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Meropenem

A Review of its Use in the Treatment of Serious Bacterial Infections

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Data Selection

Sources: Medical literature published in any language since 1980 on 'meropenem', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search term was 'meropenem'. Searches were last updated 14 March 2008.

Selection: Studies in patients with serious bacterial infections who received meropenem. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Meropenem, serous bacterial infection, pharmacodynamics, pharmacokinetics, pharmacoeconomics, therapeutic use, tolerability.

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Summary

Abstract

Meropenem (Merrem®, Meronem®) is a broad-spectrum antibacterial agent of the carbapenem family, indicated as empirical therapy prior to the identification of causative organisms, or for disease caused by single or multiple susceptible bacteria in both adults and children with a broad range of serious infections.

Meropenem is approved for use in complicated intra-abdominal infection (cIAI), complicated skin and skin structure infection (cSSSI) and bacterial meningitis (in paediatric patients aged ≥3 months) in the US, and in most other countries for nosocomial pneumonia, cIAI, septicaemia, febrile neutropenia, cSSSI, bacterial meningitis, complicated urinary tract infection (UTI), obstetric and gynaecological infections, in cystic fibrosis patients with pulmonary exacerbations, and for the treatment of severe community-acquired pneumonia (CAP).

Meropenem has a broad spectrum of *in vitro* activity against Gram-positive and Gram-negative pathogens, including extended-spectrum β-lactamase (ESBL)- and AmpC-producing Enterobacteriaceae. It has similar efficacy to comparator antibacterial agents, including: imipenem/cilastatin in cIAI, cSSSI, febrile neutropenia, complicated UTI, obstetric or gynaecological infections and severe CAP; clindamycin plus tobramycin or gentamicin in cIAI or obstetric/gynaecological infections; cefotaxime plus metronidazole in cIAI; cefepime and ceftazidime plus amikacin in septicaemia or febrile neutropenia; and ceftazidime, clarithromycin plus ceftriaxone or amikacin in severe CAP. Meropenem has also shown similar efficacy to cefotaxime in paediatric and adult patients with bacterial meningitis, and to ceftazidime when both agents were administered with or without tobramycin in patients with cystic fibrosis experiencing acute pulmonary exacerbations. Meropenem showed greater efficacy than ceftazidime or piperacillin/tazobactam in febrile neutropenia, and greater efficacy than ceftazidime plus amikacin or tobramycin in patients with nosocomial pneumonia. Meropenem is well tolerated and has the advantage of being suitable for administration as an intravenous bolus or infusion. Its low propensity for inducing seizures means that it is suitable for treating bacterial meningitis and is the only carbapenem approved in this indication. Thus, meropenem continues to be an important option for the empirical treatment of serious bacterial infections in hospitalized patients.

Pharmacological Properties

Meropenem demonstrated good *in vitro* activity against clinically relevant Enterobacteriaceae (*Citrobacter freundii*, *C. koseri*, *Enterobacter aerogenes*, *E. cloaceae*, *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Morganella morganii*, *Proteus mirabilis*, *P. vulgaris* and *Serratia marcescens*). The minimum concentration inhibiting 90% of strains (MIC_{90}) was ≤0.25 mg/L and susceptibility rates were 98–100%. Meropenem was active against ESBL- and AmpC-producing Enterobacteriaceae, with little or no change in MIC_{90} values compared with non-ESBL- and non-AmpC-producing strains. Meropenem also demonstrated good activity against *Haemophilus influenzae* and *Neisseria meningitidis* (MIC_{90} 0.25 mg/L; susceptibility rates of 99–100%). Against *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Burkholderia cepacia*, MIC_{90} values were 16–64 mg/L and susceptibility rates were 71.5–76.4%. Meropenem demonstrated good *in vitro* activity against Gram-positive pathogens, including *Staphylococcus aureus* (methicillin/oxacillin-susceptible isolates), *S. epidermidis* (oxacillin-susceptible isolates), *Streptococcus pneumoniae* (including penicillin-resistant strains) and viridans group streptococci (MIC_{90} of 0.25–2 mg/L; susceptibility rates of 95–100%), but had poor activity against *Enterococcus faecalis*. Meropenem lacked activity against methicillin/oxacillin-resistant staphylococci and *E. faecium*. Meropenem demonstrated good *in vitro* activity against a range of anaerobes, including *Clostridium difficile*, *C. perfringens*, and *Peptostreptococcus* spp. and *Prevotella* spp. (MIC_{90} 0.125–4 mg/L; susceptibility rates 100%). Against *Bacteroides fragilis*, meropenem had an MIC_{90} of 8 mg/L with a susceptibility rate of 89%.

A mathematical model has estimated that meropenem is likely to achieve an optimal bactericidal pharmacodynamic target attainment against *E. coli* and *K. pneumoniae*, but a lower attainment against *P. aeruginosa* and *A. baumannii*. Meropenem is also estimated to achieve an optimal bactericidal pharmacodynamic target attainment against most pathogens associated with nosocomial pneumonia, cIAI, nosocomial blood infection, cSSSI and paediatric meningitis.

Meropenem has rapid, time-dependent bactericidal activity and a minimal inoculum effect. Meropenem shows stability against hydrolysis by most β-lactamases, including ESBLs and AmpC β-lactamases, but may be affected by carbapenemases such as metallo-β-lactamases, serine carbapenemases and oxacillinases with carbapenemase activity (such as OXA-23, OXA-24 and OXA-58). Except for the production of carbapenemases, it appears that two or more resistance mechanisms, such as reduced permeability or overexpression of multidrug efflux pumps, are required for significant carbapenem resistance to emerge. Meropenem appears to have a low potential for selecting resistant strains *in vitro*.

Meropenem did not accumulate at steady state after intravenous administration. Plasma protein binding is low (≈2%) and meropenem achieves good penetration into a wide range of tissues, including lung, skin blister fluid, interstitial fluid, intra-abdominal tissues, peritoneal fluid and cerebrospinal fluid. Meropenem is mainly eliminated via the kidneys and clinically significant alterations to the pharmacokinetics of the drug are seen in patients with advanced or end-stage renal failure. Meropenem has a short plasma elimination half-life of ≈1 hour.

Clinical Efficacy

The efficacy of meropenem in adult and paediatric patients with serious bacterial infections has been examined in numerous well designed trials.

Meropenem showed greater efficacy than the combinations of ceftazidime plus amikacin or tobramycin in patients with nosocomial pneumonia, with end of

treatment (EOT) clinical response rates of 83% and 89% vs 66% and 72%, and bacteriological response rates of 75% and 89% vs 53% and 67%.

Meropenem was as effective as imipenem/cilastatin in four trials in patients with cIAI, with clinical cure rates at EOT or follow-up of 90–98% and 88–98% for the respective treatments, and bacteriological cure rates of 84–98% and 79–96%. In one trial, clinical cure rates were 84% and 85% with meropenem or doripenem, and the respective bacteriological cure rates were 85% and 84%. In a comparison between meropenem and tobramycin plus clindamycin, clinical and bacteriological response rates were each 96% with meropenem and 93% with tobramycin plus clindamycin. In two trials comparing the efficacy of meropenem and cefotaxime plus metronidazole, results were mixed.

In patients with septicaemiae secondary to a serious bacterial infection, meropenem was as effective as ceftazidime with or without amikacin, with clinical response rates at EOT of 92% and 94% for the respective treatments.

Meropenem was as effective as imipenem/cilastatin, cefepime, ceftazidime with or without amikacin or piperacillin/tazobactam in numerous trials in patients with febrile neutropenia, with initial response rates to unmodified treatment regimens at 72 hours of 56–88% and 40–80% of episodes. Response rates to meropenem were significantly greater than ceftazidime (56% vs 40%; $p = 0.003$) and piperacillin/tazobactam (64% vs 50%; $p < 0.05$). Treatment success at EOT, regardless of regimen modification, was seen in 44–100% of episodes treated with meropenem and 41–100% of those treated with comparators; meropenem was more effective than ceftazidime in one trial (54% vs 44%; $p < 0.05$).

Meropenem efficacy was noninferior to that of imipenem/cilastatin in patients with cSSSI in one trial, with clinical response rates of 86% and 83%, respectively, at the follow-up visit. In another trial, there were no significant differences between meropenem and imipenem/cilastatin in terms of clinical response (98% vs 95%) or bacteriological response (94% vs 91%) at EOT assessment.

The proportion of patients achieving cure with no sequelae with meropenem in two trials in paediatric patients with bacterial meningitis did not differ from that with cefotaxime at EOT (46% vs 56%) and/or follow-up (54% vs 58% and 72% vs 81%). In adult patients with meningitis, clinical cure (with or without sequelae) occurred in 100% of clinically evaluable meropenem recipients compared with 77% of cephalosporin (cefotaxime or ceftriaxone) recipients.

Meropenem was an effective alternative therapy to imipenem/cilastatin in patients with complicated UTI, evidenced by clinical responses of 99% in either treatment group and bacteriological responses in 90% of meropenem and 87% of imipenem/cilastatin recipients.

In women with obstetric or gynaecological infections, meropenem achieved similar clinical or bacteriological response rates at EOT and follow-up to clindamycin plus gentamycin (88–98% vs 86–100%). In another trial, meropenem achieved a significantly higher clinical cure rate than imipenem/cilastatin at EOT (100% vs 90%; $p = 0.026$), but not at follow-up (98% vs 97%).

In two trials in patients with cystic fibrosis, meropenem plus tobramycin improved pulmonary function at EOT in patients with acute exacerbations of infection to the same extent as ceftazidime plus tobramycin (absolute change from baseline in percentage predicted forced expiratory volume in one second of 5.1–13.8% and 6.1–11.1%), confirming results of an earlier trial of meropenem versus ceftazidime monotherapy in which 98% of meropenem and 90% of

ceftazidime recipients were classed as responders. Both combination therapy regimens decreased sputum bacterial burden.

In patients with severe CAP, meropenem achieved clinical response rates of 87–91% at EOT and 96–100% at follow-up, which were similar to those seen with imipenem/cilastatin (86–91% and 100%), ceftazidime (90% and not reported), clarithromycin plus ceftriaxone (69% and 92%) or clarithromycin plus amikacin (86% and 96%). Bacteriological response rates with meropenem, imipenem/cilastatin or ceftazidime at EOT or follow-up were 95–100%, 93% and 100%, and 92% for the respective treatments.

Pharmacoeconomic analyses of meropenem from a health payer perspective in the UK, US and Russia predicted that meropenem is a cost-effective therapy relative to other antibacterials, including imipenem/cilastatin or conventional combination antibacterial treatments in the treatment of serious bacterial infections in intensive care units. In the UK cost-utility analysis, meropenem dominated imipenem/cilastatin with regard to cost per quality-adjusted life-year gained, and was predicted to be more cost-effective than imipenem/cilastatin in the treatment of *P. aeruginosa* infections in the US and conventional combination antibacterial treatments in high-risk nosocomial infections in Russia.

Tolerability

Intravenous meropenem was generally well tolerated in adult and paediatric patients with serious bacterial infections, and most adverse events were mild to moderate in severity. The most commonly reported drug-related adverse events in patients treated with meropenem included diarrhoea, rash, and/or nausea and vomiting; in paediatric patients, diarrhoea and rash were most common. The most commonly reported laboratory adverse events included increased levels of ALT and AST and thrombocytosis. Meropenem had good CNS tolerability with an incidence of drug-related seizures in patients with infections other than meningitis of 0.07%. No seizures were considered to be related to meropenem in a trial in paediatric patients with bacterial meningitis.

1. Introduction

Serious bacterial infections can be life threatening and require prompt treatment with antibacterial agents. Empirical therapy with an antibacterial agent that has a broad spectrum of activity is administered until the infecting pathogen is identified and treatment can be switched to an agent with specific antibacterial activity against that organism.[1]

The carbapenems are members of the β-lactam class that are stable to nearly all β-lactamases. This group of agents has demonstrated bactericidal activity against a wide range of Gram-positive and Gram-negative aerobic bacteria, and against anaerobic bacteria.[2]

Meropenem (Merrem®, Meronem®)[1] is a broad-spectrum antibacterial agent of the carbapenem family. Along with imipenem/cilastatin, meropenem is one of the most established members of the carbapenem class, and is used primarily in the treatment of moderate to severely ill patients with polymicrobial or nosocomial infections.[2] Meropenem is indicated as empirical therapy prior to the identification of causative organisms, or for disease caused by single or multiple susceptible bacteria in both adults and children with a broad range of serious infections.[3]

The use of meropenem for serious bacterial infections in a variety of settings has been reviewed previously.[4-7] This review focuses on the clinical use of meropenem in the treatment of serious bacterial infections, and includes the specific indications of nosocomial pneumonia, complicated intra-abdominal infection (cIAI), septicaemia, febrile neutro-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

penia, complicated skin and skin structure infection (cSSSI), bacterial meningitis, complicated urinary tract infection (cUTI), obstetric and gynaecological infections, acute pulmonary infections in patients with cystic fibrosis, and in the treatment of severe community-acquired pneumonia (CAP).

Meropenem is approved for use in cIAI, cSSSI and bacterial meningitis (in paediatric patients aged ≥3 months) in the US.[8] In most other countries, meropenem is approved for use in nosocomial pneumonia, cIAI, septicaemia, febrile neutropenia, cSSSI, bacterial meningitis, cUTI, obstetric and gynaecological infections, pulmonary infection in patients with cystic fibrosis, and severe CAP.[9]

2. Pharmacodynamic Profile

The pharmacodynamic properties of meropenem have been previously reviewed elsewhere.[4,5] This section provides an overview of the pharmacodynamic profile of meropenem, with particular focus on antibacterial activity within the period 2000–7. Susceptibility data are from the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) database. MYSTIC is a longitudinal surveillance programme launched in 1997 to monitor antimicrobial resistance patterns in hospitals using broad-spectrum carbapenems (specifically meropenem). Data have been supplemented with results from additional susceptibility studies as required. A comparison of the percentage of isolates fully susceptible to meropenem between 1993 and 1998 showed that there have been no significant alterations in the activity of meropenem over that period.[3] Furthermore, a published overview of the MYSTIC programme results for the period 1997–2004 showed there had been no significant increase in meropenem resistance.[10]

2.1 Mechanism of Action

Meropenem is a broad-spectrum carbapenem with activity against Gram-positive and Gram-negative bacteria and anaerobic bacteria. Like other carbapenems, meropenem interferes with the synthesis of the bacterial cell wall, thus inhibiting growth and resulting in cell death.[8] The drug readily penetrates bacterial cell walls and binds with high affinity to specific penicillin-binding proteins (PBP), rendering them inactive.[2] The strongest affinities are to PBPs 2, 3 and 4 of *Escherichia coli* and *Pseudomonas aeruginosa* and PBPs 1, 2 and 4 of *Staphylococcus aureus*.[8] Meropenem has a high level of stability to hydrolysis by all serine β-lactamases,[8] and, unlike imipenem/cilastatin, is relatively stable to human dehydropeptidase-1 (DHP-1).[2]

2.2 Antibacterial Activity

This section focuses on only the causative micro-organisms predominantly identified in trials in clinical infections (section 4) for which meropenem is currently indicated. Table I shows the infections and susceptible strains of organisms specifically indicated in the US.[8] Specific organisms are not identified for each approved indication in the UK prescribing information.[9] While its broad spectrum of antibacterial activity includes numerous other bacteria, the clinical significance of these, in some cases, remains unknown. Pathogens known to be resistant to meropenem include methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecium* and *Stenotrophomonas maltophilia*.

