NAMA	:	
NRP/KELAS	:	
NO PRESENSI	:	

MODUL INFORMASI OBAT 1

SEMESTER GASAL 2019-2020

Oleh:

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Acknowledgement: Dr. Drs. A. Adji Prayitno S., M.S., Apt.

FAKULTAS FARMASI

UNIVERSITAS SURABAYA

TUJUAN PEMBELAJARAN

Modul ini dibuat untuk membantu mahasiswa dalam memahami konsep pelayanan informasi obat dan berlatih dalam memanfaatkan sumber informasi obat, khususnya sumber informasi tersier. Mahasiswa akan diajak untuk mengetahui kekhususan dari beberapa sumber informasi tersier. Modul ini hanya digunakan untuk pertemuan minggu ke 1 hingga ke 7. **Topik pertemuan ke 8 hingga ke 14 akan disampaikan lebih lanjut oleh Bapak Franciscus C. Kristanto, S.Si., M.Farm-Klin., Apt.**

METODE PEMBELAJARAN

Kuliah informasi obat I ini diselenggarakan dengan metode ceramah yang disertai dengan diskusi dua arah antara mahasiswa dan dosen pendamping. Beberapa pustaka yang dapat dipelajari sebelum pertemuan, antara lain:

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3. Hersh WR. Information retrieval: a health and biomedical perspective. 2nd ed. New York: Springer-Verlag; 2003.
4. Malone PR, Kier KL, Stanovich JE. Drug Information: A Guide for Pharmacists (3rd ed. McGrawhill; 2007.
5. Greenhalgh T. How to Read a Paper. 2nd ed. London: BMJ Books; 2001.
6. OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653.
7. Aronson JK, editor. Meyler's Side Effects of Drugs, Fifteenth Edition: The International Encyclopedia of Adverse Drug Reactions and Interactions 6 Volume Se. 15th ed. Elsevier Science; 2006.

8. Hansten PD, Horn JR. Drug interactions analysis and management 2007. St. Louis. Wolters Kluwer Health; 2007.
9. Baxter K. Stockley's drug interactions. 7th ed. London. Pharmaceutical Press; 2006.
10. Martin J, editor. British National Formulary 76. London: BMJ Group & RPS Publishing. 2018
11. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 10th edition. Philadelphia. Lippincott Williams & Wilkins; 2015.
12. Neonatal formulary: drug use in pregnancy and the first year of life. 5th edition. Victoria. Balckwell Publishing; 2007.
13. Martin J, editor. British National Formulary for Children. London: BMJ Group & RPS Publishing; 2018.
14. Selma TP, Beizer JL, Higbee MD. Lexi-Comp's Geriatric Dosage Handbook: including monitoring, clinical recommendations, and OBRA guidelines. 11th ed. Lexi Comp; 2005.
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16. Linden E, Wibowo YI, Irawati S, Setiawan E, editors. Pedoman Pemberian Obat Injeksi. Surabaya: PIOLK Ubaya; 2009.
17. Wibowo YI, Brata C, Wibowo IMP, editors. Pedoman Pemberian Obat Injeksi edisi 2. Surabaya: PIOLK Ubaya; 2018.
18. Ashley C & Dunleavy A, editor. The Renal Drug Handbook The Ultimate Prescribing Guide for Renal Practitioners. London: Taylor & Francis Group. 2019.
19. Klaassen CD, editor. Casarett & Doull's Toxicology the Basic Science of Poisons. 8th ed. United States: McGraw-Hill Education. 2013.
20. Hoffman et al. Goldfrank's Toxicologic Emergencies. 10th ed. United States: McGraw-Hill Education. 2015.

KOMPONEN PENILAIAN

	Komponen penilaian	**Nilai**
Pertemuan ke	**UTS (minggu ke 1 hingga ke 7)**	
3,4,5	Tugas individu pada modul	5 poin
6 atau 7	Tugas kelompok berupa makalah	20 poin
-	Ujian UTS	75poin
Total		**100 poin**

Nilai bonus informasi obat 1

Nilai bonus informasi obat 1 akan diberikan sebanyak 2 poin untuk setiap jawaban benar dari pertanyaan saat diskusi pada minggu ke 6 dan 7. Setiap mahasiswa maksimal dapat memperoleh **4 poin**.

Petunjuk tugas kelompok

1. Tugas berupa sebuah kasus yang dikerjakan di dalam kelompok yang masing-masing beranggotakan 4-5 orang mahasiswa. Pembagian kelompok akan ditentukan oleh dosen pendamping (1 kelas terbagi atas 16 kelompok)
2. Mahasiswa berlatih untuk menjawab kasus tersebut dengan menggunakan sumber informasi tersier yang sesuai. Jawaban kasus untuk setiap kelompok dikumpulkan dalam bentuk makalah.
3. Setiap jawaban pada makalah harus disertai dengan *screenshot* bagian pustaka yang digunakan.
4. Saran format makalah, antara lain:
    a. *Cover* makalah (berisi judul makalah, logo UBAYA, nama anggota kelompok dan NRP)
    b. Isi makalah ditulis dengan huruf Times New Roman berukuran 12 dengan margin masing-masing 3 cm pada kertas A4 dan dijilid
    c. Makalah diawali dengan kasus yang didapat dan dilanjutkan dengan informasi yang ditemukan pada sumber informasi tersier. Jawaban dapat ditampilkan dalam bentuk tabel
5. Tugas dikumpulkan saat pertemuan minggu ke 5 di masing-masing kelas. Bagi kelompok yang tidak mengumpulkan tugas tepat waktu, **tidak akan memperoleh nilai**.

6. Mahasiswa berhak menyatakan kepada dosen pendamping apabila ada mahasiswa dalam kelompok yang **tidak mengerjakan tugas** melalui surat yang menyatakan bahwa mahasiswa tersebut tidak mengerjakan tugas dan ditanda tangani oleh anggota lain dalam kelompok.

Instruksi khusus untuk perkuliahan minggu ke 3 hingga ke 5

1. Mahasiswa diharapkan membawa laptop untuk perkuliahan minggu ke 3 hingga ke 5 untuk mempermudah proses pembelajaran.
2. Mahasiswa diharapkan telah mencari dan mengunduh *ebook* terkait dengan pustaka yang akan dibahas di pertemuan ke 3 sampai 5. Detail *ebook* buku yang perlu dicari dapat dilihat pada halaman 14, 16, 19, dan 20.
3. Untuk perkuliahan minggu ke 3, mahasiswa **diwajibkan** mengerjakan modul halaman 14 (soal nomor 1) sebelum perkuliahan. Lampiran 1 (halaman 26) dapat digunakan untuk membantu menjawab soal nomor 1.
4. Untuk perkuliahan minggu ke 4, mahasiswa **diwajibkan** mengerjakan modul halaman 16 (soal nomor 1) sebelum perkuliahan. Lampiran 2 (halaman 35) dapat digunakan untuk membantu menjawab soal nomor 1.
5. Untuk perkuliahan minggu ke 5, mahasiswa **diwajibkan** mengerjakan modul halaman 19 dan 20 (soal nomor 1) sebelum perkuliahan. Lampiran 3 (halaman 44) dapat digunakan untuk membantu menjawab soal nomor 1.

JADWAL PERKULIAHAN

Minggu	SENIN (07.00-08.50)	RABU (08.50-10.40)	KAMIS (08.50-10.40)	KAMIS (13.00-14.50)	JUMAT (08.50-10.40)	TOPIK	Fasilitator
I	12 Agustus 2019	14 Agustus 2019	15 Agustus 2019		16 Agustus 2019	Pendahuluan: Peran Apoteker di dalam mendapatkan (*retrieve*) dan menyampaikan (*disseminate*) informasi obat Pengenalan Peran Pusat Informasi Obat **Pembagian tugas kelompok**	Dr. Cecilia Brata, M. Pharm., Apt.
II	19 Agustus 2019	21 Agustus 2019	22 Agustus 2019		23 Agustus 2019	Jenis-jenis sumber informasi dan *level of evidence*	
III	26 Agustus 2019	28 Agustus 2019	29 Agustus 2019		30 Agustus 2019	Sumber Informasi Tersier: Buku Umum **(Tugas di modul halaman 14-15)**	Steven Victoria H, M. Farm., Apt.
IV	2 September 2019	4 September 2019	5 September 2019		6 September 2019	Sumber Informasi Tersier: Buku Spesialis 1 **(Tugas di modul halaman 16-18)**	
V	9 September 2019	11 September 2019	12 September 2019		13 September 2019	Sumber Informasi Tersier: Buku Spesialis 2 **(Tugas di modul halaman 19-22)** **Pengumpulan tugas kelompok**	
VI	16 September 2019	18 September 2019	19 September 2019		20 September 2019	Presentasi tugas kelompok dan *feedback* tugas kelompok	Dr. Cecilia Brata, M. Pharm., Apt. Steven Victoria H, M. Farm., Apt.
VII	23 September 2019	25 September 2019	26 September 2019		27 September 2019	Presentasi tugas kelompok dan *feedback* tugas kelompok Pengenalan PICO dan merumuskan pertanyaan klinis	Dr. Cecilia Brata, M. Pharm., Apt. Steven Victoria H, M. Farm., Apt.
UTS (30 September - 11 Oktober 2019)							

TUGAS KELOMPOK

Kerjakan kasus sesuai dengan kelompok yang telah ditentukan.

