent at position C2, which is responsible for its improved chemical stability and reduced CNS effects compared with other carbapenems.
- Faropenem does not appear to select for efflux-mediated cross-resistance to the carbapenems in *Pseudomonas aeruginosa* and does not induce AmpC β-lactamase production in Enterobacteriaceae.
- Faropenem medoxomil has good bioavailability following oral administration, is highly protein bound and relatively stable to hydrolysis by dehydropeptidase I.
- Faropenem displays a postantibiotic effect and pharmacodynamically free time above the minimum inhibitory concentration is associated with bacteriological eradication.
- Indications sought from the US FDA include acute bacterial sinusitis, acute exacerbations of chronic bronchitis, community-acquired pneumonia and uncomplicated skin and skin structure infections.
- The recent FDA rejection of faropenem for all four clinical indications has resulted in Replidyne reassessing its next course of action with faropenem.

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