Susceptibility testing was generally performed using methods recommended by the Clinical and Laboratory Standards Institute (CLSI). For meropenem, the CLSI breakpoints indicating susceptibility, intermediate susceptibility and resis-

Table I. Indications and designated micro-organisms for which intravenous meropenem monotherapy is approved in the US[8]

Indication	Organism
cIAI	viridans group streptococci, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *B. thetaiotaomicron*, *Peptostreptococcus* spp.
cSSSI	Methicillin-susceptible *Staphylococcus aureus* (β-lactamase and non-β-lactamase producing), *Streptococcus pyogenes*, *S. agalactiae*, viridans group streptococci, *Enterococcus faecalis* (excluding vancomycin-resistant isolates), *P. aeruginosa*, *E. coli*, *Proteus mirabilis*, *B. fragilis*, *Peptostreptococcus* spp.
Bacterial meningitis (paediatric pts aged ≥3 months)	*S. pneumoniae* (although clinical efficacy against penicillin-nonsusceptible isolates has not been established), *Haemophilus influenzae* (β-lactamase and non-β-lactamase producing), *Neisseria meningitidis*

cIAI = complicated intra-abdominal infection; **cSSSI** = complicated skin and skin structure infection; **pts** = patients.

tance were ≤4, 8, and ≥16 mg/L for Enterobacteriaceae, *P. aeruginosa*, *Staphylococcus* spp. and anaerobes.[11,12] Susceptibility breakpoints were ≤0.25 mg/L for *Neisseria meningitidis*, and ≤0.5 mg/L for *Haemophilus* spp. and *Streptococcus* spp. (excluding *Streptococcus pneumoniae* where breakpoints for susceptibility, intermediate susceptibility and resistance were ≤0.25, 0.5 and ≥1 mg/L).[11]

2.2.1 Gram-Negative Aerobic Bacteria

Meropenem demonstrated good *in vitro* antibacterial activity against clinically relevant Enterobacteriaceae, including *Citrobacter freundii*, *C. koseri*, *Enterobacter aerogenes*, *E. cloaceae*, *E. coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Morganella morganii*, *Proteus mirabilis*, *P. vulgaris* and *Serratia marcescens*; the minimum concentration (MIC) inhibiting 90% of strains (MIC_{90}) was ≤0.25 mg/L and susceptibility rates were 98.1–100% (table II).[13]

Meropenem was active against extended-spectrum β-lactamase (ESBL)- and AmpC-producing Enterobacteriaceae. The MIC_{90} values for AmpC-producing Enterobacteriaceae versus non-AmpC-producing Enterobacteriaceae were ≤0.06 versus 0.25 mg/L for *Enterobacter* spp. and 0.12 versus 0.5 mg/L for *S. marcescens*, and for ESBL-producing Enterobacteriaceae were ≤0.06 versus ≤0.06 mg/L for *E. coli* and ≤0.06 versus 0.12 mg/L for *K. pneumoniae* (all susceptibility rates were 100%).[14] Like meropenem, imipenem/cilastatin and doripenem showed little or no increase in MIC_{90} for ESBL- and AmpC-producing isolates relative to wild-type isolates, whereas the MIC_{90} for ertapenem increased by up to four doubling dilutions.[14] With meropenem, there was no inoculum effect for ESBL-producing *E. coli*, or for the majority of the ESBL-producing *K. pneumoniae* or AmpC-producing Enterobacteriaceae strains tested.[15]

Meropenem also showed good activity against *H. influenzae* and *N. meningitidis*, with MIC_{90} values of 0.25 mg/L and susceptibility rates of ≈100% (table II). Against *Burkholderia cepacia* and *Acinetobacter baumannii*, meropenem had MIC_{90} values of 16 and 64 mg/L, and susceptibility rates of 72.9% and 71.5%; against *P. aeruginosa*, the MIC_{90} was 32 mg/L and susceptibility rate was 76.4% (table II). Meropenem and other carbapenems are not active against *S. maltophilia* because of the intrinsic production of carbapenemases by this organism.

Although meropenem activity against *P. aeruginosa*, *Acinetobacter* spp. and *B. cepacia* may be limited in some geographic regions, meropenem remains as one of the most active clinically available antimicrobial agents against these and other non-fermentative Gram-negative organisms.[16-18] Furthermore, increases in meropenem resistance rates appeared to be more related to clonal dissemination of resistant organisms than antimicrobial usage.[19,20] The retention of excellent activity of meropenem against the majority of Enterobacteriaceae was confirmed in the most recently published reports on European[21] and US[22] data from the MYSTIC 2006 programme, although in Europe, meropenem and imipenem/cilastatin showed slight decreases in activity compared with MYSTIC 2002 programme results (for Enterobacteriaceae in 2002 vs 2006, susceptibility rates for meropenem and imipenem/cilastatin were 99.9% vs 98.9% and 98.2% vs 97.9%).[21] This was considered likely to be a reflection of the occurrence of serine carbapenemases and metallo-β-lactamases, and AmpC β-lactamase hyperproduction coupled with outer membrane protein changes.[21] Susceptibility rates of *Acinetobacter* spp. to meropenem and imipenem/cilastatin were >80% in 2002, compared with <60% in 2006.[21] However, when 2006 data were broken down by country, susceptibility rates for meropenem against *Acinetobacter* spp. were 100% for Belgium (n = 11 isolates), 95.5% for Sweden (22), 96.6% for Germany (29), 75.8% for Spain (33) and 38.5% for Turkey (239), possibly reflecting resistance problems in specific countries or regions.[13] Data from the US study showed a 2-fold increase in serine carbapenemase-producing *Klebsiella* spp. between 2005 and 2006, mainly from one geographic region.[22,23]

2.2.2 Gram-Positive Aerobic Bacteria

Meropenem had good *in vitro* antibacterial activity against methicillin-susceptible *S. aureus* (MSSA), *S. epidermidis*, *S. pneumoniae* (including penicillin-resistant isolates) and viridans group streptococci, with MIC_{90} values of 0.25–2 mg/L and susceptibility rates of 95.3–100% (table III).

Table II. *In vitro* activity of meropenem (MEM) and other antibacterials against aerobic Gram-negative pathogens. Data from the MYSTIC database.[13] MYSTIC data included isolates collected from worldwide hospital centres between 2000 and 2007. Susceptibility testing was performed using Clinical and Laboratory Standards Institute (CLSI) methods. Data shown are minimum concentrations inhibiting 50% (MIC_{50}) and 90% (MIC_{90}) of strains (mg/L) and susceptibility (S; %) calculated using CLSI breakpoints[a,b]

Gram-negative pathogen	Total no. of isolates[c]	MEM			IPM			ETP			CAZ			TZP		
		MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S
Enterobacteriaceae																
Citrobacter freundii	1 601	0.032	0.125	99.6	0.5	1	99.2	≤0.008	0.25	96.9	0.5	128	70.8	4	128	
C. koseri	733	0.016	0.064	99.8	0.125	0.5	99.0	≤0.008	≤0.008	100	0.25	1	97.0	2	8	97.2
Enterobacter aerogenes	2 125	0.064	0.25	98.5	0.5	2	96.9	≤0.008	0.25	99.4	1	>128	61.9	4	64	70.5
E. cloaceae	5 949	0.064	0.25	99.3	0.25	1	98.9	0.032	1	98.5	0.5	128	68.8	4	128	74.5
Escherichia coli	15 974	0.016	0.064	99.8	0.125	0.5	99.5	≤0.008	≤0.008	99.9	0.25	8	90.8	2	16	90.9
Klebsiella pneumoniae	10 459	0.032	0.25	98.1	0.25	0.5	97.9	≤0.008	0.064	93.3	0.25	64	77.6	4	128	79.5
K. oxytoca	2 895	0.032	0.125	99.7	0.25	0.5	99.4	≤0.008	0.016	99.1	0.125	4	92.4	2	>128	79.4
Morganella morganii	1 656	0.125	0.25	99.3	2	8	89.9	≤0.008	0.032	100	0.25	16	85.9	0.5	8	94.6
Proteus mirabilis	3 817	0.064	0.25	99.7	0.5	4	96.8	≤0.008	≤0.008	100	0.064	1	96.1	0.5	4	97.7
P. vulgaris	471	0.064	0.25	100	1	4	93.4	≤0.008	≤0.008	100	0.064	1	95.9	0.5	2	99.6
Serratia marcescens	3 241	0.064	0.25	99.6	0.5	2	98.9	≤0.008	0.064	99.8	0.25	8	90.4	0.5	32	86.3
Other organisms																
Burkholderia cepacia	373	2	16	72.9	16	64		4	32		4	>128	72.1	8	>128	
Acinetobacter baumannii	4 442	1	64	71.5	1	64	71.8	8	64		32	>128	34.2	128	>128	34.9
Haemophilus influenzae	591	0.064	0.25	98.9	0.5	1	70.6	0.032	0.032	100	0.125	0.25	99.3	0.032	0.25	98.8
Neisseria meningitidis	17	≤0.008	0.25	100	0.064	0.25					0.016	64		0.016	0.25	
Pseudomonas aeruginosa	17 224	1	32	76.4	2	64	68.7	8	64		4	128	71.1	8	>128	80.8

a Current CLSI breakpoints (mg/L) for *Acinetobacter* spp., indicating susceptibility (S), intermediate susceptibility (I) and resistance (R) were ≤4, 8 and ≥16 (MEM, IPM), ≤16/4, 32/4–64/4 and ≥128/4 (TZP), and ≤8, 16 and ≥32 (CAZ); for *B. cepacia*, breakpoints indicating S, I and R were ≤4, 8 and ≥16 (MEM), and ≤8, 16 and ≥32 (CAZ); for Enterobacteriaceae, breakpoints indicating S, I and R were ≤2, 4 and ≥16 (MEM, IPM), ≤2, 4 and ≥8 (ETP), and ≤8, 16 and ≥32 (CAZ); for *H. influenzae*, breakpoints indicating S and R were ≤1/4 and ≥2/4 (TZP), and indicating S were ≤2 (CAZ), ≤0.5 (MEM, ETP) and ≤4 (IPM); for *N. meningitidis*, breakpoints indicating S were ≤0.25 for MEM; for *P. aeruginosa*, breakpoints indicating S, I and R were ≤4, 8 and ≥16 (MEM, IPM), ≤8, 16 and ≥32 (CAZ), and indicating S and R were ≤64/4 and ≥128/4 (TZP).[11]

b Current EUCAST breakpoints (mg/L) for *Acinetobacter* spp., indicating S and R were 2 and 8 (MEM, IPM); for Enterobacteriaceae, breakpoints indicating S and R were 2 and 8 (MEM, IPM), 0.5 and 1 (ETP), and 1 and 8 (CAZ); for *H. influenzae*, breakpoints indicating S were 2 (MEM, IPM) and 0.5 (ETP); for *N. meningitidis*, breakpoints indicating S were 0.25 (MEM); for *P. aeruginosa*, breakpoints indicating S and R were 2 and 8 (MEM), 4 and 8 (IPM), and 8 and 8 (CAZ).[24]

c Although all isolates were tested against MEM, not all isolates were tested against all comparators in any particular trial.

CAZ = ceftazidime; **ETP** = ertapenem; **EUCAST** = European Committee on Antimicrobial Susceptibility Testing; **IPM** = imipenem/cilastatin; **TZP** = piperacillin/tazobactam.

Table III. *In vitro* activity of meropenem (MEM) and other antibacterials against aerobic Gram-positive pathogens. Data from the MYSTIC database.[13] MYSTIC data included isolates collected from worldwide hospital centres between 2000 and 2007. Susceptibility testing was performed using Clinical and Laboratory Standards Institute (CLSI) methods. Data shown are minimum concentrations inhibiting 50% (MIC_{50}) and 90% (MIC_{90}) of strains (mg/L) and susceptibility (S; %) calculated using CLSI breakpoints[a,b]

Gram-positive pathogen	Total no. of isolates[c]	MEM			IPM			ETP			CAZ			TZP		
		MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S
Enterococcus faecalis	6 459	4	16	69.1	1	4	94.6	8	16		128	>128		4	8	
Staphylococcus aureus (methicillin/oxacillin susceptible)	13 113	0.125	0.25	99.6	0.032	0.25	99.6	0.125	0.25	100	8	16	67.7	1	4	97.2/ 93.5
S. epidermidis (oxacillin-susceptible isolates)	2 873	0.125	2	95.3	0.064	1	96.5	0.125	0.5	98.7	8	32	72.2	1	4	95.4/ 91.7
Streptococcus pneumoniae	2 623	0.016	0.25	100	0.016	0.25	99.9	≤0.008	1	88.8	0.25	4		0.125	4	
S. pneumoniae (penicillin-resistant)	261	0.25	0.5	95.8	0.125	0.5					8	16		2	8	
Viridans group streptococci	1 586	0.032	0.25	95.5	0.064	0.25	98.6	0.064	0.5		0.5	8		0.25	4	

a Current CLSI breakpoints (mg/L) for *Staphylococcus* spp., indicating susceptibility (S), intermediate susceptibility (I) and resistance (R) were ≤4, 8 and ≥16 (MEM, IPM), ≤2, 4 and ≥8 (ETP), and ≤8, 16 and ≥32 (CAZ), and indicating S and R were ≤8/4 and ≥16/2 (TZP); for *Streptococcus* spp. other than penicillin-susceptible *S. pneumoniae* and viridans group streptococci, breakpoints indicating S were ≤0.5 (MEM) and ≤1 (ETP); for penicillin-susceptible *S. pneumoniae*, breakpoints indicating S, I and R were ≤0.25, 0.5 and ≥1 (MEM), ≤1, 2 and ≥4 (ETP), and ≤0.12, 0.25–0.5 and ≥1 (IPM); for viridans group streptococci, breakpoints indicating S were ≤0.5 (MEM) and ≤1 (IPM).[11]

b Current EUCAST breakpoints (mg/L) for *Enterococcus* spp. indicating S and R were 4 and 8 (IPM) [MEM does not have EUCAST enterococcal interpretive criteria]; for *S. pneumoniae*, breakpoints indicating S and R were 2 and 2 (MEM, IPM), and 0.5 and 0.5 (ETP).[24]

c Although all isolates were tested against MEM, not all isolates were tested against all comparators in any particular trial.

CAZ = ceftazidime; **ETP** = ertapenem; **EUCAST** = European Committee on Antimicrobial Susceptibility Testing; **IPM** = imipenem/cilastatin; **TZP** = piperacillin/tazobactam.