KASUS 1 (untuk kelompok 1 dan 9)

Anda adalah seorang apoteker yang bekerja di bagian pusat informasi obat rumah sakit swasta di Surabaya. Suatu hari, Dokter YG menghubungi Anda dan menanyakan mengenai obat yang akan diresepkan untuk pasiennya, yaitu Bapak H yang berusia 67 tahun dengan gangguan kardiovaskular. Dokter YG meresepkan Concor® 1x5 mg, Plavix® 1x75 mg, dan Cholestat® 1x20 mg. Dokter YG menanyakan apakah keempat obat tersebut dapat digunakan secara bersamaan?

KASUS 2 (untuk kelompok 2 dan 10)

Anda adalah apoteker yang bekerja di Apotek "Cepat Sembuh". Suatu hari, salah seorang langganan apotek Anda, Ibu ET datang ke Apotek dan bertanya perihal anaknya (Anak BD) yang baru berusia 7 bulan (berat badan: 10 kg) yang terdiagnosis infeksi saluran kemih. Kemarin Anak BD sempat dibawa ke dokter dan mendapat resep sebagai berikut:

R/ Cotrimoxazole® suspensi
S 2 dd 1 cth

R/ Sanmol® sirup
S 3 dd 1 cth prn

Apakah dosis tersebut tepat untuk anak BD?

KASUS 3 (untuk kelompok 3 dan 11)

Seorang pasien wanita berusia 20 tahun masuk rumah sakit karena gangguan ginjal akut disertai dengan infeksi saluran kemih. Nilai kreatinin 17 mg/dl dan berdasarkan hasil perhitungan klirens kreatinin dengan mempertimbangkan berat badan dan tinggi badan pasien, diperoleh hasil <10 ml/min. Beberapa obat yang diresepkan oleh dokter, antara lain: Ciproxin® 3x200 mg secara intravena, Nexium® 1x80 mg secara intravena, dan ketorolac 2x20 mg prn secara intravena. Dokter meminta bantuan Anda untuk memeriksa obat apa yang memerlukan penyesuaian dosis pada pasien ini.

KASUS 4 (untuk kelompok 4 dan 12)

Suatu hari seorang perawat di ICU menelpon Anda di pusat informasi obat. Ia menanyakan beberapa hal mengenai 3 macam pengobatan yang diterima pasiennya, yaitu:

1. Apa pelarut yang sesuai untuk Cordarone® dan Vascon® yang akan diberikan secara infus pump?
2. Apakah Cordarone® (diberikan dalam infus pump), Vascon® (diberikan dalam infus pump), dan Flukonazol (secara infus) dapat diberikan secara *Y-site*?

Ia membutuhkan informasi tersebut agar obat dapat diberikan segera kepada pasien.

KASUS 5 (untuk kelompok 5 dan 13)

Ibu HG adalah seorang pasien berusia 45 tahun yang baru saja terdiagnosis jantung koroner. Dokter meresepkan Betablok® 1x50 mg, Ascardia® 1x80 mg, dan Lipitor® 1x20 mg. Sebelumnya, pasien sangat jarang mengkonsumsi obat karena takut terkena efek samping obat dan mengalami ketergantungan obat. Ia menanyakan efek samping apa saja yang mungkin terjadi bila menggunakan ketiga obat tersebut. Jawaban apa yang akan Anda sampaikan ke pasien terkait efek samping tiga obat tersebut?

KASUS 6 (untuk kelompok 6 dan 14)

Seorang wanita dengan usia kehamilan 22 minggu masuk rumah sakit karena merasa sakit kepala, mual, dan muntah. Berdasarkan pemeriksaan dokter, pasien mengalami *severe pre-eclamsia*. Beberapa obat yang diberikan pada pasien, antara lain: Magnesium sulfat secara intravena, OMZ® secara intravena, ascardia® secara per-oral, dan dopamet® secara per-oral. Dokter meminta bantuan Anda untuk memeriksa keamanan keempat obat tersebut untuk pasien.

KASUS 7 (untuk kelompok 7 dan 15)

Seorang dokter berencana memberikan infus Farsix® 3x2 ampul untuk pasiennya, Tn KL yang berusia 67 tahun. Ia menelpon Anda dan menanyakan beberapa hal, antara lain:

1. Apakah dosis furosemide sesuai untuk pasien?
2. Obat rencana diberikan secara infus, pelarut apa yang sesuai?
3. Apa saja efek samping furosemide yang patut diwaspadai?

KASUS 8 (untuk kelompok 8 dan 16)

Suatu hari seorang saudara menelpon Anda untuk menanyakan terkait penyakit yang ia alami. Ia baru saja terdiagnosis diabetes melitus dan memperoleh metformin 3x500 mg. Ia bertanya kepada Anda:

1. Apa itu diabetes melitus?
2. Apa penyebab diabetes melitus?
3. Obat apa saja yang bisa digunakan selain metformin?

MINGGU I - PENDAHULUAN

Lecture note

1. Berdasarkan perkuliahan hari ini, apa peran apoteker yang bekerja di pusat informasi obat?

2. Pada *setting* apa saja apoteker dapat berperan dalam pelayanan informasi obat?

3. Apa saja tahapan dalam memberikan informasi obat? Jelaskan!

4. Apa saja fungsi pusat informasi obat?

MINGGU II – JENIS SUMBER INFORMASI DAN *LEVEL OF EVIDENCE*

Lecture note

1. Jelaskan klasifikasi sumber informasi obat!

Jenis sumber informasi	Contoh

2. Jelaskan mengenai 6s model pada *level of evidence*!

3. Apakah ada hubungan antara jenis sumber informasi dan *level of evidence*? Jelaskan!

4. Apakah tipe pertanyaan berhubungan dengan desain penelitian yang digunakan?

MINGGU III – SUMBER INFORMASI TERSIER: BUKU UMUM

1. Informasi apa saja yang terdapat dimasing-masing buku?

Nama buku	**Informasi yang tersedia**
Martindale: the complete drug reference	
British National Formulary (BNF)	
Drug information handbook (DIH)	
AHFS *drug information*	
MIMS/ISO	
Medicines Compendium (emc.vhn.net)	

2. Berdasarkan kasus kelompok yang Anda peroleh, pustaka umum apa yang dapat Anda gunakan?

Pengarang	Nama buku	Jawaban yang diperoleh

MINGGU IV – SUMBER INFORMASI TERSIER: BUKU KHUSUS (1)

1. Informasi apa saja yang terdapat di buku-buku berikut ini?

Nama buku	Informasi yang tersedia
Meyler's side effect of drugs	
Stockley's drug interaction	
Stockley's herbal medicine interactions	
Drug interactions analysis and management	
Drug in pregnancy and lactation	

Nama buku	Informasi yang tersedia
British national formulary (BNF) for *children*	
Pediatric&neonatal dosage handbook	
Geriatric dosage handbook	

2. Informasi khusus apa yang menjadi ciri khas buku berikut ini?

Nama buku	Informasi spesifik pada buku
Meyler's side effect of drugs	
Stockley's drug interaction	
Stockley's herbal medicine interactions	
Drug interactions analysis and management	
Drug in pregnancy and lactation	
British national formulary (BNF) for *children*	
Pediatric&neonatal dosage handbook	
Geriatric dosage handbook	

3. Berdasarkan kasus kelompok yang Anda peroleh, pustaka spesifik apa yang dapat Anda gunakan?

Pengarang	Nama buku	Jawaban yang diperoleh

MINGGU V – SUMBER INFORMASI TERSIER: BUKU KHUSUS (2)

1. Informasi apa saja yang ada di buku-buku berikut ini?

Nama buku	**Informasi yang tersedia**
The renal drug handbook	
Handbook on injectable drugs	
Injectable medicines administration guide (UCLH)	
Injectable drug guide	
Gahart's intravenous medication	

Nama buku	**Informasi yang tersedia**
Pedoman pemberian obat injeksi edisi 2	
Pharmacotherapy: a pathophysiologic approach	
Applied therapeutics: the clinical use of drugs	
Symptoms in the pharmacy	
Casarett&Doull's toxicology	

2. Informasi khusus apa yang menjadi ciri khas buku berikut ini?

Nama buku	**Informasi spesifik pada buku**
The renal drug handbook	
Handbook on injectable drugs	
Injectable medicines administration guide (UCLH)	
Injectable drug guide	
Gahart's intravenous medication	
Pedoman pemberian obat injeksi edisi 2	
Pharmacotherapy: a pathophysiologic approach	
Appied therapeutics: the clinical use of drugs	
Symptoms in the pharmacy	
Casarett&Doull's toxicology	

3. Berdasarkan kasus kelompok yang Anda peroleh, pustaka apa yang dapat Anda gunakan?

Pengarang	**Nama buku**	**Jawaban yang diperoleh**

Pengarang	Nama buku	Jawaban yang diperoleh

MINGGU VI – DISKUSI KASUS

1. Tuliskan 2 pertanyaan yang ingin Anda tanyakan pada presentasi kasus hari ini?

2. Hal apa yang Anda pelajari dari presentasi kasus 5 kelompok pada pertemuan hari ini?

MINGGU VII – PICO DAN DISKUSI KASUS

1. Apa itu PICO? Apa fungsi PICO?

2. Tuliskan 2 pertanyaan yang ingin Anda tanyakan pada presentasi kasus hari ini?

3. Hal apa yang Anda pelajari dari 3 kelompok yang presentasi kasus pada pertemuan hari ini?

LAMPIRAN 1

(untuk minggu ke III)

Monografi obat (meropenem) di *Drug Information Handbook* (DIH)

Ulcerative colitis (unlabeled use):
Initial: 50 mg once daily; titrate dose up if clinical remission not achieved or down if leukopenia occurs (Lobel, 2004) **or**
Initial: 50 mg (25 mg if heterozygous for TPMT activity) once daily; titrate up to goal of 1.5 mg/kg (0.75 mg/kg if heterozygous for TPMT activity) if WBC >4000/mm^3 (and at least 50% of baseline) and LFTs and amylase are stable (Siegel, 2005) **or**
Maintenance: 1-1.5 mg/kg/day (Carter, 2004) **or**
Remission maintenance: 1.5 mg/kg/day (Danese, 2011)
Dosage adjustment with concurrent allopurinol: Reduce mercaptopurine dosage to 25% to 33% of the usual dose.
Dosage adjustment in TPMT-deficiency: Not always established; substantial reductions are generally required only in homozygous deficiency.
Elderly: Due to renal decline with age, initiate treatment at the low end of recommended dose range

Dosing adjustment in renal impairment: The manufacturer's labeling recommends starting with reduced doses in patients with renal impairment to avoid accumulation; however, no specific dosage adjustment is provided. The following adjustments have been used by some clinicians (Aronoff, 2007): Children:
Cl_{cr} <50 mL/minute/1.73 m^2: Administer every 48 hours
Hemodialysis: Administer every 48 hours
Continuous ambulatory peritoneal dialysis (CAPD): Administer every 48 hours
Continuous renal replacement therapy (CRRT): Administer every 48 hours

Dosing adjustment in hepatic impairment: The manufacturer's labeling recommends considering a reduced dose in patients with hepatic impairment; however, no specific dosage adjustment is provided.

Dietary Considerations Should not be administered with meals.

Administration Preferably on an empty stomach (1 hour before or 2 hours after meals)

For the treatment of ALL in children (Schmiegelow, 1997): Administration in the evening has demonstration superior outcome; administration with food did not significantly affect outcome.

Monitoring Parameters CBC with differential (weekly initially, although clinical status may require increased frequency); bone marrow exam (to evaluate marrow status), liver function tests (weekly initially, then monthly; monitor more frequently if on concomitant hepatotoxic agents), renal function, urinalysis; consider TPMT genotyping to identify TPMT defect (if severe toxicity occurs)
For use as immunomodulatory therapy in CD or UC, monitor CBC with differential weekly for 1 month, then biweekly for 1 month, followed by monitoring every 1-2 months throughout the course of therapy. LFTs should be assessed every 3 months. Monitor for signs/symptoms of malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss).

Test Interactions TPMT testing: Recent transfusions may result in a misinterpretation of the actual TPMT activity. Concomitant drugs may influence TPMT activity in the blood.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product
Tablet, oral: 50 mg
Purinethol®: 50 mg [DSC] [scored]

Extemporaneous Preparations Hazardous agent: Use appropriate precautions for handling and disposal.

A 50 mg/mL oral suspension may be prepared in a vertical flow hood with tablets and a mixture of sterile water for injection (SWFI), simple syrup, and cherry syrup. Crush thirty 50 mg tablets in a mortar and reduce to a fine powder. Add ~5 mL SWFI and mix to a uniform paste; then add ~10 mL simple syrup; mix while continuing to add cherry syrup to make a final volume of 30 mL; transfer to a calibrated bottle. Label "shake well" and "caution chemotherapy". Stable for 35 days at room temperature.
Allabadi HM, Romanick M, Desai S, et al, "Effect of Buffer and Antioxidant on Stability of a Mercaptopurine Suspension," *Am J Health Syst Pharm*, 2008, 65(5):441-7.

◆ **6-Mercaptopurine (error-prone abbreviation)** See Mercaptopurine *on page 1176*

◆ **Mercapturic Acid** *see* Acetylcysteine *on page 35*

Meropenem (mer oh PEN em)

Brand Names: U.S. Merrem® I.V.
Brand Names: Canada Merrem®
Pharmacologic Category Antibiotic, Carbapenem
Additional Appendix Information
Dosing Considerations for the Critically-Ill Patient With Morbid Obesity *on page 2153*

Use
Treatment of intra-abdominal infections (complicated appendicitis and peritonitis); treatment of bacterial meningitis in pediatric patients ≥3 months of age caused by *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*; treatment of complicated skin and skin structure infections caused by susceptible organisms

Canadian labeling: Additional indications (not in U.S. labeling): Treatment of lower respiratory tract infections (community-acquired and nosocomial pneumonias), complicated urinary tract infections, gynecologic infections (excluding chlamydia), and septicemia; treatment of bacterial meningitis in adults caused by *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* (use in adult meningitis based on pediatric data)

Unlabeled Use *Burkholderia pseudomallei* (melioidosis), febrile neutropenia, liver abscess, otitis externa

Pregnancy Risk Factor B

Pregnancy Considerations Adverse events were not observed in animal reproduction studies. Incomplete transplacental transfer of meropenem was found using an ex *vivo* human perfusion model.

Lactation Excreted in breast milk/use caution

Contraindications Hypersensitivity to meropenem, any component of the formulation, or other carbapenems (eg, doripenem, ertapenem, imipenem); patients who have experienced anaphylactic reactions to other beta-lactams

Warnings/Precautions Serious hypersensitivity reactions, including anaphylaxis, have been reported (some without a history of previous allergic reactions to beta-lactams). Carbapenems have been associated with CNS adverse effects, including confusional states and seizures (myoclonic); use caution with CNS disorders (eg, brain lesions and history of seizures) and adjust dose in renal impairment to avoid drug accumulation, which may increase seizure risk. Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. Use with caution in patients with renal impairment; dosage adjustment required in patients with moderate-to-severe renal dysfunction. Thrombocytopenia has been reported in patients with renal dysfunction. Lower doses (based upon renal function) are often required in the elderly. May decrease divalproex sodium/valproic acid concentrations leading to breakthrough seizures; concomitant use not recommended. Alternative antimicrobial agents should be considered; if concurrent meropenem is necessary, consider additional antiseizure medication.

Adverse Reactions

1% to 10%:

Central nervous system: Headache (2% to 8%), pain (≤5%)

Dermatologic: Rash (2% to 3%, includes diaper-area moniliasis in infants), pruritus (1%)

Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Diarrhea (4% to 7%), nausea/vomiting (1% to 8%), constipation (1% to 7%), oral moniliasis (up to 2% in pediatric patients), glossitis (1%)

Hematologic: Anemia (≤6%)

Local: Inflammation at the injection site (2%), phlebitis/thrombophlebitis (1%), injection site reaction (1%)

Respiratory: Apnea (1%), pharyngitis, pneumonia

Miscellaneous: Sepsis (2%), shock (1%)

<1% (Limited to important or life-threatening): Abdominal enlargement, abdominal pain, agitation/delirium, agranulocytosis, alkaline phosphatase increased, ALT increased, AST increased, anemia (hypochromic), angioedema, anorexia, anxiety, aPTT decreased, asthma, back pain, bilirubin increased, bradycardia, BUN increased, cardiac arrest, chest pain, chills, cholestatic jaundice/jaundice, confusion, cough, creatinine increased, depression, diaphoresis, dizziness, dyspepsia, dyspnea, dysuria, eosinophilia, epistaxis, erythema multiforme, fever, flatulence, gastrointestinal hemorrhage, hallucinations, heart failure, hematuria, hemoglobin/hematocrit decreased, hemolytic anemia, hemoperitoneum, hepatic failure, hyper-/hypotension, hypervolemia, hypokalemia, hypoxia, ileus, injection site edema, injection site pain, insomnia, intestinal obstruction, LDH increased, leukocytosis, leukopenia, melena, MI, nervousness, neutropenia, paresthesia, pelvic pain, peripheral edema, platelets decreased/increased, pleural effusion, PT decreased, pulmonary edema, positive Coombs test, pulmonary embolism, renal failure, respiratory disorder, seizure, skin ulcer, somnolence, Stevens-Johnson syndrome, syncope, tachycardia, toxic epidermal necrolysis, urinary incontinence, urticaria, vaginal moniliasis, weakness, WBC decreased, whole body pain

Drug Interactions

Metabolism/Transport Effects None known.