Table IV. *In vitro* activity of meropenem (MEM) and other antibacterials against anaerobic pathogens. Data from the MYSTIC database.[13] MYSTIC data included isolates collected from worldwide hospital centres between 2000 and 2007. Susceptibility testing was performed using Clinical and Laboratory Standards Institute (CLSI) methods. Data shown are minimum concentrations inhibiting 50% (MIC_{50}) and 90% (MIC_{90}) of strains (mg/L) and susceptibility (S; %) calculated using CLSI breakpoints[a]

Anaerobic pathogen	Total no. of isolates[b]	MEM			IPM			TZP		
		MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S	MIC_{50}	MIC_{90}	S
Bacteroides fragilis	18	1	8	88.9	0.5	4	100	32	64	77.8/33.3
Clostridium difficile	8	2	4	100	8	16	37.5	4	8	100/87.5
C. perfringens	14	≤0.008	0.25	100	0.064	0.5	100	0.25	2	100/100
Peptostreptococcus spp.	60	0.016	0.125	100	0.032	0.25	100	0.064	1	100/98.3
Prevotella spp.	18	0.064	0.25	100	0.064	0.25	100	1	16	100/88.9

a For anaerobes, current CLSI breakpoints (mg/L) indicating susceptibility (S), intermediate susceptibility (I) and resistance (R) were ≤4, 8 and ≥16 (MEM, IPM), and ≤32/4, 64/4 and ≥128/4 (TZP); current EUCAST breakpoints (mg/L) indicating S and R were 2 and 8 (MEM, IPM).[24,26]

b Although all isolates were tested against MEM, not all isolates were tested against all comparators in any particular trial.

EUCAST = European Committee on Antimicrobial Susceptibility Testing; **IPM** = imipenem/cilastatin; **TZP** = piperacillin/tazobactam.

Meropenem activity against MRSA, *Enterococcus faecium* and *E. faecalis* was poor, with MIC_{90} values of 32, >16 and 16 mg/L, respectively.[2] In the published report on European data from the MYSTIC 2006 programme, the percent susceptibility of the carbapenems (meropenem and imipenem/cilastatin) for *S. pneumoniae* was slightly decreased compared with 2002 rates (from 100% to 95.2% for meropenem and 100% to 90.4% for imipenem/cilastatin); this was attributed to an increased incidence of penicillin-resistant strains.[21]

2.2.3 Anaerobic Bacteria

Meropenem demonstrated *in vitro* activity against a range of anaerobic pathogens including *Bacteroides fragilis*, *Clostridium difficile*, *C. perfringens*, *Peptostreptococcus spp.* and *Prevotella* spp. (table IV); MIC_{90} values were 0.125–4 mg/L with susceptibility rates of 100% for all listed anaerobes, with the exception of *B. fragilis* (MIC_{90} of 8 mg/L; 88.9% susceptibility).[13] imipenem/cilastatin, ertapenem, doripenem and piperacillin/tazobactam also showed anti-anaerobic activity, apart from imipenem/cilastatin against *C. difficile* (MIC_{90} of 16 mg/L; 37.5% susceptibility).[2,13,25]

2.3 Resistance Mechanisms

Meropenem shows stability against hydrolysis by most β-lactamases, including AmpC β-lactamase and ESBLs. As discussed in section 2.2.1, there was little or no change in MIC_{90} values in comparisons of wild-type and ESBL-producing *E. coli* or *K. pneumoniae* isolates, or wild-type and AmpC-producing *Enterobacter* spp. or *S. marcescens*.[14] Carbapenemases can affect the activity of meropenem. Among the most potent are the class B metallo-β-lactamases, the production of which is intrinsic in *S. maltophilia*, but can also be acquired by *P. aeruginosa* and other Gram-negative species.

The poor binding affinity of carbapenems to some PBPs present in some bacteria (such as *Enterococcus* spp. and MRSA) confer inherent resistance to β-lactam antibacterial drugs. Reduced susceptibility to carbapenems can also arise with overexpression of multidrug efflux pumps detected in some Gram-negative bacteria including *P. aeruginosa*. Increasing meropenem resistance in *P. aeruginosa* isolates as a result of the overexpression of

efflux pumps has been documented,[27] although there may be other, yet to be described, mechanisms involved in *P. aeruginosa* carbapenem resistance.[28]

Carbapenems enter Gram-negative bacteria via passive diffusion through porins situated in the cell membrane.[4] Organisms that lack porins have reduced susceptibility to carbapenem antimicrobial agents because of the consequent reduction in permeability. Outer membrane porin protein (Opr) D2 deficiency is associated with reduced susceptibility to carbapenem but not other β-lactam agents. However, it is thought that a combination of resistance mechanisms, such as the presence of carbapenemases and reduced permeability, or overexpression of multidrug efflux pumps and reduced permeability are required for significant carbapenem resistance to emerge. For example, both reduced permeability and the presence of a carbapenemase are required in *K. pneumoniae* in order for detectable resistance to be achieved.[29] The combination of reduced permeability and overexpression of multidrug efflux pumps required for meropenem resistance is considered less likely to occur than the combination required for imipenem/cilastatin resistance (AmpC-β-lactamase expression plus loss of permeability (porin OprD).[30,31]

Meropenem generally appears to have a low potential for selecting resistant strains *in vitro*.[5] In a study comparing the potencies of meropenem, imipenem/cilastatin and doripenem for the prevention of carbapenem-resistant mutants of *P. aeruginosa*, mutants lacking or with decreased expression of the outer membrane protein OprD were predominantly selected; relative potencies were doripenem > meropenem > imipenem/cilastatin.[32] Cross-resistance has been seen with isolates that are resistant to other carbapenems.[8]

2.4 Bactericidal Activity

Meropenem had rapid, time-dependent bactericidal activity against staphylococci, pneumococci and Enterobacteriaceae, such as *K. pneumoniae* (including ESBL-producing isolates) and *P. aeruginosa in vitro*.[33-35] For example, at a concentration of 4 μg/mL (the mean steady-state serum concentration achieved with meropenem 1 g three times daily in healthy volunteers) against standard (5×10^5 cfu/mL) and high (1×10^7 cfu/mL) inocula of *K. pneumoniae*, meropenem achieved a 99.9% kill at 6–8 hours that was maintained over 24 hours.[33] Conversely, increasing the inoculum size from 10^6 cfu/mL to 10^8 cfu/mL resulted in decreased bactericidal activity against a laboratory strain of *S. aureus* (99.9% kill at 6 hours at 2 × MIC vs no bactericidal activity at 2–16 × MIC) and a clinical isolate of *P. aeruginosa* (99.9% kill at 4 hours at 16 × MIC vs no bactericidal activity at 2–16 × MIC).[35] Bactericidal concentrations of meropenem (defined as a $3\log_{10}$ reduction in bacterial cell counts within 12–24 hours) are generally up to 2-fold higher than bacteriostatic concentrations of the drug,[8] although activity against *Listeria monocytogenes* is bacteriostatic and not bactericidal.[36] Meropenem also showed bactericidal activity (99.9% kill) against a variety of anaerobes, including *B. fragilis*, *B. thetaiotaomicron*, *P. bivia*, *Fusobacterium nucleatum*, *F. mortiferum*, *Peptostreptococcus asaccharolyticus*, *C. perfringens* and *C. difficile* at 4 × MIC after 24 hours.[37]

2.5 Pharmacodynamic/Pharmacokinetic Relationship

For the time-dependent antibacterials (including meropenem; section 2.4), bactericidal activity is best when unbound drug concentrations are maintained above the MIC for specific proportions of the dosing interval (%T > MIC).[38] For concentration-dependent antibacterials, bactericidal activity occurs with an optimal maximum plasma concentration (C_{max})/MIC ratio, area under the plasma concentration-time curve (AUC)/MIC ratio, or both.[38]

The OPTAMA (Optimizing Pharmacodynamic Attainment using the MYSTIC Antibiogram) programme uses data from the MYSTIC programme to identify the most appropriate empirical antibacterial therapy for common nosocomial pathogens (i.e. antibacterial agents with the greatest probability of achieving bactericidal exposures, while taking into account variability in pharmacokinetics, dosages and MIC distribution).[39]

Bactericidal exposures were modelled for each of the antibacterial agents studied against *E. coli*, *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* in various geographic regions using MIC data from the MYSTIC programme and pharmacokinetic data in healthy volunteers. Results are available for data

Table V. Probability of target attainment (PTA; %)[39-41] or cumulative fraction of response (CFR; %)[42] at defined bactericidal pharmacodynamic targets, and percentage susceptibility (S) for various intravenously administered antimicrobial agents against selected Enterobacteriaceae collected in North America,[40] South America[41] and Europe[39] in 2002, and in North America in 2004.[42] Bactericidal pharmacodynamic targets were defined as %T > MIC ≥40% for meropenem 0.5 g or 1 g q8h (MEM) and imipenem/cilastatin 1 g q8h or 0.5 g q6h (IPM), %T > MIC ≥50% for cefepime 1 or 2 g q12h (FEP), ceftazidime 1 or 2 g q8h (CAZ) or piperacillin/tazobactam 3.375 g q4h or q6h or 4.5 g q8h (TZP) and as AUC/MIC ratio ≥125 for ciprofloxacin 400 mg q8h or q12h (CIP)

Organism	PTA or CFR [S] (%)					
	MEM	IPM	FEP	CAZ	TZP	CIP
Escherichia coli						
North America 2002	100 [100]	100 [100]	100 [100]	96 [96]	95 [98]	85 [93]
North America 2004	100 [100]	100 [100]	99 [99]	97 [97]	96 [98]	79 [79]
South America	98	98	94	92	66	48
Northern Europe	100 [100]	99 [100]	99 [99]	97 [97]	85 [96]	81 [89]
Southern Europe	99 [100]	99 [100]	99–100 [100]	95 [95]	77 [93]	63 [79]
Eastern Europe	99 [100]	99 [100]	79–84 [80]	81 [80]	62 [79]	58 [63]
Klebsiella pneumoniae						
North America 2002	100 [100]	99 [100]	99 [100]	90 [90]	89 [95]	80 [98]
North America 2004	99 [100]	100 [100]	98 [99]	94 [95]	94 [96]	90 [95]
South America	99	100	78	78	60	64
Northern Europe	99 [88–98]	99 [99]	99 [99]	88 [99]	70 [88]	72 [92]
Southern Europe	96–98 [97]	97 [96]	96 [100]	83 [83]	59 [83]	69 [88]
Eastern Europe	98–99 [99]	99 [99]	67–77 [71]	52 [52]	37 [54]	61 [74]
Pseudomonas aeruginosa						
North America 2002	91 [92]	89 [87]	82–93 [88]	84–89 [84]	70–85 [93]	53–59 [74]
North America 2004	89 [90]	91 [88]	68–83 [82]	73–82 [82]	70–81 [88]	58 [75]
South America	60	62	50–65	55–62	26	33–37
Northern Europe	81–87 [87]	81 [80]	81 [74]	79–84 [79]	47 [87]	39–48 [70]
Southern Europe	68–76 [75]	65 [64]	63 [54]	70–80 [71]	39 [89]	23–31 [60]
Eastern Europe	59–63 [63]	57 [56]	55 [49]	54–60 [48]	28 [63]	28–38 [49]
Acinetobacter baumannii						
North America 2002	88 [88]	92 [91]	50–67 [55]	59–69 [61]	56–65 [62]	41–46 [69]
North America 2004	70 [70]	83 [78]	42–50 [49]	40–52 [51]	43–50 [49]	42 [49]
South America	73	73	29–43	27–35	24	14–24
Northern Europe	89–93 [93]	95 [95]	73 [62]	71–79 [73]	46 [64]	40–52 [76]
Southern Europe	66–82 [82]	73 [72]	54 [54]	22–38 [23]	14 [30]	11–16 [28]
Eastern Europe	54–58 [56]	54 [54]	35 [23]	22–29 [23]	12 [21]	14–18 [25]

AUC = area under the plasma concentration-time curve; **MIC** = minimum inhibitory concentration; **q*x*h** = every *x* hours; **%T > MIC** = the proportion of dosing interval above the MIC.

collected in North America,[40] South America[41] and Europe[39] in 2002, and North America in 2004[42] for Enterobacteriaceae (table V; only those for meropenem are discussed here), and for data in pathogens associated with the following indications: nosocomial pneumonia,[43] nosocomial bloodstream infections,[44] paediatric meningitis,[45] cSSSI,[46] and cIAI.[47]

Another OPTAMA report used data from two centres in the US to assess the likelihood of achieving an optimal pharmacodynamic target in *P. aeruginosa* infections in children.[48] A bactericidal cumulative fraction of response (CFR; defined as the probability of achieving the targeted exposure with a given dosage regimen for a select population of organisms[38], and similar to the probability of target attainment [PTA][38] [%T > MIC≥40% for meropenem]) ≥90% was considered optimal.[48]

The 2002 analysis estimated that meropenem 0.5 or 1 g three times daily administered as an intrave-

nous bolus would achieve an optimal CFR against *E. coli* (99–100%) and *K. pneumoniae* (96–100%) in all regions. However, estimates for *P. aeruginosa* varied according to region, with an optimal CFR seen only in North America (91%).[40] CFRs were 81–87% in Northern Europe, 68–76% in Southern Europe, 59–63% in Eastern Europe[39] and 60% in South America.[41] Estimates for *A. baumannii* also varied by region; an optimal CFR was achieved with meropenem 1 g three times daily in Northern Europe (93%), but not with a 500 mg three times daily dosage (CFR of 89%).[39] CFRs were 88% in North America,[40] 66–82% in Southern Europe,[39] 73% in South America[41] and 54–58% in Eastern Europe.[39] A high level of agreement between susceptibility percentages and the PTA was shown for meropenem 1 g three times daily against all pathogens studied (agreement of 0.25 [95% CI −1.65, 2.15] in Europe and 0.5 [95% CI −0.64, 1.64] in South America).