Avoid Concomitant Use

Avoid concomitant use of Meropenem with any of the following: BCG; Probenecid

Increased Effect/Toxicity

The levels/effects of Meropenem may be increased by: Probenecid

Decreased Effect

Meropenem may decrease the levels/effects of: BCG; Divalproex; Sodium Picosulfate; Typhoid Vaccine; Valproic Acid

Stability Dry powder should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F). Meropenem infusion vials may be reconstituted with SWFI or a compatible diluent (eg, NS). The 500 mg vials should be reconstituted with 10 mL, and 1 g vials with 20 mL. May be further diluted with compatible solutions for infusion. Consult detailed reference/product labeling for compatibility.

Injection reconstitution: Stability in vial when constituted (up to 50 mg/mL) with:

SWFI: Stable for up to 2 hours at controlled room temperature of 15°C to 25°C (59°F to 77°F) or for up to 12 hours under refrigeration.

Sodium chloride: Stable for up to 2 hours at controlled room temperature of 15°C to 25°C (59°F to 77°F) or for up to 18 hours under refrigeration.

Dextrose 5% Injection: Stable for 1 hour at controlled room temperature of 15°C to 25°C (59°F to 77°F) or for 8 hours under refrigeration.

Infusion admixture (1-20 mg/mL): Solution stability when diluted in NS is 4 hours at controlled room temperature of 15°C to 25°C (59°F to 77°F) or 24 hours under refrigeration. Stability in D_5W is 1 hour at controlled room temperature of 15°C to 25°C (59°F to 77°F) or 4 hours under refrigeration. For other diluents, see prescribing information.

Mechanism of Action Inhibits bacterial cell wall synthesis by binding to several of the penicillin-binding proteins, which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis; bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested

Pharmacodynamics/Kinetics

Distribution: V_d: Adults: 15-20 L, Children: 0.3-0.4 L/kg; penetrates well into most body fluids and tissues; CSF concentrations approximate those of the plasma

Protein binding: ~2%

Metabolism: Hepatic; metabolized to open beta-lactam form (inactive)

Half-life elimination:

Normal renal function: 1-1.5 hours

Cl_{cr} 30-80 mL/minute: 1.9-3.3 hours

Cl_{cr} 2-30 mL/minute: 3.82-5.7 hours

Time to peak, tissue: 1 hour following infusion

Excretion: Urine (~70% as unchanged drug)

Dosage

Usual dosage ranges:

Children ≥3 months: I.V.: 30-120 mg/kg/day divided every 8 hours (maximum dose: 6 g/day)

Adults: I.V.: 1.5-6 g/day divided every 8 hours

Extended infusion method (unlabeled dosing): I.V.: 0.5-2 g over 3 hours every 8 hours (Crandon, 2011; Dandekar, 2003). **Note:** Dosing used at some centers and is based on pharmacokinetic/pharmacodynamic modeling and not clinical efficacy data.

Indication-specific dosing:

Children ≥3 months (<50 kg): I.V.:

Febrile neutropenia (unlabeled use): 20 mg/kg every 8 hours (maximum dose: 1 g every 8 hours)

Intra-abdominal infections (complicated): 20 mg/kg every 8 hours (maximum dose: 1 g every 8 hours)

Meningitis: 40 mg/kg every 8 hours (maximum dose: 2 g every 8 hours)

Pneumonia (community-acquired): Canadian labeling (not in U.S. labeling): 10-20 mg/kg every 8 hours (maximum dose: 1 g every 8 hours)

Skin and skin structure infections:

Complicated: U.S. labeling: 10 mg/kg every 8 hours (maximum dose: 500 mg every 8 hours)

Uncomplicated: Canadian labeling (not in U.S. labeling): 10-20 mg/kg every 8 hours (maximum dose: 1 g every 8 hours)

Urinary tract infection (complicated): Canadian labeling (not in U.S. labeling): 10 mg/kg every 8 hours (maximum dose: 500 mg every 8 hours)

Children >50 kg and Adults: I.V.:

***Burkholderia pseudomallei* (melioidosis) (unlabeled use), *Pseudomonas*:** 1 g every 8 hours

Cholangitis, intra-abdominal infections, complicated: 1 g every 8 hours. **Note:** 2010 IDSA guidelines recommend treatment duration of 4-7 days (provided source controlled). Not recommended for mild-to-moderate, community-acquired intra-abdominal infections due to risk of toxicity and the development of resistant organisms (Solomkin, 2010).

Febrile neutropenia, otitis externa, pneumonia (unlabeled uses): 1 g every 8 hours

MEROPENEM

Liver abscess (unlabeled use): 1 g every 8 hours for 2-3 weeks, then oral therapy for duration of 4-6 weeks
Meningitis: Canadian labeling (not in U.S. labeling): 2 g every 8 hours
Mild-to-moderate infection, other severe infections (unlabeled use): 1.5-3 g/day divided every 8 hours
Pneumonia (community-acquired): Canadian labeling (not in U.S. labeling): 500 mg every 8 hours
Skin and skin structure infections:
Complicated: U.S. labeling: 500 mg every 8 hours; diabetic foot: 1 g every 8 hours
Uncomplicated: Canadian labeling (not in U.S. labeling): 500 mg every 8 hours
Urinary tract infections (complicated): Canadian labeling (not in U.S. labeling): 500 mg every 8 hours. **Note:** Up to 1 g every 8 hours may be administered (Pallett, 2010).
Adults: Canadian labeling (not in U.S. labeling): I.V.:
Gynecologic and pelvic inflammatory disease: 500 mg every 8 hours
Pneumonia (nosocomial): 1 g every 8 hours
Septicemia: 1 g every 8 hours

Dosing adjustment in renal impairment:
Children (unlabeled dosing; Aronoff, 2007):
GFR 30-50 mL/minute: Administer 20-40 mg/kg every 12 hours
GFR 10-29 mL/minute: Administer 10-20 mg/kg every 12 hours
GFR <10 mL/minute: Administer 10-20 mg/kg every 24 hours
Intermittent hemodialysis (IHD): 10-20 mg/kg every 24 hours (administer after hemodialysis on dialysis days)
Peritoneal dialysis (PD): 10-20 mg/kg every 24 hours
Continuous renal replacement therapy (CRRT): 20-40 mg/kg every 12 hours

Adults:
Cl_{cr} 26-50 mL/minute: Administer recommended dose based on indication every 12 hours
Cl_{cr} 10-25 mL/minute: Administer one-half recommended dose based on indication every 12 hours
Cl_{cr} <10 mL/minute: Administer one-half recommended dose based on indication every 24 hours
Alternative dosing recommendations: (unlabeled dosing; Aronoff, 2007):
GFR 10-50 mL/minute: Administer recommended dose (based on indication) every 12 hours
GFR <10 mL/minute: Administer recommended dose (based on indication) every 24 hours
Intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): Meropenem and its metabolite are readily dialyzable: 500 mg every 24 hours **Note:** Dosing dependent on the assumption of 3 times/week, complete IHD sessions.
Peritoneal dialysis (unlabeled dose): Administer recommended dose (based on indication) every 24 hours (Aronoff, 2007).
Continuous renal replacement therapy (CRRT) (Heintz, 2009; Trotman, 2005): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug concentrations in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1-2 L/hour and minimal residual renal function) and should not supersede clinical judgment:
CVVH: Loading dose of 1 g followed by either 0.5 g every 8 hours **or** 1 g every 12 hours
CVVHD/CVVHDF: Loading dose of 1 g followed by either 0.5 g every 6-8 hours **or** 1 g every 8-12 hours
Note: Consider giving patients receiving CVVHDF dosages of 750 mg every 8 hours **or** 1500 mg every 12 hours (Heintz, 2009). Substantial variability exists in various published recommendations, ranging from 1-3 g/day in 2-3 divided doses. One gram every 12 hours achieves a target trough of ~4 mg/L.
Dietary Considerations Some products may contain sodium.
Administration Administer I.V. infusion over 15-30 minutes; I.V. bolus injection (5-20 mL) over 3-5 minutes. Extended infusion administration (unlabeled dosing): Administer over 3 hours (Crandon 2011; Dandekar, 2003). **Note:** Must consider meropenem's limited room temperature stability if using extended infusions.
Monitoring Parameters Perform culture and sensitivity testing prior to initiating therapy. Monitor for signs of anaphylaxis during first dose. During prolonged therapy, monitor renal function, liver function, CBC.
Test Interactions Positive Coombs' [direct]
Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.
Injection, powder for reconstitution: 500 mg, 1 g
Merrem®: I.V.: 500 mg [contains sodium 45.1 mg as sodium carbonate (1.96 mEq)]
Merrem®: I.V.: 1 g [contains sodium 90.2 mg as sodium carbonate (3.92 mEq)]