The 2004 OPTAMA report showed little change in meropenem CFRs and susceptibilities in North America between 2002 and 2004, apart from *A. baumannii* resistance to carbapenems, which increased from 9% to 22% for meropenem and 8% to 11% for imipenem/cilastatin.[42]

Subsequent OPTAMA programme reports used the prevalence of individual bacteria causing infections to estimate CFRs for the empirical treatment of various infections. In each of these analyses it was estimated that meropenem 0.5 or 1 g three times daily would achieve optimal CFRs against most pathogens associated with nosocomial pneumonia, nosocomial blood infection, paediatric meningitis, cSSSI and cIAI (CFRs of 94.3–99.7%).[43-47]

In the analysis of *P. aeruginosa* infections in paediatric patients, the meropenem CFR was 92% in one institution and 58% in the other.[48] Pathogens included in the nosocomial pneumonia analysis were MSSA, *P. aeruginosa*, *S. pneumoniae*, *Klebsiella* spp., *Enterobacter* spp., *E. coli*, *Serratia* spp., *Acinetobacter* spp., *P. mirabilis* and *Citrobacter* spp.[43] Those included in the nosocomial bloodstream infections analysis were MSSA, coagulase-negative staphylococci, β- or viridans-group streptococci, *S. pneumoniae*, *Enterobacter* spp., *E. coli*, *Klebsiella* spp., *P. aeruginosa* and *Serratia* spp.[44] When the prevalence of MRSA and methicillin-resistant coagulase-negative staphylococci were added back into the nosocomial pneumonia and bloodstream infection models or the prevalence of MRSA was increased beyond 10%, meropenem CFRs dropped below 90%.[38,43,44,46] *S. pneumoniae*, *H. influenzae* and *N. meningitidis* were included in the paediatric meningitis analysis,[45] *S. aureus*, *P. aeruginosa*, *E. coli*, *Enterobacter* spp., *Klebsiella* spp., coagulase-negative staphylococci, *Proteus* spp., β-haemolytic streptococci and *Serratia* spp. were included in the cSSSI analysis[46] and *P. aeruginosa* was included in the cIAI analysis.[47]

Several other analyses estimated a bactericidal CFR of 72–86% for meropenem 1 or 2 g three times daily as a bolus or a 1- or 3-hour infusion,[49,50] and that the probability of attaining an optimal outcome against *P. aeruginosa* with meropenem was greatest when administered as a high-dose, 3 g/day 24-hour infusion (83%) rather than as a low-dose, 1.5 g/day 24-hour infusion (76%), or as a high- or low-dose, intermittent infusion (64% and 52%).[51] Nevertheless, other factors, including the instability of the meropenem solution at room temperature and the need for dedicated intravenous line, may limit the usefulness of continuous infusion regimens.[51,52]

3. Pharmacokinetic Profile

The pharmacokinetic profile of meropenem is well established and has been reviewed in detail previously.[2,4-6,53]

3.1 Distribution

Mean C_{max} and corresponding AUC values for intravenous meropenem administered as a 30-minute infusion in healthy volunteers increase with increasing dosages of meropenem, but there is no absolute dose-proportionality over a dose range of 250 mg to 2 g.[9] When meropenem was administered in healthy volunteers as a 30-minute intravenous infusion, the C_{max} after a 500 mg dose was ≈23 μg/mL, and that after a 1 g dose was ≈49 μg/mL.[9] Administering meropenem as an intravenous bolus over 5 minutes in healthy volunteers achieved C_{max} values of ≈52 and ≈112 μg/mL, respectively, with a 500 mg and 1 g dose; C_{max} values with a shorter infusion period (2 or 3 minutes) did not differ from that with a 5-minute bolus infusion.[9]

AUC values following 500 mg and 1 g intravenous infusions in healthy volunteers were 27.2–32.4 mg • h/L and 66.9–77.5 mg • h/L.[2] At 6 hours after intravenous administration of a 500 mg dose, plasma meropenem levels are ≤1 μg/mL.[9] Plasma protein binding of meropenem is negligible (2%).[9] Meropenem distributes into a wide variety of tissues and fluids (including interstitial fluid) and has an apparent volume of distribution at steady state (Vd_{ss}) of between 12.5 and 20.7 L in healthy volunteers.[54] Meropenem penetrates tissues well, achieving drug concentrations at or above those required to inhibit susceptible bacteria.[8] After a single intravenous dose of meropenem 500 mg or 1 g, peak concentrations were achieved in most tissues and/or fluids (including gynaecological tissues [0.3–10.2 μg/g; 500 mg], skin [0.5–12.6 and 1.3–16.7 μg/g; 500 mg and 1 g], interstitial fluid [3.2–8.6 and 20.9–37.4; 500 mg and 1 g], intra-abdominal tissues [2.5–3.9 μg/g; 1 g], peritoneal fluid [7.4–54.6 μg/mL; 1 g], bronchial mucosa [1.3–11.1 μg/g; 1 g], fascia [1.5–20 μg/g; 1 g] and cardiac tissues [5.2–25.5 μg/g; 1 g]), within 0.5-1.5 hours. The exceptions were lung tissue (1.4–8.2 μg/g; 1 g), muscle (5.3–6.9 μg/g; 1 g), bile (4.0–25.7 μg/mL; 1 g) and inflamed cerebrospinal fluid (CSF [0.2–2.8 μg/mL; 20 mg/kg and 0.9–6.5 μg/mL; 40 mg/kg]), where peak concentrations were seen 2–3 hours after administration.[8]

3.2 Metabolism and Elimination

Meropenem has one metabolite, which is microbiologically inactive.[9] Most of an intravenously administered dose of meropenem is not metabolized.[9] The elimination half-life ($t_{1/2}$) of meropenem in individuals with normal renal function is ≈1 hour, and 70% of an administered intravenous dose is excreted in the urine as the unchanged drug over 12 hours, with negligible urinary excretion thereafter.[9] In healthy volunteers administered single doses between 250 and 1000 mg, meropenem had an apparent total body clearance of 188–328 mL/min and a renal clearance of 139–252 mL/min[54]. Over a dose range of 250 mg to 2 g, a total plasma clearance reduction from 287 mL/min to 205 mL/min has been seen.[9] Up to 5 hours after intravenous administration of a 500 mg dose, urinary concentrations of meropenem are >10 μg/mL.[8] The peritoneal $t_{1/2}$ of meropenem was similar to the plasma $t_{1/2}$ value.[55] Meropenem does not accumulate in plasma or urine after repeated intravenous administration (500 mg 8-hourly or 1 g 6-hourly) in healthy volunteers.[8]

3.3 Special Populations

The pharmacokinetics of meropenem in paediatric patients aged ≥2 years are consistent with those in adult patients and are linear over a dose range of 10–40 mg/kg.[8] The $t_{1/2}$ of meropenem in paediatric patients aged 3 months to 2 years is increased to 1.5 hours.[8] Meropenem is not licensed for use in paediatric patients aged <3 months.[8]

In elderly patients, reductions in the plasma clearance of meropenem are correlated with age-related reductions in creatine clearance[9] and dosage reductions may be required.

Pharmacokinetics of meropenem are unchanged in patients with hepatic impairment.[9]

The pharmacokinetics of meropenem in patients with infection can vary from those in healthy volunteers, for example higher Vd_{ss}[56,57] and nonrenal clearance of the drug.[56] Such changes could be due to the disease state or physiological changes associated with previous treatment (e.g. surgery), rather than the infections themselves.[56,57] The pharmacokinetics of meropenem in patients with moderate or severe infection were unchanged during the course of treatment.[58] Obesity[59] and cystic fibrosis[60] as the underlying disease had no clinically significant effect on the pharmacokinetics of meropenem.

3.3.1 Renal Impairment

Meropenem is predominantly excreted via the kidneys; consequently, plasma clearance of the drug is reduced in renal impairment. Pharmacokinetic studies have shown that meropenem plasma clearance is correlated with serum creatinine clearance;[8] thus, dosage adjustments are required in adult patients with a creatinine clearance <51 mL/min (3.06 L/h). Meropenem has not been evaluated in paediatric patients with renal impairment.

Although meropenem is cleared by haemodialysis, pharmacokinetic data in patients requiring haemodialysis are considered insufficient in the US to draw any conclusions about the use of meropenem in these patients;[8] in the UK, if treatment with meropenem is required in this patient group,

the unit dose appropriate for the infection should be administered after haemodialysis is completed.[9] The drug has not been evaluated in adult patients undergoing peritoneal dialysis.

3.4 Potential Drug Interactions

The protein binding of meropenem is low (section 3.1); therefore, interactions based upon this mechanism are not expected.[3] The only specific drug interaction studies conducted for meropenem to date are with probenecid. Concomitant probenecid treatment increases the $t_{1/2}$ and plasma concentrations of meropenem due to competition for active tubular secretion.[3] As meropenem achieves an adequate antibacterial potency and duration of action when administered alone, probenecid coadministration is not required, and, in fact, not recommended.[8]

Meropenem may also reduce serum valproic acid (sodium valproate) concentrations, resulting in subtherapeutic levels in some individuals[3,61] Of note, a similar interaction has been reported with valproic acid and the carbapenem panipenem/betamipron, suggesting a possible class effect.[62]

4. Clinical Efficacy

The efficacy of meropenem as empirical therapy in serious bacterial infections has been evaluated in numerous randomized active-comparator-controlled trials in adult and paediatric patients.[63-101] Most were open-label trials;[63-76,78,80-90,93-96,98-106] four were of double-blind design[79,92,107-109] (one[103] also included a placebo arm) and four[77,91,96,110] were of single-blind design. The majority were multicentre trials that evaluated a single type of infection (nosocomial pneumonia [section 4.1], cIAI [section 4.2], febrile neutropenia [section 4.4], cSSSI [section 4.5], bacterial meningitis [section 4.6], complicated UTI [section 4.7], obstetric or gynaecological infection [section 4.8], chronic pulmonary infection in cystic fibrosis [section 4.9], and severe CAP [section 4.10]) and these are discussed in detail. Of the trials that included patients with different types of infections,[63-74] only those that included an evaluation of the efficacy of meropenem in patients with septicaemia[63,65,67,70-72] (section 4.3) are included.

The main comparator agents were another carbapenem (imipenem/cilastatin or doripenem), a third-generation cephalosporin with or without an aminoglycoside or with metronidazole, and a macrolide or a penicillin plus a β-lactamase inhibitor with or without an aminoglycoside. Meropenem was administered as an intravenous bolus or infusion over 20–30 minutes; comparator agents were usually administered as an intravenous infusion over 20–60 minutes.

All patients in these trials were hospitalized prior to beginning treatment. Exclusion criteria common to most trials included a history of immediate hypersensitivity to β-lactam antibacterials, renal or hepatic impairment, CNS disease, current seizure disorder or history of seizures, acquired or congenital immune deficiency, neutropenia (except in febrile neutropenia trials [section 4.4]), cystic fibrosis (except in cystic fibrosis trials [section 4.9]) and severe, and/or rapidly progressing and/or terminal disease or underlying medical conditions that would preclude study treatment evaluation. Patients were also excluded if they had been exposed to another investigational drug concomitantly or in the 30 days prior to study entry or had received treatment with another antibacterial agent within 3–30 days of study commencement unless persistent infection was established or drug was ineffective. Concomitant therapy with systemic antibacterial agents was generally not permitted.

In most trials, the primary efficacy endpoint was clinical or bacteriological response at end of treatment (EOT) and/or the follow-up visit. Although definitions varied between trials, clinical response was usually defined as disappearance or improvement of clinical signs and symptoms of infection and bacteriological response was usually defined as eradication or presumed eradication of the infecting pathogen(s). The EOT assessment occurred within 24 hours of ceasing treatment and the follow-up assessment occurred 1–6 weeks after treatment cessation. In trials in patients with bacterial meningitis (section 4.6), clinical efficacy assessments were based on Infectious Diseases Society of America (IDSA) guidelines, with endpoints of cure without neurological and/or audiological sequelae, and survival with neurological and/or audiological sequelae (mild or severe in one study[77]), assessed at EOT,

and at 5–7 weeks and 5–7 months after treatment, or death. Microbiological efficacy was assessed by repeated CSF sample 18–36 hours (or occasionally after 36 hours[76]) after starting treatment and bacteriological response was defined as eradication, eradication with relapse, delayed sterilization (second sample positive, but with significant bactericidal effect and subsequent sterile CSF cultures) or persistence (treatment failure). In patients with febrile neutropenia (section 4.4), the primary endpoint was usually the percentage of patients in whom treatment was unmodified after 72 hours of treatment or clinical response at EOT. Efficacy endpoints in trials in patients with cystic fibrosis related to changes in pulmonary function and inflammatory status (section 4.9).

Several trials examined the noninferiority of meropenem to comparator regimens.[79-81,107] Meropenem was considered noninferior if the lower limit of the two-sided 95% confidence interval for the difference between treatments (meropenem response minus the comparator response) was no less than −10%[107] or −15%.[79-81]

Unless specified otherwise, this section focuses on results of per-protocol analyses (in clinically or bacteriologically evaluable patients), and does not discuss results of the supportive intent-to-treat (ITT) or modified ITT analyses that were conducted in most studies. Some studies discussed in this section are reported as abstracts and/or posters.[73,79-81]

4.1 Nosocomial Pneumonia

Three randomized comparative trials have investigated the efficacy of meropenem in the treatment of adult patients with nosocomial pneumonia.[111-113] In one of the studies, meropenem was compared with a ceftazidime plus tobramycin combination in patients with nosocomial lower respiratory tract infection (primarily pneumonia).[111] In the other two studies meropenem was compared with combinations of ceftazidime plus amikacin[112] or meropenem plus ciprofloxacin[113] in patients with ventilator-associated pneumonia (VAP). Pathogens isolated at enrolment in the latter open-label study included *S. aureus*, *H. influenzae*, *Enterobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp. (although patients with known *Pseudomonas* or MRSA colonization or infection, or who were immunocompromized, had been excluded from this trial prior to randomization [n = 740]).[113] The most common pathogens isolated at baseline in the other two trials were *P. aeruginosa*,[111,112] *H. influenzae*,[112] MRSA[111,112] and *K. pneumoniae*.[111] Diagnoses were based on clinical, microbiological and radiographic evidence.

Meropenem monotherapy was effective in the treatment of patients with nosocomial pneumonia,[113] and a useful alternative to conventional combination therapies of ceftazidime with tobramycin[111] or amikacin (table VI).[112]

In the study comparing meropenem with ceftazidime plus tobramycin, analyses of the clinically evaluable patients showed significantly higher rates of satisfactory clinical (89% vs 72%; $p = 0.04$) and bacteriological (89% vs 67%; $p = 0.006$) response at the EOT in meropenem recipients.[111] Of the pathogens isolated from evaluable patients in this study, 80% of Gram-positive aerobes and 93% of Gram-negative aerobes were eradicated or presumed eradicated with meropenem versus 65% and 79%, respectively, with ceftazidime plus tobramycin.[111]

In one of the studies enrolling patients with VAP, EOT satisfactory clinical and bacteriological response rates were significantly ($p < 0.05$) greater in meropenem than ceftazidime plus amikacin recipients.[112] Overall and attributed mortality rates did not significantly differ between patient groups treated with meropenem or ceftazidime plus amikacin.[112]

In the other study involving patients with suspected VAP, 28-day all-cause mortality (the primary endpoint; 18.7% overall) did not significantly differ between patients treated with meropenem (1 g three times daily) plus ciprofloxacin (400 mg twice daily) or meropenem monotherapy (relative risk in the combination therapy versus monotherapy group = 1.05; 95% CI 0.78, 1.42; $p = 0.74$).[113] Overall, 93.1% of patients in the combination therapy group versus 85.1% of those treated with meropenem alone ($p = 0.01$) were considered to have received adequate initial antibiotic therapy.[113] There were no significant between-group differences in clinical or bacteriological responses (data not presented) overall, or in the subgroup of patients (n = 56) infected with *Pseudomonas* spp., *Acinetobacter* spp. and/or another multidrug-resistant Gram-negative pathogen at enrolment. However, in this subgroup,

Table VI. Efficacy of meropenem (MEM) in patients (pts) with nosocomial pneumonia. Results of two randomized open-label trials that compared MEM monotherapy with ceftazidime (CAZ) plus tobramycin (TOB) or amikacin (AMK). Study drugs were administered intravenously. Response was evaluated in the clinically evaluable population at end of treatment (EOT) and/or follow-up (FU)

Study	No. of pts randomized	Treatment regimen	Treatment duration (mean, d) [recommended duration]	Clinical response (% pts) [evaluable pts][a]		Bacteriological response (% pts) [evaluable pts][a]	
				EOT	FU	EOT	FU
Alvarez-Lerma[112]	69	MEM 1 g tid	9.3 [10]	83 [57][c]	90 [31]	75 [51]	
	71	CAZ 2 g tid + AMK 15 mg/kg/d bid[b]	8.3/ 7.6 [10]	66 [59]	84 [25]	53 [45][d]	
Sieger et al.[111]	104	MEM 1 g tid	[2–28]	89 [63][f]	84 [19]	89 [63]	64 [11]
	107	CAZ 2 g tid + TOB 1 mg/kg tid[e]		72 [58]	92 [13]	67 [58]	78 [9]

a Primary efficacy endpoint.

b AMK dosage was modified according to degree of renal impairment.

c Between-group difference 16.7%; 95% CI 2.8, 30.5; p = 0.04.