◆ Merrem® (Can) *see* Meropenem *on page 1178*
◆ Merrem® I.V. *see* Meropenem *on page 1178*

Mesalamine (me SAL a meen)

Brand Names: U.S. Apriso™; Asacol®; Asacol® HD; Canasa®; Lialda®; Pentasa®; Rowasa®; sfRowasa™
Brand Names: Canada 5-ASA; Asacol®; Asacol® 800; Mesasa®; Mezavant®; Novo-5 ASA; Novo-5 ASA-ECT; Pentasa®; Salofalk®; Salofalk® 5-ASA
Index Terms 5-Aminosalicylic Acid; 5-ASA; Fisalamine; Mesalazine
Pharmacologic Category 5-Aminosalicylic Acid Derivative
Use
Oral:
Asacol®, Lialda®, Mezavant®, Pentasa®: Treatment and maintenance of remission of mildly- to moderately-active ulcerative colitis
Apriso™: Maintenance of remission of ulcerative colitis
Asacol® HD: Treatment of moderately-active ulcerative colitis
Rectal: Treatment of active mild-to-moderate distal ulcerative colitis, proctosigmoiditis, or proctitis
Pregnancy Risk Factor B/C (product specific)
Pregnancy Considerations Animal reproduction studies with mesalamine have not demonstrated teratogenicity or fertility impairment. Dibutyl phthalate (DBP) is an inactive ingredient in the enteric coating of Asacol® and Asacol® HD; adverse effects in male rats were noted at doses greater than the recommended human dose. Mesalamine is known to cross the placenta. An increased rate of congenital malformations has not been observed in human studies. Preterm birth, still birth and decreased birth weight have been observed; however, these events may also be due to maternal disease.
Lactation Enters breast milk/use caution
Contraindications Hypersensitivity to mesalamine, aminosalicylates, salicylates, or any component of the formulation

Canadian labeling (Mezavant®): Additional contraindications: Severe renal impairment (GFR <30 mL/minute/1.73m²); severe hepatic impairment

Monografi obat (meropenem) di AHFS *DRUG INFORMATION*

imipenem and no accumulation of cilastatin appears to occur following repeated (i.e., every 12 hours) IM doses.

If imipenem is administered alone, the drug is partially hydrolyzed in the kidneys by DHP I to a microbiologically inactive metabolite and only 5–43% of the dose is excreted unchanged in urine. However, when cilastatin sodium is administered concurrently with imipenem in a 1:1 ratio as a suspension or solution, approximately 50 or 70% of the imipenem dose, respectively, and approximately 75% of the cilastatin dose are excreted unchanged in urine within 10 hours. In adults, maximal urinary concentrations of active imipenem are obtained with a 4:1 ratio of imipenem to cilastatin; however, a 1:1 ratio of imipenem to cilastatin ensures that DHP I is inhibited for up to 8–10 hours. Urinary imipenem concentrations may be greater than 10 mcg/mL for up to 8 hours following a single 500-mg IV dose of imipenem and cilastatin sodium. Urinary imipenem concentrations exceed 10 mcg/mL for at least 12 hours after IM administration of 500- or 750-mg doses of the commercially available suspension of the drug.

Imipenem is also metabolized to some extent by a nonrenal mechanism unrelated to DHP I. Approximately 20–30% of an imipenem dose is inactivated by nonspecific hydrolysis of the β-lactam ring. Although the microbiologically inactive metabolite is identical to that formed by renal DHP I, this nonspecific hydrolysis is unaffected by concurrent administration of cilastatin.

Cilastatin is partially metabolized in the kidneys to *N*-acetylcilastatin, which is also an effective inhibitor of DHP I. Approximately 70–80% of an IV dose of cilastatin is excreted in urine unchanged and 12% is excreted as *N*-acetylcilastatin. The metabolic fate of the remainder of the dose has not been elucidated to date.

Imipenem, cilastatin, and their metabolites are excreted principally in urine by both glomerular filtration and tubular secretion. Approximately 20–30% of the renal clearance of imipenem occurs by tubular secretion; however, cilastatin competitively inhibits active tubular secretion of imipenem. Less than 1% of an imipenem dose and less than 2% of a cilastatin dose are excreted in feces following IV administration.

In adults with normal renal function, plasma clearance of imipenem and of cilastatin ranges from 165–207 and 207–218 mL/minute per 1.73 m^2, respectively. Plasma clearance of imipenem averages 270 mL/minute per 1.73 m^2 in children 2–12 years of age and 3.4 mL/minute per kg in neonates 1–10 days of age.

The serum half-lives of both imipenem and cilastatin are prolonged in patients with impaired renal function; however, the half-life of cilastatin is prolonged to a greater extent than that of imipenem. The serum half-life of IV imipenem and of cilastatin averages 2.1 and 2.5 hours, respectively, in adults with creatinine clearances of 17–33 mL/minute per 1.73 m^2, and 2.7–3.7 and 7–17 hours, respectively, in adults with creatinine clearances less than 10 mL/minute per 1.73 m^2.

Both imipenem and cilastatin are removed by hemodialysis; however, the amount of the drugs removed during hemodialysis varies considerably depending on several factors (e.g., type of coil used, dialysis flow rate). In patients who received a single 250- or 500-mg dose of imipenem and cilastatin sodium, a 3- to 4-hour period of hemodialysis removed 20–90% of the imipenem dose and 38–82% of the cilastatin dose into the dialysate. Imipenem and cilastatin are removed by peritoneal dialysis.

Chemistry and Stability

■ **Chemistry** Imipenem and cilastatin sodium is a fixed combination of imipenem monohydrate and the sodium salt of cilastatin.

Imipenem is a semisynthetic carbapenem antibiotic and is the crystalline *N*-formimidoyl derivative of thienamycin, a carbapenem antibiotic produced by *Streptomyces cattleya*. Carbapenems are β-lactam antibiotics that contain a fused β-lactam ring and 5-membered ring system similar to that contained in penicillins; however, the 5-membered ring in carbapenems is unsaturated and contains a carbon rather than a sulfur atom. Imipenem has a hydroxyethyl group at position 6 of the β-lactam ring rather than the acylamino group present at this position in penicillins and cephalosporins; the hydroxyethyl group in imipenem has a *trans* configuration unlike the acylamino groups in penicillins and cephalosporins which have a *cis* configuration. These structural differences result in increased antibacterial activity and stability against hydrolysis by most β-lactamases. Imipenem contains a basic alkylthio side chain on the 5-membered ring; this side chain results in antipseudomonal activity.

Cilastatin sodium, the sodium salt of a derivatized heptenoic acid, is a specific and reversible inhibitor of dehydropeptidase I (DHP I). DHP I is a dipeptidase present on the brush border of proximal renal tubular cells which inactivates imipenem by hydrolyzing the β-lactam ring. Concomitant use of cilastatin prevents in vivo metabolism of imipenem by DHP I and results in urinary concentrations of active imipenem that are higher than could be obtained following use of the antibiotic alone. (See Pharmacokinetics.)

Imipenem and cilastatin sodium is commercially available as a sterile powder for injection for IV use and as a sterile powder for injectable suspension for IM use; these powders contain a 1:1 ratio of imipenem to cilastatin. Commercially available imipenem and cilastatin sodium for injection or for injectable suspension contains 3.2 or 2.8 mEq of sodium per gram of imipenem, respectively. Potency of imipenem monohydrate is expressed in terms of imipenem, calculated on the anhydrous basis, and potency of cilastatin sodium is expressed in terms of cilastatin.

Imipenem monohydrate occurs as a white or off-white, nonhygroscopic, crystalline compound and has solubilities of 11 mg/mL in water at room temperature and approximately 0.2 mg/mL in alcohol at 25°C. Cilastatin sodium occurs as an off-white to yellowish-white, hygroscopic, amorphous powder and has solubilities of greater than 2 g/mL in water and approximately 6 mg/mL in alcohol at 25°C.

When reconstituted as directed, solutions of imipenem and cilastatin sodium prepared from the powder for injection for IV use are clear and colorless to yellow, have a pH of 6.5–7.5, and have osmolarities that approximate those of the diluents. Reconstituted suspensions of the drug prepared from the powder for IM use are white to light tan in color; variations of color within this range do not affect potency.

■ **Stability** Commercially available imipenem and cilastatin sodium sterile powders for injection or for injectable suspension should be stored at less than 25°C. Solutions and suspensions of imipenem and cilastatin sodium may darken (i.e., IV solutions may turn deep yellow or IM suspensions may turn light tan) with time; this color change does not indicate loss of potency. However, IV solutions of the drug should be discarded if they become brown.