d Odds ratio 1.4; 95% CI 1.02, 1.92; p = 0.03.

e Initial TOB loading dose of 1.5–2 mg/kg. TOB could be discontinued if the pre-treatment pathogen was shown to be susceptible to CAZ.

f Between-group difference 21.8%; 95% CI 7.5, 36.1; p = 0.006.

bid = twice daily; **tid** = three times daily.

the adequacy of initial antibiotic therapy (84.2% vs 18.8%; p < 0.001) and bacteriological eradication rates (64.1% vs 29.4%; p = 0.05) were significantly higher in the group of patients treated with combination therapy versus monotherapy.[113] The authors commented that empirical combination therapy may be a better strategy when treating patients at high risk of infection with multidrug resistant or other difficult-to-treat organisms.[113]

4.2 Complicated Intra-Abdominal Infection

Numerous randomized comparative trials have investigated the efficacy of intravenous meropenem 1.5 or 3 g/day in the treatment of patients with cIAI. Active comparators included doripenem,[79-81] imipenem/cilastatin,[82-85] cefotaxime/metronidazole,[86,87] and tobramycin/clindamycin.[88,89,108]

In all studies, enrolled patients were aged ≥18 years (mean age 30–62 years), were hospitalized with signs and symptoms of intra-abdominal infection requiring surgical intervention and had no known sensitivity to β-lactam antibacterial drugs. Disease severity was graded as mild to moderate,[83] moderate,[82] or moderate to severe,[86] with APACHE (Acute Physiology and Chronic Health Evaluation) II scores of ≤18,[82] ≤20[85] or ≤35.[108] Disease severity in one study ranged from mild to severe.[84] Concomitant nystatin or vancomycin treatment was permitted in one study.[108] The most common pathogens isolated at baseline in these trials were *E. coli*[79,82-87,108] and *B. fragilis*.[79,82,84,85,87,108]

Primary endpoints were clinical[85] or bacteriological response rates as assessed at EOT, and/or at follow-up visits between 1 and 6[82-88,108] weeks after the end of study therapy. The studies comparing meropenem and doripenem were noninferiority studies.[79-81]

Meropenem was as clinically and microbiologically effective as standard regimens of imipenem/cilastatin in the treatment of patients with cIAI (table VII).[82-85] Clinical response at EOT and or follow-up with meropenem 1.5 or 3 g/day was 90–98% and that with imipenem/cilastatin 1.5 or 3 g/day was 88–98%; the respective bacteriological responses were 84–98% with meropenem and 79–96% with imipenem/cilastatin.

Furthermore, clinical cure rates (84% vs 85%) and microbiological outcomes (85% vs 84%) did not differ between patients treated with meropenem or doripenem for cIAI (table VII) and doripenem was non-inferior to meropenem.[79-81]

In the trials comparing meropenem with cefotaxime/metronidazole,[86,87] meropenem achieved high

Table VII. Efficacy of meropenem (MEM) in patients (pts) with complicated intra-abdominal infections. Results of randomized (two double-blind,[79,108] six open-label)[82-87] trials that compared MEM with doripenem (DOR), imipenem/cilastatin (IPM), cefotaxime + metronidazole (CTX/MTR) and tobramycin + clindamycin (TOB/CLI). Study drugs were administered intravenously. Response was evaluated in the clinically evaluable population at end of treatment (EOT) and/or follow-up (FU)

Study	No. of pts randomized	Treatment regimen	Treatment duration (mean, d) [recommended duration]	Clinical response (% pts) [evaluable pts]		Bacteriological response (% pts) [evaluable pts]	
				EOT	FU	EOT	FU
vs DOR							
Solomkin et al.[79]a	476	MEM 1 g tid	[5–14]b		84 [309]c		85 [309]
	486	DOR 500 mg tid			85 [325]c		84 [325]
vs IPM							
Basoli et al.[83]	100	MEM 1 g tidd	7.2 [≥5]		95 [100]		98 [100]
	101	IPM 500 mg tid	6.7 [≥5]		98 [101]		96 [101]
Brismar et al.[85]	132	MEM 500 mg tid	5.4 [≤17]		98 [99]		95 [94]
	117	IPM 500 mg tid	5.1 [≤17]		96 [90]		96 [81]
Geroulanos[84]	116	MEM 1 g tidd	7.8 [5–10]	96 [82]	90 [63]	84 [82]	84 [62]
	116	IPM 1 g tidd	8.3 [5–10]	94 [88]	88 [66]	81 [88]	79 [70]
Zanetti et al.[82]	82	MEM 500 mg tidd	9.5 [5–10]	92 [71]	96 [52]	87e	
	79	IPM 500 mg qidd	8.4 [5–10]	94 [64]	91 [44]	93e	
vs CTX/MTR							
Huizinga et al.[86]	77	MEM 1 g tidd	6.5 [5–10]	91 [70]*	98 [54]	90 [48]	93 [42]
	83	CTX/MTR 2 g tid/500 mg tidd	6.0 [5–10]	100 [78]	97 [64]	92 [52]	92 [48]
Kempf et al.[87]	48	MEM 1 g tid	7.3 [5–10]	95 [43]**		94 [33]	
	46	CTX/MTR 2 g tid/5 g tid	6.9 [5–10]	75 [40]		81 [32]	
vs TOB/CLI							
Wilson[108]	132	MEM 1 g tid	7.2 [≥5]	96 [97]c	98 [66]f	96 [97]c	100 [57]f
	134	TOB/CLI 5 mg/kg/d tid/ 900 mg tid	7.5 [≥5]	93 [94]c	93 [56]f	93 [94]c	100 [49]f

a Results from this trial also published in two separate studies by Lucasti et al.[80] and Malafaia et al.[81]

b Pts could be switched to oral amoxicillin/clavulanate after nine doses of study drug.

c Primary efficacy endpoint.

d Dosages were modified according to degree of renal impairment.

e Percent of pathogens.

f Follow-up at 4–14 days. At 28- to 42-day follow-up visit, a satisfactory clinical response was seen in 94% of MEM and 100% of TOB/CLI recipients, and a satisfactory bacteriological response was seen in 94% of MEM and 100% of TOB/CLI recipients.

qid = four times daily; **tid** = three times daily; * p = 0.008 (95% CI for between-group difference−15, −2); ** p = 0.008 (95% CI for between-group difference 5.5, 35.2) vs comparator.

clinical and bacteriological response rates (table VII), and was associated with a significantly better overall clinical response rate at EOT in one trial;[87] clinical response rates were significantly higher in the cefotaxime/metronidazole recipients in the second trial.[86] Both treatments were effective against Gram-positive aerobes, Gram-negative aerobes and anaerobes.[86]

Meropenem and tobramycin/clindamycin did not differ with respect to efficacy in the treatment of patients with intra-abdominal bacterial infection predominantly secondary to complicated appendicitis (table VII).[108]

4.3 Septicaemia

Of the studies that investigated the efficacy of meropenem in the treatment of a wide range of serious bacterial infections, six[63,65,67,70-72] specifically described outcomes of subgroups of patients with septicaemia. Across trials, satisfactory clinical response rates for meropenem were 62–100% compared with 40–100% for comparator regimens (imi-

penem/cilastatin,[67,70] ceftazidime with or without amikacin,[71,72] and cefotaxime-based regimens).[63,65] Satisfactory bacteriological response rates were 85–100% with meropenem and 50–100% with comparator regimens.

In a study enrolling 153 patients with septicaemia secondary to a range of serious bacterial infections, meropenem was an effective empirical therapy and a useful alternative to ceftazidime with or without amikacin.[71] At treatment end, satisfactory clinical responses were achieved in 92% of clinically evaluable meropenem recipients and 94% of clinically evaluable patients receiving ceftazidime with or without amikacin.[71]

4.4 Febrile Neutropenia

The efficacy of intravenous meropenem as empirical monotherapy for neutropenic paediatric or adult patients with cancer has been assessed in numerous randomized comparative trials using cefepime,[90,91] imipenem/cilastatin,[114] ceftazidime with[95,96] or without amikacin,[92-94] and piperacillin plus tazobactam[98] as active comparators.

Across trials, patients generally had undergone cancer chemotherapy and presented with fever (>38.3°C or >37.9°C on two occasions within 12 hours) and neutropenia (absolute neutrophil count <500/mm^3 or <1000/mm^3 and expected to be <500/mm^3 within 24–48 hours); treatment durations were mostly ≥7 days.

In some trials, patients were permitted to re-enter studies more than once in the event of repeated episodes of neutropenia and fever.[93,114] Where indicated, concomitant glycopeptide[98] or aminoglycoside[98] antibacterials were allowed.

The most common bacterial pathogens isolated included *Staphylococcus* spp.,[90,91,93-96,98] *Streptococcus* spp.,[90,92-96,98] *E. coli*,[92-96,98] *Klebsiella* spp.[90,92-94,98] and *P. aeruginosa*.[92,96]

Meropenem was an effective empirical monotherapy in adult and paediatric patients with cancer-related febrile neutropenia (table VIII). No significant differences in initial response rates to unmodified treatment were seen in the majority of trials that compared meropenem with other established antibacterial regimens for the treatment of high-risk patients with febrile neutropenia at 72 hours or response at EOT with or without treatment modification.[90,91,94-96,114] In three trials, significantly ($p < 0.05$) greater initial treatment success rates at 72 hours occurred in meropenem than ceftazidime[92,93] or piperacillin/tazobactam[98] recipients. A meta-analysis of randomized comparative trials of empirical antibiotic monotherapy in patients with febrile neutropenia concluded that meropenem, imipenem/cilastatin, ceftazidime, and the piperacillin/tazobactam combination were suitable treatment options.[115] However, cefepime was associated with higher all-cause mortality than other β-lactam antibacterial agents and careful consideration prior to its use in this patient group was recommended, pending further investigation.[115]

4.5 Complicated Skin and Skin Structure Infection

The efficacy of intravenous meropenem 1.5 g/day has been compared with that of imipenem/cilastatin in hospitalized patients with cSSSI.[75,107] Enrolled patients (mean age 44–49 years) presented with complicated abscess or cellulitis,[75,107] infected ulcer,[75,107] surgical site or traumatic wound infection,[107] or other bacterial skin and soft tissue infections.[75,107] In one trial, patients who were subsequently found to have a pre-treatment pathogen resistant to meropenem or imipenem/cilastatin (including MRSA) were considered ineligible and were withdrawn from the study.[107] Underlying medical conditions included diabetes mellitus in approximately 30–37% of participants, and peripheral vascular disease in 5–10%.

Patients in the double-blind trial were permitted to switch to appropriate oral antibacterial therapy (most commonly amoxicillin/clavulanic acid and cefalexin) after at least 3 days of parenteral treatment, provided they demonstrated a clinical improvement in infection and were able to tolerate oral medications.[107] In the open-label study, routine oral antibacterials were prescribed at the end of study treatment where required.[75]

The primary endpoint in the double-blind trial, which was a noninferiority study, was the clinical response at post-treatment follow-up in the clinically evaluable and modified ITT populations.[107] Clinical response and bacterial response at EOT and

Table VIII. Efficacy of meropenem (MEM) in patients (pts) with febrile neutropenia. Results of randomized (one double-blind,[92] one single-blind[91] and seven open-label)[90,93-96,98,114] trials that compared MEM with imipenem/cilastatin (IPM), cefepime (FEP), ceftazidime (CAZ) ± amikacin (AMK), and piperacillin/tazobactam (TZP). Study drugs were administered intravenously. Response was evaluated in the clinically evaluable population at 72 hours and/or at end of treatment (EOT)

Study[a]	No. of evaluable episodes (pts)[b]	Treatment regimen	Treatment duration (mean, d) [recommended duration]	Unmodified treatment success at 72 h (% [no.] evaluable episodes)	Treatment success (± regimen modification) at EOT (% [no.] evaluable episodes)
vs IPM					
Shah et al.[114]	33 (31)	MEM 1 g tid	9.8 [7–28]	81 [31][c]	90 [31]
	33 (30)	IPM 1 g tid	8.6 [7–28]	80 [30][c]	80 [30]
vs FEP					
Kutluk et al.[91]	24 (30)	MEM 60 mg/kg/d tid	[≥7]	88 [24]	
	25	FEP 150 mg/kg/d tid		68 [25]	
Oguz et al.[90]	33 (25)	MEM 60 mg/kg/d tid	[≥7]	61 [33][c]	100 [33]
	32 (23)	FEP 150 mg/kg/d tid		66 [32][c]	100 [32]
vs CAZ/AMK					
de la Camara et al.[95]	46 (46)	MEM 1 g tid	[7–28]	80 [46][c]	89 [46]
	47 (47)	CAZ/AMK 2 g tid/ 15 mg/kg/d bid or tid	[7–28]	77 [47][c]	70 [47]
Cometta et al.[96]	483 (483)	MEM 1 g tid[d]	[≥7]	56 [483]	
	475 (475)	CAZ/AMK 2 g tid/ 20 mg/kg/d od	[≥7]	52 [475]	
Feld et al.[92]	206 (196)	MEM 1 g tid	8 [7]		54 [206]**[c]
	203 (215)	CAZ 2 g tid	7 [7]		44 [203][c]
Fleischhack et al.[93]	172 (164)	MEM 60 mg/kg/d tid[e]	6 [≥3]	56 [172]*[f]	99 [172]
	170	CAZ 100 mg/kg/d tid	7 [≥3]	40 [170][f]	99 [170]
The Meropenem Study Group of Leuven[94]	153 (112)	MEM 1 g tid	10.7		44 [153][c]
	151 (109)	CAZ 2 g tid	11.3		41 [151][c]
vs TZP					
Reich et al.[98]	116 (116)	MEM 1 g tid	[≥3]	64 [116]**[c]	94 [116]
	116 (116)	TZP 4.5 g tid	[≥3]	50 [116][c]	93 [116]

a Paediatric,[90,91,93] adult[92,94,95,98,114] or mixed[96] patient population.

b Some pts had more than one episode.

c Primary efficacy endpoint.

d MEM 20 mg/kg tid and CAZ 35 mg/kg tid for children weighing <50 kg.

e Each single dose did not exceed 1 g/day (MEM) or 2 g/day (CAZ).

f At 48 hours.

bid = twice daily; **od** = once daily; **tid** = three times daily; * p = 0.003 (95% CI for between-group difference 0.05, 0.26); ** p = 0.05 vs comparator.

post-treatment follow-up were the primary efficacy endpoints in the open-label study.[75]

The main pathogens isolated included methicillin-susceptible *S. aureus*,[75,107] *Streptococcus* spp.,[75,107] *E. coli*,[75,107] *E. faecalis*[107] and *P. aeruginosa*.[107] Approximately 50–60% of patients had infections caused by a single organism, predominantly Gram-positive aerobes. Thirty-eight percent of patients in one study,[107] and 47% in the other,[75] had evidence of polymicrobial infections at study entry. Most infections in patients with polymicrobial infections were due to a mixture of Gram-positive and Gram-negative aerobes.