Imipenem and cilastatin sodium is stable for 4 hours at room temperature or 24 hours when refrigerated at 5°C following reconstitution with 100 mL of one of the following IV solutions: 0.9% sodium chloride injection, 5% dextrose; 5% dextrose and 0.225, 0.45, or 0.9% sodium chloride; 0.15% potassium chloride in 5% dextrose; or 5, or 10% mannitol. Following reconstitution of ADD-Vantage® vials containing imipenem and cilastatin sodium with the diluent provided by the manufacturer (i.e., 100 mL of 0.9% sodium chloride injection or 5% dextrose injection), solutions of the drug are stable for 4 hours at room temperature.

Following reconstitution of the powder for injectable suspension with 1% lidocaine hydrochloride 1% injection (without epinephrine), the imipenem and cilastatin sodium suspension should be used within 1 hour.

The stability of imipenem is temperature and pH dependent. Solutions of imipenem and cilastatin sodium should not be frozen since freezing at temperatures warmer than −70°C results in decomposition of the drug similar to that observed with ampicillin. The drug is inactivated at alkaline or acidic pH but is generally stable at neutral pH. Imipenem is unstable in vitro at room temperature, 35–37°C, or −20°C in serum or urine and in certain media used for in vitro susceptibility testing. Serum, urine, and dialysate specimens to be assayed for imipenem should be stabilized immediately following collection by the addition of appropriate buffers and then frozen at −70 to −80°C. The manufacturer should be consulted for specific information on how to stabilize imipenem in serum, urine, or dialysate specimens.

Because of the potential for incompatibility, the manufacturer states that imipenem and cilastatin sodium solution or suspension and other anti-infective agents should not be admixed.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Imipenem and Cilastatin Sodium

Parenteral		
For injectable suspension, for IM use only	500 mg (of anhydrous imipenem) and 500 mg (of cilastatin)	**Primaxin® I.M.**, Merck
	750 mg (of anhydrous imipenem) and 750 mg (of cilastatin)	**Primaxin® I.M.**, Merck
For injection, for IV infusion	250 mg (of anhydrous imipenem) and 250 mg (of cilastatin)	**Primaxin® I.V.** (available in infusion bottles and vials), Merck **Primaxin® ADD-Vantage®**, Merck
	500 mg (of anhydrous imipenem) and 500 mg (of cilastatin)	**Primaxin® I.V.** (available in infusion bottles and vials), Merck **Primaxin® ADD-Vantage®**, Merck

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Meropenem

■ Meropenem is a synthetic carbapenem β-lactam antibiotic that is structurally and pharmacologically related to imipenem, but does not require concomitant administration with a dehydropeptidase I (DHP I) inhibitor such as cilastatin.

Uses

Meropenem is used for the treatment of intra-abdominal infections (e.g., peritonitis), skin and skin structure infections caused by susceptible bacteria. The drug also is used for the treatment of respiratory tract infections†, bacteremia†, and urinary tract infections† caused by susceptible bacteria and as empiric anti-infective therapy in febrile neutropenic patients†.

Prior to initiation of meropenem therapy, appropriate specimens should be obtained for identification of the causative organism and in vitro susceptibility tests. Meropenem can be initiated empirically pending completion of susceptibility testing, with continuance or alteration (e.g., substitution of an appropriate alternative anti-infective) determined by the results of culture and susceptibility tests.

■ **Intra-abdominal Infections** Meropenem is used for the treatment of intra-abdominal infections, including complicated appendicitis and peritonitis, caused by susceptible bacteria. The drug may be used as monotherapy for the treatment of intra-abdominal infections caused by susceptible viridans streptococci, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *B. thetaiotaomicron*, or *Peptostreptococcus*. Because meropenem has a broad spectrum of antibacterial activity, the drug may be used empirically to treat intra-abdominal infections before identification of the causative organism.

The Infectious Diseases Society of America (IDSA) states that patients with community-acquired intra-abdominal infections of mild to moderate severity may receive initial treatment with an empiric regimen that has a narrower spectrum of activity since unnecessary use of broad spectrum agents in such infections may contribute to emergence of resistance. Therefore, IDSA recommends use of the fixed combination of ampicillin and sulbactam, cefazolin or cefuroxime in conjunction with metronidazole, the fixed combination of ticarcillin and clavulanate, ertapenem monotherapy, or a fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin) in conjunction with metronidazole for treatment of mild to moderate community-acquired intra-abdominal infections. Patients who are immunosuppressed or have more severe community-acquired intra-abdominal infections, however, should receive a regimen that has a broader spectrum of activity. Regimens recommended by IDSA for such individuals include meropenem monotherapy; imipenem and cilastatin monotherapy; a third or fourth generation cephalosporin (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, cefepime) in conjunction with metronidazole; ciprofloxacin in conjunction with metronidazole; the fixed combination of piperacillin and tazobactam; or aztreonam in conjunction with metronidazole. Other clinicians suggest that severely ill patients and those with prolonged hospitalization should receive an initial regimen that includes an antipseudomonal agent such as an antipseudomonal penicillin (ticarcillin and clavulanate, piperacillin and tazobactam), a carbapenem (imipenem or meropenem), ceftazidime, or cefepime used in conjunction with metronidazole. These clinicians state that an aminoglycoside also could be included in the empiric regimen; however, IDSA states that aminoglycosides should not be used routinely in patients with community-acquired intra-abdominal infections but may be included in empiric regimens for treatment of nosocomial intra-abdominal infections, depending on local patterns of in vitro susceptibility of nosocomial isolates. Postoperative (nosocomial) intra-abdominal infections usually require treatment with multiple-drug regimens and, since these infections often involve resistant organisms, IDSA recommends that empiric regimens be selected based on local nosocomial susceptibility patterns.

In clinical studies in patients with intra-abdominal infections, meropenem monotherapy was similar in efficacy to a 2-drug regimen of tobramycin and clindamycin or monotherapy with imipenem and cilastatin sodium. At follow-up 7 or more days after empiric anti-infective therapy was completed, clinical cure was achieved in 69, 76, or 65% of evaluable patients treated with meropenem, tobramycin combined with clindamycin, or imipenem and cilastatin, respectively, and the respective rate of microbiologic eradication was 67, 76, or 62%. In one study, meropenem monotherapy was less effective than a 2-drug regimen of cefotaxime and metronidazole for empiric treatment of complicated intra-abdominal infections; however, the difference in efficacy may have resulted from uneven assignment of patients with more severe infection to the group that received meropenem.

■ **Meningitis** Meropenem is used for the treatment of bacterial meningitis caused by susceptible *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), or *Neisseria meningitidis* in children 3 months of age and older. The drug also is used in the treatment of meningitis in adults†. Efficacy of meropenem for the treatment of meningitis caused by highly penicillin- or cephalosporin-resistant *S. pneumoniae* has not been established.

Meropenem can be used as monotherapy for the treatment of meningitis caused by susceptible bacteria. Although meropenem usually is not considered an initial drug of choice, it is recommended as an alternative agent in children and adults for the treatment of meningitis caused by *S. pneumoniae*, *H. influenzae*, and various other bacteria and may be useful for meningitis caused by susceptible gram-negative bacteria (e.g., *Enterobacter*†, *Citrobacter*†, *Serratia marcescens*†) that are resistant to usually recommended regimens.

IDSA states that meropenem monotherapy is one of several alternatives that can be used for empiric treatment of meningitis in adults† when the causative organism has been presumptively identified by CSF gram stain as *S. pneumoniae*, *H. influenzae*, *Listeria monocytogenes*†, or *E. coli*†, and the regimens of choice cannot be used. In addition, if in vitro susceptibility tests indicate that the causative organism is susceptible to meropenem, IDSA states that the drug can be used as an alternative to penicillin G, ampicillin, or third generation cephalosporins (ceftriaxone or cefotaxime) for the treatment of meningitis caused by *S. pneumoniae* or *N. meningitidis* (only if the strains have penicillin MICs of 1 mcg/mL or less), as an alternative to penicillin G or ampicillin for meningitis caused by *L. monocytogenes*†, as an alternative to third generation cephalosporins (ceftriaxone or cefotaxime) for meningitis caused by *E. coli*† or other Enterobacteriaceae†, as an alternative to cefepime or ceftazidime for meningitis caused by *Ps. aeruginosa*†, or as an alternative to nafcillin or oxacillin for meningitis caused by oxacillin-susceptible (methicillin-susceptible) *S. aureus*. IDSA also recommends meropenem used in conjunction with vancomycin as one of several regimens of choice for empiric therapy in patients with purulent meningitis associated with penetrating head trauma, recent neurosurgery, or a CSF shunt.