Meropenem and imipenem/cilastatin were both effective treatments in patients with cSSSI (table IX).[75,107]

Clinical response rates were 94% and 92% with meropenem and imipenem/cilastatin in the double-blind study, and noninferiority of meropenem to imipenem/cilastatin was demonstrated (95% CI for

between-group difference −3.0, 5.6; estimated from a graph [table IX]).[107] Clinical response rates did not differ when patients were analysed by age or gender, pre-treatment pathogen, or infection diagnosis.[107] Furthermore, the frequency of surgical intervention (debridement, incision and drainage, amputation) did not significantly differ between treatment groups (27% of meropenem vs 25% of imipenem/cilastatin recipients; ITT analysis). A *post-hoc* subgroup analysis of this study based on the presence or absence of underlying diabetes showed similar clinical outcomes in the two subgroups.[116]

In the open-label study, clinical and bacteriological response rates did not significantly differ between treatment groups (table IX), nor when assessed according to infection diagnosis.[75] Eradication or presumed eradication rates for susceptible organisms were 82–100% in meropenem recipients and 50–100% in imipenem/cilastatin recipients.[75]

4.6 Bacterial Meningitis

The efficacy of intravenous meropenem 40 mg/kg (up to a maximum of 6 g/day[78]) in patients with bacterial meningitis has been evaluated in four randomized comparative trials, two involving paediatric patients[76,77] and two involving adults.[78] Data from the trials in adult patients are reported as combined data.[78] Enrolled patients were hospitalized with clinical symptoms and signs of bacterial meningitis,[76-78] caused by pathogens likely to be susceptible to the study medication.[77,78]

Patients with a previous history of meningitis,[76-78] polymicrobial meningitis,[77] and penetrating wounds, fractures or foreign bodies in the CNS,[76,78] or with known behavioural, motor, developmental and hearing deficits were excluded from these studies.[77]

Concurrent treatment with dexamethasone was permitted.[76-78] In one trial, a proportion of patients had been treated unsuccessfully with other antibacterials prior to study entry,[78] and in another, children who had received antibacterials within 24 hours of study entry were included provided CSF and blood samples had been obtained prior to enrolment and the initial assessment included documented evidence of bacterial meningitis.[77] Efficacy parameters included rates of death, cure without sequelae (neurological and/or audiological) or survival with sequelae. Comparator drugs were cefotaxime[76-78] and ceftriaxone.[78] The most common pathogens isolated were *H. influenzae*,[76-78] *N. meningitidis*,[76,78] *S. pneumoniae*[76-78] and *K. pneumoniae*.[77]

Meropenem was effective in the treatment of bacterial meningitis in both adult[78] and paediatric[77] patients (table X). When meropenem and cefotaxime were compared in children with bacterial meningitis who ranged from good to critical clinical condition, there were no significant between-group differences with respect to cure, survival with sequelae or death (table X).[77] The majority of sequelae were audiological; between-treatment differences in rate or severity of behavioural/devel-

Table IX. Efficacy of meropenem (MEM) in patients (pts) with complicated skin and skin structure infections. Results of two randomized trials (one double-blind,[107] the other open-label[75]) that compared MEM with imipenem/cilastatin (IPM). Study drugs were administered intravenously. Response was evaluated in the clinically evaluable population at end of treatment (EOT) and follow-up (FU)

Study	No. of pts randomized	Treatment regimen	Treatment duration (mean, d) [recommended duration][a]	Clinical response (% pts) [evaluable pts]		Bacteriological response (% pts) [evaluable pts]	
				EOT	FU	EOT	FU
Fabian et al.[107][b]	510	MEM 500 mg tid	5.8 [3–14]	94	86[c]		
	527	IPM 500 mg tid	6.0 [3–14]	92	83[c]		
Nichols et al.[75]	184	MEM 500 mg tid	7.1 [3–10]	98 [123][c]	92 [86]	94 [123][c]	92 [63]
	193	IPM 500 mg qid	7.3 [3–10]	95 [126][c]	89 [81]	91 [126][c]	82 [61]

a Oral antibacterial treatment continued for a further mean 9 days in Fabian et al.[107] and an unreported period in Nichols et al.[75]

b Noninferiority trial. MEM was considered noninferior to IPM if the lower limit of the two-sided 95% CI for the difference between the two treatments was no less than −10%.

c Primary efficacy endpoint.

qid = four times daily; **tid** = three times daily.

Table X. Efficacy of meropenem (MEM) in patients (pts) with bacterial meningitis. Results of two randomized trials (one single-blind, the other open-label), that compared MEM with cefotaxime (CTX) and ceftriaxone (CRO). Study drugs were administered intravenously. Response was evaluated in the clinically evaluable population at end of treatment (EOT) and/or follow-up (FU)

Study	No. of pts randomized	Treatment regimen	Treatment duration (mean, d)[b]	Clinical response (% pts) [evaluable pts][a]				Deaths (pts)	
				cure with no sequelae at EOT	cure with no sequelae at FU	survival with sequelae at EOT	survival with sequelae at FU	EOT	FU
Adult pts									
Schmutzhard	28	MEM 40 mg/kg tid[c]	10.6	30 [23]			70 [23]	3	
et al.[78]	17	CTX 75–100 mg/kg tid[c]	14.4	50 [12]			50 [12]	1	
	11	CRO 80 mg/kg od[c]	10.5	50 [10]			50 [10]	0	
Paediatric pts									
Odio et al.[77]	129	MEM 40 mg/kg tid	≥7	46 [79]	54 [76]	52 [79]	45 [76]	2	1
	129	CTX 45 mg/kg qid	≥7	56 [75]	58 [72]	40 [75]	40 [72]	3	1

a Primary efficacy endpoint.

b Minimum duration of treatment. Maximum duration was determined by the severity of the infection and the patient's clinical and microbiological response.

c To a maximum of MEM 6 g/day, CTX 12 g/day and CRO 4 g/day; initial CRO loading dose of 100 mg/kg.

od = once daily; **qid** = four times daily; **tid** = three times daily.

opmental or neurological sequelae were not significant at any timepoint (assessed at EOT, 5–7 weeks' follow-up and 5–7 months' follow-up).[77] In the study comparing meropenem, cefotaxime and ceftriaxone in adults with bacterial meningitis, clinical cure with or without sequelae was achieved in 100% of clinically evaluable meropenem recipients and 77% of cephalosporin recipients (5 of 22 patients failed to respond to treatment).[78]

All pre-treatment bacterial isolates were eradicated with meropenem treatment across trials.[76-78] In an early study comparing meropenem and cefotaxime in paediatric patients with bacterial meningitis, both agents were efficacious, achieving 100% bacteriological eradication of the causative pathogens from CSF.[76] CSF sterilization was achieved within 18–36 hours in the majority of patients.[76] In patients with culture-proven bacterial meningitis, clinical cure at EOT was achieved in all meropenem, and all but two cefotaxime recipients (both of these patients died during antibacterial treatment, but death was not considered to be drug related).[76] At follow-up, most patients (72% of meropenem and 81% of cefotaxime recipients) were cured with no evidence of sequelae, while 28% and 16% of patients in the respective treatment groups had audiological and/or neurological sequelae.[76] Audiological sequelae were evident in 13% of meropenem and 13% of cefotaxime recipients, and neurological sequelae occurred predominantly in patients with pre-existing neurological abnormalities.[76]

In the second study involving paediatric patients, bacteriological eradication was achieved in all but five subjects after 24–36 hours of treatment; *H. influenzae* was the infecting pathogen in these subjects with delayed sterilization.[76] One meropenem recipient who relapsed had head trauma prior to the initial diagnosis of meningitis was discharged from hospital clinically and bacteriologically cured, and was then readmitted 10 days later with a new episode of meningitis.[76]

According to pooled data from four trials enrolling 446 patients with bacterial meningitis, rates of clinical cure according to infecting organism in meropenem recipients were 71% for *S. pneumoniae*, 80% for β-lactamase-producing *H. influenzae*, 75% for non-β-lactamase-producing (or untested) *H. influenzae* and 86% for *N. meningitidis*.[8]

Approximately 60% of the 139 patients with positive CSF cultures also had positive blood cultures prior to receiving treatment. At 18–36 hours after commencing treatment, all cefotaxime and all but two meropenem recipients had negative blood cultures; however, CSF cultures taken at the same time in both of these patients were sterile.[76]

4.7 Complicated Urinary Tract Infection

Intravenous meropenem 500 mg three times daily was an effective alternative to imipenem/cilastatin 500 mg four times daily in a randomized, open-label study of 235 hospitalized patients with complicated UTI.[117] Infection was community-acquired in 92% of patients, had been present for a mean of 9.1 days prior to hospitalization, and required treatment with parenteral antibacterial drugs.[117] UTI was confirmed by positive urine culture; *E. coli* was the most commonly isolated pathogen. Mean treatment duration was 7.5 days for meropenem and 7.3 days for imipenem/cilastatin. Satisfactory clinical and bacteriological responses were seen in 99% and 90% of meropenem recipients, and in 99% and 87% of imipenem/cilastatin recipients.[117] Two meropenem and five imipenem/cilastatin recipients developed superinfections. The rates of relapse at ≥21 days after ceasing treatment did not significantly differ between groups, occurring in five meropenem and seven imipenem/cilastatin recipients.[117]

4.8 Obstetric and Gynaecological Infections

In hospitalized women with gynaecological or obstetric pelvic infections, intravenous meropenem 1.5 g/day was an effective alternative to imipenem/cilastatin[118] or the combination of clindamycin plus gentamicin[119] (table XI). Two studies of randomized open-label design enrolled patients (mean ages 26[119] and ≈40[118] years) with endometritis, pelvic inflammatory disease, pelvic cellulitis or other pelvic infection caused by at least one pathogen susceptible to the study treatments.[118,119] Infection was identified as hospital-acquired in 75% of patients in one study.[119] The most common organisms identified at baseline included *Bacteroides* spp., *Prevotella* spp., *E. coli* and *E. faecalis*.

Rates of satisfactory clinical and bacteriological responses in evaluable patients did not significantly differ between groups treated with meropenem or clindamycin/gentamicin (table XI). There were no significant differences between meropenem and the clindamycin/gentamicin combination in terms of pathogen eradication.[119] In the comparison between meropenem and imipenem/cilastatin, meropenem recipients achieved a higher clinical response rate at EOT. However, at the follow-up visit response rates did not differ (table XI).[118] All isolated organisms were eradicated at the end of meropenem or imipenem/cilastatin treatment, although the number of bacteriologically evaluable patients was small.[118]

4.9 Pulmonary Infection in Patients with Cystic Fibrosis

The efficacy of intravenous meropenem ≤6 g/day with or without tobramycin in the treatment of chronic pulmonary infection in patients aged ≥2 years with cystic fibrosis has been investigated in three randomized clinical trials using ceftazidime with or without tobramycin as the active comparator.[105,106,110] Patients were treated for acute exacerbation of chronic pulmonary infection,[105,106,110]

Table XI. Efficacy of meropenem (MEM) in patients (pts) with obstetric and gynaecological infections. Results of randomized, open-label trials that compared MEM with clindamycin + gentamicin (CLI/GEN) and imipenem/cilastatin (IPM). Study drugs were administered intravenously. Response was evaluated in the clinically evaluable population at end of treatment (EOT) and/or follow-up (FU)

Study	No. of pts randomized	Treatment regimen	Treatment duration (mean, d) [recommended duration]	Clinical response (% pts)[a] [evaluable pts]		Bacteriological response (% pts)[a] [evaluable pts]	
				EOT	FU	EOT	FU
Hemsell et al.[119]	259	MEM 500 mg tid	4.5 [4–10, ≤28]	88 [211]	98 [145]	88 [211]	95 [105]
	256	CLI/GEN 900 mg tid/1.5 mg/kg tid[b]	4.4 [4–10, ≤28]	90 [184]	100 [129]	86 [184]	100 [92]
Maggioni et al.[118]	52	MEM 500 mg tid	5.1	100* [46]	98 [40]		
	53	IPM 500 mg tid	4.7	90 [49]	97 [38]		

a Primary efficacy variable.

b Initial GEN loading dose of 2 mg/kg.

tid = three times daily; * p = 0.026 vs comparator.

Table XII. Efficacy of meropenem (MEM) in patients (pts) with pulmonary infection associated with cystic fibrosis. Results of two randomized trials (one open label,[106] one with both investigator-blinded and open-label arms)[110] that compared MEM + tobramycin (TOB) with ceftazidime (CAZ) + TOB. Study drugs were administered intravenously. Response was evaluated in the clinically evaluable population at end of treatment (EOT)[106,110]

Study	No. of pts randomized	Treatment regimen	Treatment duration (mean, d) [recommended duration]	Absolute change in % predicted FEV_1[b] [evaluable pts]	Relative change in % predicted FEV_1[b,c]	Responders (% pts)[a] [evaluable pts]	Bacterial sputum burden (log_{10} cfu/g)	
							baseline	EOT[d] [evaluable pts]
Blumer et al.[110]	19[e]	MEM ≤2 g tid + TOB[f]	15.6 [14]	7.5*	12.5	33 [18]	7.66	−2.8* [16]
	50[g]	MEM ≤2 g tid + TOB[f]	13.5 [14]	13.8***	38.8**	64 [47]	5.98	−3.6* [39]
	52[g]	CAZ ≤2 g tid + TOB[f]	14.1 [14]	11.1***	29.4**	58 [50]	5.98	−3.5* [44]
Latzin et al.[106][h]	63	MEM ≤2 g tid + TOB[f]	[14–21]	5.1 [59]			8.37	8.10 [59]
	64	CAZ 200–400 mg/kg/d bid or tid + TOB[f]		6.1 [59]			8.31	7.74 [59]

a Defined as patients with ≥15% relative increase from baseline in % predicted FEV_1.

b From baseline at EOT.

c Primary efficacy endpoint.

d Estimated from a graph; mean log_{10} change in sputum bacterial burden from baseline.[110]

e Open-label arm in pts with *Burkholderia cepacia* complex or CAZ-resistant *Pseudomonas aeruginosa* infection.

f TOB dosage adjusted to yield peak serum concentrations of ≥8 μg/mL[110] and trough serum concentrations of <2 μg/mL.[106,110]

g Investigator-blinded arms in pts with acute pulmonary exacerbations.

h Patients required therapy for chronic *P. aeruginosa* infection with no pulmonary exacerbation, *P. aeruginosa* infection with acute exacerbation, or eradication of *P. aeruginosa* after first infection.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 sec; **tid** = three times daily; * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0005$ vs baseline.

suppression of infection without exacerbation,[105,106] or eradication of *P. aeruginosa* when first detected in pulmonary secretions.[106] Where permitted, patients could be re-entered into trials more than once provided intervals between treatments were ≥8[106] or 12 weeks.[105]

Throughout studies, patients continued to receive standard care for cystic fibrosis, but non-study antimicrobial agents were not allowed.[105,106,110] Oral corticosteroids or nonsteroidal anti-inflammatory drugs were specifically excluded in one study.[106]

Meropenem with or without tobramycin significantly improved pulmonary function in the treatment of acute pulmonary infection,[105,106,110] and when utilized as a routine therapy to suppress chronic *P. aeruginosa* infection,[105] in patients with cystic fibrosis (table XII). In an early trial of meropenem versus ceftazidime monotherapy, in which repeated courses of treatment were permitted, clinical response rates at EOT were 98% and 90% in meropenem and ceftazidime recipients. At 4- to 6-week follow-up, the corresponding rates were 86% and 85%, and bacterial counts were reduced in 59 episodes and 20 episodes in the two respective groups.[105] Decreases in sputum production were considered to be clinically significant, with reductions from 20.8 to 8.7 mL in meropenem recipients and from 20.5 to 7.8 mL in ceftazidime recipients.[105]

The majority of improvement in pulmonary function (measured by change in forced expiratory volume in one second from baseline) occurred over the first 7 days of treatment in the combination therapy trial in which patients with acute pulmonary exacerbations received meropenem or ceftazidime plus tobramycin.[110] After 1 week of treatment, the proportion of responders was significantly greater in the patients in the investigator-blinded treatment arms

who were randomized to receive meropenem plus tobramycin or ceftazidime plus tobramycin (62% vs 44%; p = 0.04).[110] Both treatments were associated with significant decreases in sputum bacterial burden (table XII) and suppression of antibacterial-resistant *P. aeruginosa* emergence.[110]

In the third trial, both meropenem plus tobramycin and ceftazidime plus tobramycin combinations improved lung function and reduced bacterial sputum burden with no significant between-group difference (table XII). In addition, both treatments improved systemic inflammatory status from baseline (C-reactive protein decreased from 18.8 and 21.4 mg/L at baseline to 12.1 and 11.0 mg/L at EOT in meropenem plus tobramycin and ceftazidime plus tobramycin recipients). This was the only study to assess the effects of parenteral combination antibacterial therapy on inflammatory status.[106]

4.10 Severe Community-Acquired Pneumonia

Four randomized comparative trials have investigated the efficacy of intravenous meropenem in the treatment of severe CAP.[99,100,120] One reports combined data from two trials.[120] Comparators included imipenem/cilastatin,[99,100] ceftazidime[120] and combinations of clarithromycin with amikacin or ceftriaxone.[100] Enrolled patients were aged ≥18[99,120] or ≥70[100] years and were hospitalized with CAP requiring intravenous antibacterial treatment; diagnoses were confirmed by chest radiography.[99,100,120] In the study reporting combined data, ≈20% of patients needed mechanical ventilation.[120] The most common pathogens isolated at baseline included *S. pneumoniae*,[99,100,120] *P. aeruginosa*,[99,120] *S. aureus*,[99,100,120] *Haemophilus* spp.[99,100,120] and *K. pneumoniae*.[100]

Meropenem was an effective monotherapy in the empirical treatment of hospitalized patients with CAP, with satisfactory clinical responses seen in 87–91% of evaluable patients at EOT and 96–100% of patients at follow-up (table XIII).[99,100,120] Satisfactory bacteriological response rates were also high (table XIII). Neither rates significantly differed from the corresponding clinical and bacteriological response rates seen in patients treated with imipenem/cilastatin,[99,100] ceftazidime,[120] or combinations of clarithromycin + amikacin[100] or clarithromycin + ceftriaxone[100] (table XIII).

In the ventilated subgroup of patients, 86% and 82% of meropenem and ceftazidime recipients achieved satisfactory clinical responses at the EOT, with corresponding satisfactory bacteriological response rates of 89% and 87%.[101]

Table XIII. Efficacy of meropenem (MEM) in patients (pts) with community-acquired pneumonia. Results of four randomized open-label trials that compared MEM monotherapy with imipenem/cilastatin (IPM),[99,100] ceftazidime (CAZ)[120] and clarithromycin (CLR) plus ceftriaxone (CRO) or amikacin (AMK).[100] Study drugs were administered intravenously. Response was evaluated in the clinically evaluable population at end of treatment (EOT) and/or follow-up (FU)

Study	No. of pts randomized	Treatment regimen	Treatment duration (mean, d) [recommended duration]	Clinical response (% pts) [evaluable pts][a]		Bacteriological response (% pts) [evaluable pts]	
				EOT	FU	EOT	FU
Bartoloni et al.[99]	71	MEM 500 mg tid	10 [5–10]	89 [64]	100 [36]	100 [8]	100 [6]
	73	IPM 1 g bid	9.7 [5–10]	91 [66]	100 [32]	93 [14]	100 [5]
Finch et al.[120]	204	MER 500 mg tid	[5–28]	91 [198]		95 [113]	
	205	CAZ 1 g tid	[5–28]	90 [195]		92 [117]	
Romanelli et al.[100]	52	MEM 500 mg tid	8.7	87 [52]	96 [50]	77[a,b]	
	51	IPM 500 mg qid	9.1	86 [51]	100 [51]	71[b]	
	52	CLR 500 mg bid/ CRO 1 g bid	12.8	69 [52]	92 [51]	61[b]	
	49	CLR 500 mg bid/ AMK 250 mg bid	8.9	86 [49]	96 [47]	77[b]	

a Primary efficacy endpoint.

b Percentage of isolates eradicated/presumed eradicated.

bid = twice daily; **qid** = four times daily; **tid** = three times daily.

5. Tolerability

The tolerability profile of meropenem is well established, and the safety of the drug has been reviewed extensively elsewhere.[62,121,122] This section provides a brief overview of data from the most recently published in-depth review of the safety profile of meropenem, supplemented by data from the UK and US prescribing information for meropenem.[8,9]

Meropenem is generally well tolerated with favourable CNS and gastrointestinal tolerability when used in the treatment of serious bacterial infections.[62]

Data for the retrospective safety analysis was gathered from 54 predominantly international clinical studies in 6154 hospitalized patients with presumed or documented bacterial infections, including >1000 paediatric patients, who were treated with meropenem (6308 exposures). Three trials were noncomparative and 51 were randomized, controlled, prospective trials. Most trials (49 studies) were open-label in design; of the remainder, three were double-blind and two were single-blind. Comparators in the controlled studies included imipenem/cilastatin, cephalosporin-based regimens (with/without an aminoglycoside) or clindamycin plus an aminoglycoside (total of 4483 patients [4593 exposures]). Exclusion criteria included known hypersensitivity to β-lactam or other study drugs, marked hepatic disease, hepatic or renal failure and CNS disease or a history of seizures (except in trials enrolling patients with meningitis). Intravenous meropenem (adult patients: 500 mg or 1 g, three times daily, paediatric patients: 10, 20 or 40 mg/kg, three times daily) was administered as an infusion over 20–30 minutes or 5-minute bolus; comparator agents were given according to manufacturer recommendations (an intravenous infusion over 20–60 minutes is recommended for imipenem/cilastatin).[123] In three studies, meropenem was administered intramuscularly. Adverse events were self-reported or recorded by an observing clinician.[62]

The incidence of any adverse events reported with meropenem was 40% of patient exposures compared with 36–42% for the comparator regimens (imipenem/cilastatin, cephalosporin-based regimens and clindamycin-aminoglycoside-based regimens). Drug-related adverse events were reported in 16% of meropenem exposures and 12–21% of comparator regimen exposures. Diarrhoea, rash and/or nausea/vomiting were the most frequently reported adverse events possibly or probably related to treatment for all treatment regimens, although incidences were low (figure 1). For meropenem and cephalosporin- or clindamycin-based regimens, the

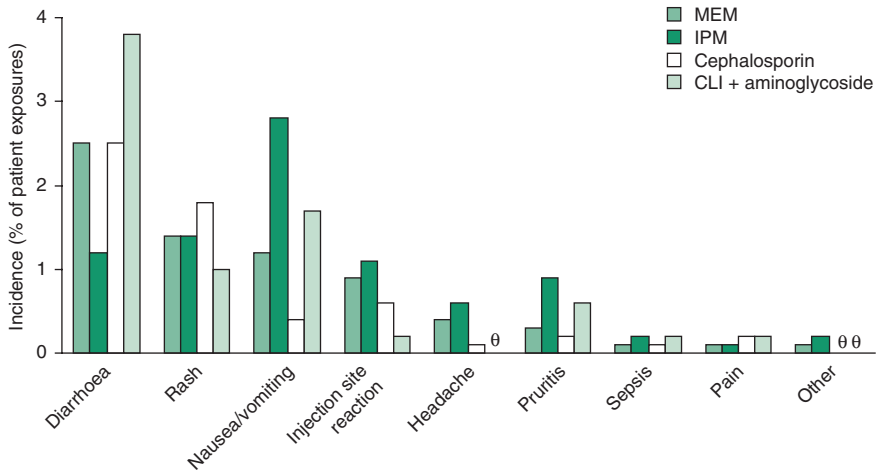

Fig. 1. Comparative tolerability of meropenem (MEM). Incidence of adverse events, possibly or probably related to treatment, occurring in >1% of patient exposures. Data were taken from safety analyses of 54 clinical trials in patients with serious bacterial infections. There were 6308 treatment exposures to MEM and 5898 exposures to comparator regimens. Other events included constipation, glossitis, hypotension, oral candidiasis and renal failure. θ = 0% of exposures; **CLI** = clindamycin; **IPM** = imipenem/cilastatin.[62]

most frequently reported adverse event was diarrhoea (2.5%, 2.5% and 3.8% of patient exposures, respectively), and for imipenem/cilastatin was nausea/vomiting (2.8% of patient exposures).[62]

In paediatric patients with serious bacterial infections, drug-related adverse events were seen in 16% of meropenem recipients and 11% of children treated with cephalosporin-based regimens.[62] The only meropenem-related adverse events occurring in >1% of patients were diarrhoea (4.5%) and rash (2.2%), with other gastrointestinal events being uncommon.[62]

Patient withdrawals due to adverse events were low with meropenem (2.5% of patient exposures) and the comparator regimens (1.1–3.2%), and the incidence of deaths (during or within 30 days of treatment) was 4.3% of patient exposures for meropenem and cephalosporin-based therapy, 5.9% for imipenem/cilastatin and 0% for clindamycin-based therapy.[62] There were no significant differences between the four treatment regimens in terms of the incidence of laboratory adverse events. Thrombocytosis was the most commonly occurring drug-related haematological event in meropenem recipients (1.3% of patient exposures vs 1.2–4.6% with comparator regimens). Increased ALT (3.7% vs 2.4–5.7% of patient exposures) and AST (2.9% vs 1.9–4.6%) levels were the most commonly occurring drug-related biochemical events with meropenem or the comparator regimens.[62] Other drug-related adverse events associated with meropenem treatment were uncommon (incidence of <0.1% of treatment exposures).[62]

Serious cross-hypersensitivity reactions to meropenem (and other β-lactams) have been seen in some patients with a history of penicillin hypersensitivity.[8] A review of retrospective studies of patients with documented or reported penicillin allergy found the incidence of carbapenem cross-hypersensitivity to be between 9% and 11%,[124] with no significant differences in the occurrence of allergic-type reactions seen between meropenem and imipenem/cilastatin.[125] There were no reports of meropenem-related anaphylaxis or Stevens-Johnson syndrome in any of the trials reviewed by Linden.[62]

5.1 CNS Adverse Events

Meropenem has good CNS tolerability and is the only carbapenem antibacterial to be approved for the treatment of bacterial meningitis, having a lower neurotoxic potential than imipenem/cilastatin.[121] While seizures and other adverse CNS events have been reported with meropenem treatment, events most commonly occurred in patients with CNS disorders, bacterial meningitis, and/or renal function impairment.[8] The incidence of drug-related seizures in patients with infections other than meningitis was 0.07% of patient exposures with meropenem, 0.04% with cephalosporin-based therapy, 0% with clindamycin plus aminoglycoside-based therapy, and 0.23% with imipenem/cilastatin. All meropenem recipients had pre-existing contributing factors.[8] No seizures were considered to be meropenem-related in a trial involving children with bacterial meningitis.[62]

6. Pharmacoeconomic Considerations

This section provides a brief overview of recent pharmacoeconomic analyses of meropenem in the treatment of serious bacterial infections in intensive care units (ICUs), including a fully published cost-utility analysis[126] and two cost-effectiveness analyses (available as abstracts plus posters).[127,128] The studies included are limited to well designed analyses that incorporated approved meropenem dosage regimens, appropriate comparative clinical data, cost values for the year 2002 or later and, for prospective studies, data for >50 patients in each treatment arm.

Pharmacoeconomic analyses from a healthcare payer perspective in the UK,[126] US[127] and Russia[128] predict that meropenem is a cost-effective therapy option relative to other antibacterials in patients with severe infection in ICUs (table XIV). Although the acquisition cost of meropenem was greater than that of comparator antibacterials in analyses[126,128] that considered the cost of hospital stay (table XIV), overall costs were lower with meropenem, as its higher clinical efficacy meant that meropenem recipients spent less time in an ICU[126,128] and/or did not require treatment with additional antibacterials.[128]

Table XIV. Summary of pharmacoeconomic analyses with meropenem (MEM) in the treatment of adult patients (pts) with serious bacterial infections in an intensive care unit (ICU). Analyses were conducted from a healthcare payer perspective. Where stated,[126,127] agents were administered intravenously

Key study design details	Results
Modelled cost-utility analysis in pts with severe infection in the UK[126]	
Comparators: MEM 1 g tid vs IPM 1 g tid Year of values: 2002/2003 Markov model with seven possible health states and a cycle length of 1 d Max treatment duration per infection or relapse: 14 d Max hospital stay: 104 d Source of input data: literature and expert opinion Costs included: daily drug acquisition costs (MEM £86 and IPM £72) and hospital (ICU, high-dependency unit and general ward) costs Annual benefit discount rate: 3.5%	MEM was dominant over IPM with regard to cost per QALY gained (i.e. less costly and more effective) Incremental cost per pt (MEM vs IPM): −£647 (£14 938 vs £15 585) Incremental benefit per pt (MEM vs IPM): 0.082 QALY (7.495 vs 7.413 QALYs gained) Varying the base-case pt age (59 y) changed the incremental benefit per pt (MEM vs IPM) to 0.207 QALYs gained if pt age was assumed to be 16 y and to 0.0003 QALYs gained if pt age was assumed to be 86 y (costs remained consistent regardless of pt age)
Modelled cost-effectiveness analysis in pts with *Pseudomonas aeruginosa* infection in the US[127]a	
Comparators: MEM 1 g tid vs IPM 0.5 g qid for 10 d Year of values: 2005 Model incorporating CFR obtained from pharmacodynamic modelling in 5000 pts as a surrogate marker for antibacterial efficacy in 100 pts Cost included: MEM and IPM acquisition based on either Hartford Hospital (Hartford [CT]) costs or US AWP	Hartford Hospital costs: MEM dominated IPM with regard to the cost per successfully treated pt (i.e. less costly [$US887 vs $US1126] and more effective [CFR 89.4% vs 87.8%]) US AWP: ICER (MEM vs IPM) per additional successfully treated pt $US309 (AWP $US1800 vs $US1306 and CFR 89.4% vs 87.8%)
Prospective cost-effectiveness analysis in pts with nosocomial infection in Russia[128]a	
Comparators: MEM 1.5–3.0 g/d (n = 62) vs conventional CAT (n = 73) Prospective, randomized, open-label, multicentre trial Cost included: antibacterial acquisition and ICU costs	Mean cost per successfully treated pt was lower with MEM than with CAT (€2008 vs €4432) MEM had a higher clinical response rate (81% vs 47%; $p < 0.01$) and lower mean direct medical costs per pt (€1619 vs €2066) than CAT Cost of MEM accounted for 59% and ICU costs accounted for 41% of the total direct cost per MEM recipient (no additional antibacterials required) Cost of initial CAT accounted for 26%, cost of additional antibacterials prescribed due to the ineffectiveness of initial therapy accounted for 26% and ICU costs accounted for 48% of the total direct cost per CAT recipient

a Available as abstract plus poster.