In clinical studies that included children who were at least 3 months of age but younger than 17 years of age, clinical cure of bacterial meningitis was achieved in 78% of those receiving meropenem monotherapy (40 mg/kg IV every 8 hours) or 77% of those receiving monotherapy with usual dosages of cefotaxime or ceftriaxone. When results were stratified according to the most frequent causative organisms, the clinical cure rate in those receiving meropenem or a comparator drug was 71 or 63%, respectively, if meningitis was caused by *S. pneumoniae*; 80 or 100%, respectively, if caused by β-lactamase-producing *H. influenzae*; 75 or 73%, respectively, if caused by *H. influenzae* that either did not produce β-lactamase or was not tested for such; and 86 or 90%, respectively, if caused by *N. meningitidis*. Sequelae was the most common reason patients were assessed as clinically not cured; a few patients receiving meropenem were considered not cured because of relapse or continued growth of *Ps. aeruginosa*.

■ **Respiratory Tract Infections** Meropenem is used in the treatment of respiratory tract infections†, including community-acquired pneumonia (CAP) and nosocomial pneumonia, caused by susceptible bacteria.

Community-acquired Pneumonia Although meropenem generally is active against *S. pneumoniae* (including drug-resistant *S. pneumoniae*), the American Thoracic Society (ATS), IDSA, and other clinicians state that the drug usually is considered an alternative, not a drug of first choice, for empiric treatment of CAP† caused by *S. pneumoniae*. ATS and IDSA suggest that use of meropenem in the treatment of CAP be reserved for when the infection may be caused by *Ps. aeruginosa*, *Klebsiella*, or other gram-negative bacteria. Factors that increase the risk of *Ps. aeruginosa* infection in CAP patients include severe CAP requiring treatment in an intensive care unit (ICU), structural lung disease (bronchiectasis, cystic fibrosis), corticosteroid therapy (prednisone dosage exceeding 10 mg daily), broad-spectrum anti-infective therapy given for longer than 7 days within the past month, and malnutrition. In CAP patients with risk factors for *Ps. aeruginosa*, the empiric regimen should include 2 antipseudomonal agents and also provide coverage for drug-resistant *S. pneumoniae* and *Legionella*. The ATS and IDSA suggest that this can be accomplished with a regimen that includes an IV antipseudomonal β-lactam anti-infective (e.g., cefepime, piperacillin and tazobactam, imipenem, meropenem) in conjunction with an IV antipseudomonal fluoroquinolone (e.g., ciprofloxacin) or a regimen that includes one of these IV antipseudomonal β-lactam anti-infectives, an IV aminoglycoside, and either an IV macrolide (e.g., azithromycin) or an IV nonpseudomonal quinolone.

If anaerobic bacteria have been identified or are suspected in patients with pulmonary infections, IDSA recommends use of clindamycin, a β-lactam/β-lactamase inhibitor combination, imipenem, or meropenem.

Nosocomial Pneumonia Meropenem is considered a drug of choice for empiric treatment of nosocomial pneumonia†. ATS, IDSA, and other clinicians recommend use of an antipseudomonal cephalosporin (cefepime, ceftazidime), antipseudomonal penicillin (piperacillin and tazobactam, ticarcillin and clavulanate), or an antipseudomonal carbapenem (imipenem or meropenem) for initial therapy of hospital-acquired pneumonia, ventilator-associated pneumonia, or health care associated pneumonia because these drugs have a broad spectrum of activity against gram-positive, gram-negative, and anaerobic bacteria. In severely ill patients or in those with late-onset disease or risk factors for multidrug resistant bacteria, the initial regimen should also include an aminoglycoside (amikacin, gentamicin, tobramycin) or antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) to improve coverage against *Pseudomonas*. In hospitals where oxacillin-resistant (methicillin-resistant) *Staphylococcus* are common or if there are risk factors for these strains, the initial regimen also should include vancomycin or linezolid. In hospitals where multidrug-resistant *Ps. aeruginosa* are frequent causes of nosocomial pneumonia, some clinicians suggest that the initial regimen of choice is cefepime or a carbapenem (imipenem or meropenem) in conjunction with an aminoglycoside.

■ **Septicemia** Meropenem has been used for the treatment of septicemia† caused by susceptible bacteria. There is evidence that concurrent bacteremia associated with bacterial meningitis has been eliminated during meropenem meningitis treatment.

The choice of anti infective agent for the treatment of sepsis syndrome should be based on the probable source of infection, gram-stained smears of appropriate clinical specimens, the immune status of the patient, and current patterns of bacterial resistance within the hospital and local community. For the treatment of gram-negative sepsis, a parenteral third or fourth generation cephalosporin (cefepime, cefotaxime, ceftizoxime, ceftriaxone, ceftazidime), an antipseudomonal penicillin (piperacillin and tazobactam or ticarcillin and clavulanate), a carbapenem (imipenem or meropenem), or aztreonam can be used. The antipseudomonal penicillins or carbapenems offer the advantages of activity against most strains of *Ps. aeruginosa* and activity against anaerobes. For initial treatment of life-threatening sepsis in adults, some clinicians recommend a regimen that includes either a parenteral third or fourth generation

cephalosporin (cefepime, cefotaxime, ceftriaxone, ceftazidime), the fixed combination of piperacillin and tazobactam, or a carbapenem (imipenem or meropenem) in conjunction with an aminoglycoside (amikacin, gentamicin, tobramycin). Vancomycin (alone or in conjunction with gentamicin and/or rifampin) may be included in the initial regimen if oxacillin-resistant (methicillin-resistant) *S. epidermidis* is suspected.

■ **Skin and Skin Structure Infections** Meropenem is used for the treatment of complicated skin and skin structure infections caused by susceptible *Staphylococcus aureus* (including β-lactamase-producing strains, but not oxacillin-resistant [methicillin resistant] strains), *S. pyogenes* (group A β-hemolytic streptococci), *S. agalactiae* (group B streptococci), viridans streptococci, *Enterococcus faecalis* (except vancomycin-resistant strains), *Ps. aeruginosa*, *E. coli*, *Proteus mirabilis*, *B. fragilis*, or *Peptostreptococcus*.

Some clinicians state that reasonable choices for empiric treatment of complicated skin and skin structure infections are imipenem, meropenem, the fixed combination of piperacillin and tazobactam, or the fixed combination of ticarcillin and clavulanate; however, vancomycin or linezolid should be included in the empiric regimen whenever oxacillin-resistant (methicillin-resistant) *S. aureus* may be involved.

Safety and efficacy of meropenem for the treatment of complicated skin and skin structure infections were evaluated in a randomized, double-blind trial in adults with complicated cellulitis, complex abscesses, perirectal abscesses, or infections requiring IV anti-infectives, hospitalization, and surgical intervention (37% had diabetes, 12% had peripheral vascular disease, 67% required surgical intervention). Patients were randomized to receive meropenem (500 mg IV every 8 hours) or imipenem and cilastatin (500 mg of imipenem IV every 8 hours). In clinically evaluable patients, the success rate at follow-up was 86% in those who received meropenem and 83% in those who received imipenem. In the group that received meropenem, the clinical cure rate was 90–93% for infections caused by *S. aureus* (oxacillin-susceptible strains), *S. pyogenes*, or viridans streptococci; 71 or 75% for those caused by *S. agalactiae* or *E. faecalis*, respectively; 80 or 85% for those caused by *E. coli* or *P. mirabilis*, respectively; 73% for those caused by *Ps. aeruginosa*; and 91 or 77% for those caused by *B. fragilis* or *Peptostreptococcus*, respectively.

■ **Urinary Tract Infections** Although safety and efficacy have not been established, meropenem has been used for the treatment of complicated urinary tract infections† caused by susceptible bacteria. Some clinicians suggest that urinary tract infections in hospitalized patients should be treated with a third generation cephalosporin, a fluoroquinolone, fixed combination of ticarcillin and clavulanate, fixed combination of piperacillin and tazobactam, imipenem, or meropenem, an aminoglycoside should be used concomitantly, especially in patients with sepsis. (See Uses: Septicemia.)

■ **Acinetobacter Infections** Meropenem used alone or in conjunction with an aminoglycoside (amikacin, gentamicin, tobramycin) is a drug of choice for the treatment of infections caused by *Acinetobacter*†.

■ **Anthrax** Although data are not available regarding in vivo activity of meropenem against *Bacillus anthracis*, the drug has in vitro activity against the organism, and it has been suggested that meropenem is one of several anti-infectives that can be included in multiple-drug regimens used for the treatment of anthrax†, including inhalational anthrax and anthrax meningitis.