AWP = average wholesale price; **CAT** = combined antibacterial treatment (penicillin ± β-lactamase inhibitor, third- or fourth-generation cephalosporin or fluoroquinolone + aminoglycoside ± anaerobic agent); **CFR** = cumulative fraction of response (percent likelihood that tested regimen achieved the target pharmacodynamic exposure); **ICER** = incremental cost-effectiveness ratio; **IPM** = imipenem/cilastatin; **max** = maximum; **QALY** = quality-adjusted life-year; **qid** = four times daily; **tid** = three times daily.

In the UK cost-utility analysis,[126] meropenem dominated imipenem/cilastatin with regard to the cost per quality-adjusted life-year (QALY) gained in patients with severe infections (table XIV). The clinical response was higher with meropenem than with imipenem/cilastatin, resulting in predicted lower overall costs, fewer infection-related deaths in the ICU and a greater number of QALYs gained for meropenem relative to imipenem/cilastatin.[126] The results were robust to plausible changes in the input parameters, including patient age, costs and benefits. Of note, this model did not take into account the significant ($p = 0.02$) 13% relative reduction in all combined adverse events with meropenem relative to imipenem/cilastatin identified in the systematic review,[129] or the costs associated with the preparation and administration of the antibacterials. The analysis, therefore, potentially underestimated the cost difference between the two treatments, as imipenem/cilastatin would be associated with more frequent adverse events and also higher preparation and administration costs than meropenem.[126]

In preliminary cost-effectiveness analyses, meropenem was also predicted to be a cost effective initial empirical treatment with regard to the cost per successfully treated patient relative to imipenem/cilastatin in the treatment of *P. aeruginosa* infections in the US[127] and relative to conventional combination antibacterial treatments in high-risk patients with nosocomial infections in Russia[128] (table XIV).

Pharmacoeconomic analyses of meropenem, in common with all pharmacoeconomic analyses, are subject to a number of limitations. Pharmacoeconomic analyses based on clinical trials extrapolate the results of such trials to the general population; however, patient populations, rates of compliance and major outcomes in clinical trials may differ from those observed in real-life practice. Modelled analyses[126,127] rely on a number of assumptions and use data from a variety of sources, whereas prospective analyses[128] are limited by their sample size. Results of pharmacoeconomic analyses may not be applicable to other geographical regions because of differences in healthcare systems, medical practice and unit costs.

7. Dosage and Administration

Meropenem is available as a sterile powder (containing meropenem as the trihydrate blended with anhydrous sodium carbonate) for reconstitution prior to intravenous administration by either bolus injection over 5 minutes, or infusion over 15–30 minutes.[8] Following reconstitution with normal saline, meropenem is stable for 10 hours at controlled room temperature (15–25°C) and 48 hours at 4°C; stability in other infusion media ranges from 2–8 hours at room temperature and 8–48 hours under refrigeration.[3]

In adults, the dosage range is 1.5–6 g/day administered in three divided doses, generally with 500 mg to 1 g given every 8 hours dependent on the type and severity of infection, susceptibility of the pathogen, and patient condition. Exceptions to this general recommendation are in the treatment of chronic respiratory tract infection in patients with cystic fibrosis and for meningitis where 2 g should be given every 8 hours, and febrile neutropenia where the dosage should be 1 g every 8 hours.[9]

The adult dosage is recommended for use in children weighing over 50 kg. In infants and children aged between 3 months and 12 years who weigh <50 kg, the recommended dosage is 10–40 mg/kg intravenously every 8 hours, again dependent on type and severity of infection, susceptibility of the pathogen, and patient condition. For febrile neutropenia in children, a 20 mg/kg dose given every 8 hours is recommended, and 40 mg/kg should be given every 8 hours in children with meningitis and for chronic respiratory tract infection in association with cystic fibrosis.[3]

Local prescribing information should be consulted for more detailed information, including contraindications and precautions.

8. Place of Meropenem in the Management of Serious Bacterial Infections

Many studies have confirmed the importance of appropriate initial antimicrobial treatment to improve survival and reduce morbidity in patients with serious bacterial infections.[1,130-134] Where empirical antimicrobial therapy has been ineffective, the underlying cause is often bacterial resistance, coupled with inappropriate choice of antibacterial agent; this frequently contributes to subsequent patient morbidity and mortality.[131] Accordingly, there has been a shift in the recommendation regarding empirical therapy selection to the use of more broad-spectrum agents, often in combination with another drug of a different class, with a view to providing adequate cover for the anticipated pathogens.[40] Following identification and susceptibility testing, treatment is narrowed to target the causative pathogen.[1,131] Ultimately, this would mean appropriate therapy for the majority of patients, based on local resistance patterns.[40] As microbiological culture results are rarely available at the time of therapeutic decision making, the success or failure of treatment depends on current, accurate and local information on the bacterial aetiology of infection and susceptibility patterns.[135]

As well as careful selection of the appropriate antibacterial agent, the dose and duration of treatment, route of administration, and use of antimicrobial resistance surveillance data are important factors in the rational use of antibacterial drugs

necessary to avoid the development of ever-increasing resistance.[136] Surveillance programmes such as MYSTIC and SENTRY monitor antimicrobial resistance and play a vital role in the fight against pathogenic bacteria[40] in that the selection of suitable antibacterial agents for empirical therapy is based on results from surveillance studies.[39] An observed increase in antimicrobial resistance (including the emergence of multidrug-resistant strains) is driving the "right first time" approach to empirical therapy, and the use of the full-spectrum carbapenems.[137]

The carbapenems were identified as a new class of broad-spectrum β-lactam antibacterials in the 1970s.[2] Imipenem/cilastatin, meropenem and ertapenem are currently the most widely available carbapenems.[2] Doripenem is a new carbapenem that was approved in the US in late 2007 for use in adult patients with cIAI or complicated UTIs.[138] Meropenem, imipenem/cilastatin or doripenem are appropriate choices for serious bacterial infections, including nosocomial infections, because of their broad spectrum of antibacterial activity; however, ertapenem is best suited for use in community-acquired infections, because of an absence of activity against non-fermentative Gram-negative pathogens.[139]

Unlike imipenem/cilastatin, meropenem is stable to the human renal enzyme DHP-1 and does not need to be administered with cilastatin to achieve clinical efficacy.[140] It is also resistant to inactivation by most β-lactamases (section 2). Although the short $t_{1/2}$ of meropenem (section 3) requires 8-hourly administration, the low incidence of nausea and vomiting, even when administered rapidly (section 5), means that it can be administered as an intravenous bolus injection or a 15- to 30-minute infusion (section 7).[62] For imipenem/cilastatin, 250 or 500 mg doses should be administered as a 20- to 30-minute infusion; the 1 g dose should be administered as a 40- to 60-minute infusion (and the infusion rate slowed in patients who develop nausea).[62,123] Doripenem must also be administered as a 1-hour intravenous infusion.[138]

Plasma concentrations of meropenem are estimated to achieve an optimal bactericidal pharmacodynamic target attainment against most pathogens associated with nosocomial pneumonia, cIAI, nosocomial bloodstream infection, cSSSI and paediatric meningitis (section 2.5), and the drug has shown good penetration into a wide range of tissues, including lung, skin blister fluid, interstitial fluid, intra-abdominal tissues, peritoneal fluid and CSF (section 3). Meropenem demonstrated *in vitro* activity against a wide range of Gram-negative, Gram-positive and anaerobic organisms associated with serious or nosocomially acquired infections (section 2). This broad spectrum of activity means that it is very suitable for use as an empirical treatment for serious bacterial infections, such as nosocomial pneumonia, cIAI, septicaemia, cSSSI, complicated UTI, gynaecological and obstetric infections, pulmonary infections associated with with cystic fibrosis and serious CAP, especially as these conditions are often polymicrobial, including mixed aerobic/anaerobic, infections. Moreover, the good *in vitro* activity against organisms, such as meningococci, *N. meningitidis* and *H. influenzae* (section 2.2), good tolerability and low propensity for inducing seizures (section 5), means that meropenem is a valuable empirical treatment in paediatric patients aged ≥3 months who have been diagnosed with bacterial meningitis, and is the only carbapenem approved in this indication.[2]

Numerous well designed clinical trials have shown meropenem to be an effective and well tolerated treatment in patients with a wide range of serious bacterial infections. Meropenem was as effective as comparator antibacterials, such as imipenem/cilastatin in cIAI (section 4.2), febrile neutropenia (section 4.4), cSSSI (section 4.5), complicated UTI (section 4.7), obstetric or gynaecological infections (section 4.8) and severe CAP (section 4.10), clindamycin plus tobramycin or gentamicin in cIAI or obstetric or gynaecological infections, cefotaxime/metronidazole in cIAI, cefepime, ceftazidime plus amikacin in septicaemia or febrile neutropenia, and ceftazidime, clarithromycin plus ceftriaxone or amikacin in severe CAP. Meropenem also showed similar efficacy to cefotaxime in paediatric and adult patients with bacterial meningitis (section 4.6), and, with or without tobramycin, to ceftazidime with or without tobramycin in patients with cystic fibrosis experiencing acute pulmonary exacerbations (section 4.9). Meropenem showed greater efficacy than ceftazidime plus amikacin or tobramycin in patients with nosocomial pneumonia (section 4.1), and cef-

tazidime or piperacillin/tazobactam in febrile neutropenia (section 4.4).

Of interest, a meta-analysis of 27 trials of meropenem versus imipenem/cilastatin in the treatment of serious infections concluded that meropenem therapy was associated with greater clinical and bacteriological response rates and fewer adverse events than imipenem/cilastatin.[129]

Pharmacoeconomic analyses from a UK, US or Russian perspective estimated meropenem to be a cost-effective therapy relative to imipenem/cilastatin or conventional combination antibacterial treatments in patients with serious bacterial infections in ICUs (section 6); in the UK analysis, meropenem dominated imipenem/cilastatin.

IDSA guidelines support the use of meropenem as an option in the initial treatment of polymicrobial necrotizing infections of the skin, fascia and muscle, incisional surgical site infection after intestinal or genital tract surgery, infections after a human or an animal bite,[141] in severe intra-abdominal infections,[142] in high-risk patients with febrile neutropenia (with or without an aminoglycoside or vancomycin),[143] and as an option in combination with vancomycin in bacterial meningitis secondary to head trauma, a CSF shunt or neurosurgery.[144]

American Thoracic Society[145] and European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases[146] guidelines recommend meropenem as an option in the initial empirical therapy for nosocomial pneumonia and/or severe CAP (in combination with ciprofloxacin and where there is a risk of *P. aeruginosa* infection in Europe). European Urological Association guidelines recommend carbapenems (including meropenem) for the treatment of complicated UTIs such as urosepsis.[147] Meropenem plus tobramycin is an alternative option to more established β-lactams plus an aminoglycoside in the treatment of exacerbations of chronic pseudomonal respiratory infection in patients with cystic fibrosis.[148] Many of the alternative therapies recommended require the use of combination therapy; as mentioned, meropenem monotherapy demonstrated similar efficacy to some of these combination regimens.

Increased and/or inappropriate use of broad-spectrum antibacterial agents, such as the third-generation cephalosporins, in serious bacterial infections has resulted in a global increase in resistant bacterial strains, including ESBL- and AmpC-producing Enterobacteriaceae and multidrug-resistant *P. aeruginosa*.[1,132,133,140,149] Because of their broad spectrum of activity, carbapenems are considered first-line options in the empirical treatment of serious infections that may be associated with *P. aeruginosa* or ESBL-producing Enterobacteriaceae.[149] Importantly, meropenem retains activity against ESBL- and AmpC-producing Enterobacteriaceae, with little or no increase in MIC_{90} values when compared with wild-type Enterobacteriaceae, and has a minimal inoculum effect (sections 2.2 and 2.3).

Despite having MIC_{90} values ≥32 mg/L, cumulative global data from the MYSTIC programme for the period 2000–7 showed that all antibacterial agents studied (including meropenem) inhibited >50% of *P. aeruginosa* isolates (section 2.2); susceptibility results for *P. aeruginosa* did not change appreciably in Europe between 2002 and 2006.[21] For *Acinetobacter* spp., the other nonfermentative Gram-negative bacillus of interest, susceptibility for most antibacterial agents tested had decreased considerably between 2002 and 2006 (from 83–84% to 57–58% for the carbapenems), reflecting the increasing incidence of multidrug-resistant *Acinetobacter* strains in Europe.[21] Regardless, meropenem is an appropriate choice as empirical monotherapy for *Acinetobacter* spp. and *Pseudomonas* spp. infections, or as part of combination therapy, depending on the treating unit's antibiograms for these pathogens. *Acinetobacter* spp. are often implicated in nosocomial pneumonia (particularly VAP), nosocomial bloodstream infections, surgical site infection (including post-surgical meningitis) and UTI.[150] Group II carbapenems (including meropenem) are the standard of care for the treatment of serious bacterial infections caused by susceptible isolates of *Acinetobacter* spp.,[150] with combination antibacterial treatment often utilized for multidrug-resistant strains.[150,151]

As with other other currently available carbapenems, methicillin/oxacillin-resistant *S. aureus*, *E. faecium* and *S. maltophilia* are inherently resistant to meropenem (section 2.2).

Results from the OPTAMA programme (section 2.5) confirm that meropenem continues to be of value in a wide range of infections, including those

where nosocomial pathogens of concern, such as *E. coli*, *K. pneumoniae*, and *P. aeruginosa* are likely pathogens. Although the prevalence of acquired metallo-β-lactamases and carbapenemases is increasing (section 2.3),[152] carbapenem resistance remains uncommon and Enterobacteriaceae resistance to meropenem (and other carbapenems) is rare (section 2.3).[31,149] However, it is important that meropenem (and other carbapenems) are used appropriately as empirical treatment to limit the likelihood of increasing future resistance.[1] As well as the strategies discussed, using the most active, rather than the least active member of an antibacterial class has also been suggested as a strategy, to reduce the risk of mechanisms of resistance that affect the whole class developing.[134] Ideally, meropenem should be used only in a hospital setting in severe infections for the shortest possible duration.

In conclusion, meropenem has a broad spectrum of *in vitro* activity against Gram-positive and Gram-negative pathogens, including ESBL- and AmpC-producing Enterobacteriaceae. It has similar efficacy to comparator antibacterial agents, including imipenem/cilastatin in cIAI, febrile neutropenia, cSSSI, complicated UTI, obstetric or gynaecological infections, and severe CAP; clindamycin plus tobramycin or gentamicin in cIAI or obstetric or gynaecological infections; cefotaxime/metronidazole in cIAI; cefepime, ceftazidime plus amikacin in septicaemia or febrile neutropenia; and ceftazidime, clarithromycin plus ceftriaxone or amikacin in severe CAP. Meropenem has also shown similar efficacy to cefotaxime in paediatric and adult patients with bacterial meningitis, and to ceftazidime when both agents were administered with or without tobramycin in patients with cystic fibrosis experiencing acute pulmonary exacerbations. Meropenem showed greater efficacy than ceftazidime plus amikacin or tobramycin in patients with nosocomial pneumonia and ceftazidime or piperacillin/tazobactam in febrile neutropenia. Meropenem is well tolerated and has the advantage of being suitable for administration as an intravenous bolus or infusion. Its low propensity for inducing seizures means that it is suitable for treating bacterial meningitis, and is the only carbapenem approved in this indication. Thus, meropenem continues to be an important option for the empirical treatment of serious bacterial infections in hospitalized patients.

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