Based on clinical experience from the bioterrorism-related anthrax exposures of 2001 and the possibility that a *B. anthracis* strain resistant to one or more anti-infectives might be used in a future bioterrorism event, CDC and other experts (e.g., US Working Group on Civilian Biodefense) recommend that treatment of clinically apparent inhalational anthrax in adults, adolescents, or children that occurs as the result of exposure to anthrax spores in the context of biologic warfare or bioterrorism be initiated with a multiple-drug parenteral regimen that includes ciprofloxacin or doxycycline and 1 or 2 additional anti-infectives predicted to be effective. Other drugs to be included in the initial treatment regimen with ciprofloxacin or doxycycline should be selected based on in vitro susceptibility, possibility of efficacy, adverse effects, and cost. Based on in vitro data, other drugs that have been suggested as possibilities to augment ciprofloxacin or doxycycline in such multiple-drug regimens include chloramphenicol, clindamycin, rifampin, vancomycin, clarithromycin, imipenem, meropenem, penicillin, or ampicillin. Optimum regimens for treatment of anthrax meningitis are unknown. However, if meningitis is established or suspected, early and aggressive anti-infective treatment is critical. Some clinicians suggest a multiple drug regimen that includes a fluoroquinolone (e.g., ciprofloxacin) and 2 additional agents with good CSF penetration (e.g., ampicillin or penicillin, meropenem, rifampin, vancomycin).

For information on treatment of anthrax and recommendations for prophylaxis following exposure to anthrax spores, see Uses: Anthrax, in Ciprofloxacin 8:12.18.

■ **Bacillus Infections** Meropenem is used for the treatment of infections caused by *Bacillus cereus*†. Although vancomycin is considered the drug of choice, carbapenems (imipenem or meropenem) or clindamycin are alternatives.

■ **Burkholderia Infections** ***Melioidosis*** Meropenem is used as an alternative to imipenem or ceftazidime for the treatment of melioidosis† caused by *Burkholderia pseudomallei*.

B. pseudomallei may cause subclinical illness and localized infections or fulminant septicemia; disseminated infections may include hepatic and splenic abscesses. The incubation period usually is 1–21 days; however, in some asymptomatic individuals, the disease has remained dormant for prolonged periods and active melioidosis was not evident for up to 29 years later, usually at a time when the patient was immunosuppressed. If left untreated, severe septicemic infections can be fatal within 24–48 hours after onset. *B. pseudomallei* is widely distributed in water and soil in many tropical and subtropical countries and melioidosis is endemic in Southeast Asia and northern Australia. Person-to-person spread occurs only rarely. *B. pseudomallei* usually is transmitted to humans from contaminated materials (e.g., soil) via contact with nasal, oral, or conjunctival mucous membranes, contact with abraded or lacerated skin, or, rarely, by inhalation. Laboratory workers have become infected via aerosols from *B. pseudomallei* cultures.

Patients with localized or mild disease may be effectively treated with a prolonged regimen of oral anti-infectives (e.g., oral doxycycline in conjunction with oral co-trimoxazole). However, patients with severe illness should receive an initial parenteral regimen of ceftazidime, imipenem, or meropenem (some clinicians recommend that co-trimoxazole also be included, especially if the patient is septicemic) followed by a prolonged maintenance regimen of oral anti-infectives (e.g., co-trimoxazole with or without doxycycline). (See Burkholderia Infections under Dosage and Administration: Adult Dosage.) In patients with melioidosis septic shock, adjunctive use of filgrastim (granulocyte colony-stimulating factor; G-CSF) during initial treatment has been suggested. After the maintenance regimen is completed, life-long follow-up is recommended since relapse of melioidosis can occur despite effective anti-infective therapy.

B. pseudomallei has been studied for and is considered a potential pathogen for aerosol distribution in the context of biologic warfare or bioterrorism. Acute respiratory or systemic infection probably would occur following high dose aerosol exposure to *B. pseudomallei*. Some experts (e.g., US Army Medical Research Institute of Infectious Diseases [USAMRIID], European Commission's Task Force on Biological and Chemical Agent Threats [BICHAT]) state that the same treatment regimens recommended for naturally occurring melioidosis should be used if the disease occurs in the context of biologic warfare or bioterrorism.

Glanders Meropenem has been recommended for the treatment of glanders† caused by *B. mallei*.

Human infection with *B. mallei* is rare and has occurred principally in veterinarians, horse and donkey caretakers, and abattoir workers exposed to infected animals (usually horses, mules, or donkeys). There have been no naturally acquired cases of human glanders reported in the US for more than 50 years, and the disease currently is reported only sporadically in Asia, Africa, the Middle East, and South America. *B. mallei* occurs only in infected, susceptible hosts, and the transmission rate from infected animals to humans appears to be low. Person-to-person spread occurs only rarely.

Because experience is limited regarding the treatment of human cases of glanders, optimum regimens have not been identified. Some clinicians suggest that streptomycin in conjunction with a tetracycline is the regimen of choice and alternatives are streptomycin in conjunction with chloramphenicol or imipenem monotherapy. Other clinicians suggest that, pending results of in vitro susceptibility tests, regimens recommended for treatment of melioidosis can be used for initial empiric treatment of glanders since these *Burkholderia* species are similar and efficacy data are available regarding use of these regimens in patients with melioidosis.

B. mallei has been studied for and is considered a possible pathogen for aerosol distribution in the context of biologic warfare or bioterrorism. Some experts (e.g., USAMRIID, BICHAT) state that the same treatment regimens recommended for naturally occurring glanders should be used if the disease occurs in the context of biologic warfare or bioterrorism.

■ **Campylobacter Infections** Meropenem is used for the treatment of systemic infections caused by *Campylobacter fetus*†. Some clinicians suggest that the drug of choice for these infections is a third generation cephalosporin or gentamicin, and alternatives are ampicillin, imipenem, or meropenem.

■ **Capnocytophaga Infections** Meropenem has been recommended for the treatment of infections caused by *Capnocytophaga canimorsus*†.

Optimum regimens for the treatment of infections caused by *Capnocytophaga* have not been identified. Some clinicians recommend use of penicillin G or, alternatively, a third generation cephalosporin (cefotaxime, ceftizoxime, ceftriaxone), a carbapenem (imipenem or meropenem), vancomycin, a fluoroquinolone, or clindamycin.

■ **Clostridium Infections** Meropenem is recommended by some clinicians as an alternative to penicillin G for the treatment of infections caused by *Clostridium perfringens*† in individuals with penicillin hypersensitivity or for polymicrobial infections.

■ **Nocardia Infections** Meropenem is used for the treatment of infections caused by *Nocardia*†. Co-trimoxazole usually is considered the drug of first choice for *Nocardia* infections; alternatives include sulfisoxazole, a tetracycline (e.g., doxycycline, minocycline), a carbapenem (imipenem or meropenem), amikacin, ceftriaxone, fixed combination of amoxicillin and clavulanate, cycloserine, or linezolid. In vitro susceptibility testing, if available, is recommend for isolates from patients with invasive disease and those unable to tolerate a sulfonamide.

■ **Rhodococcus Infections** Meropenem in conjunction with vancomycin is recommended for the treatment of infections caused by *Rhodococcus equi*†. Optimum regimens for these infections have not been identified. Some

clinicians suggest that the regimen of choice is vancomycin with or without a fluoroquinolone, rifampin, a carbapenem (imipenem or meropenem), or amikacin.

■ **Empiric Therapy in Febrile Neutropenic Patients** Meropenem is used alone or in conjunction with other anti-infectives for empiric anti-infective therapy of presumed bacterial infections in febrile neutropenic patients†.

Successful treatment of infections in granulocytopenic patients requires prompt initiation of empiric anti-infective therapy (even when fever is the only sign or symptom of infection) and appropriate modification of the initial regimen if the duration of fever and neutropenia is protracted, if a specific site of infection is identified, or if organisms resistant to the initial regimen are present. The initial empiric regimen should be chosen based on the underlying disease and other host factors that may affect the degree of risk and on local epidemiologic data regarding usual pathogens in these patients and data regarding their in vitro susceptibility to available anti-infective agents. The fact that gram-positive bacteria have become a predominant pathogen in febrile neutropenic patients should be considered when selecting an empiric anti-infective regimen.

No empiric regimen has been identified that would be appropriate for all patients. Regimens that have been recommended for empiric therapy in febrile neutropenic patients with presumed bacterial infections include *monotherapy* with a third or fourth generation cephalosporin (i.e., ceftazidime, cefepime) or a carbapenem (e.g., imipenem and cilastatin sodium, meropenem) or *combination therapy* consisting of a β-lactam antibiotic (e.g., ceftazidime, ceftriaxone), a carbapenem (e.g., imipenem, meropenem), an extended-spectrum penicillin (e.g., ticarcillin), or a fixed combination of an extended-spectrum penicillin and a β-lactamase inhibitor (e.g., piperacillin and tazobactam, ticarcillin and clavulanate) given in conjunction with an aminoglycoside (e.g., amikacin, gentamicin, tobramycin).

IDSA recommends use of a parenteral empiric regimen in most febrile neutropenic patients; use of an oral regimen (e.g., oral ciprofloxacin and oral amoxicillin and clavulanate) should be considered only in selected adults at low risk for complications who have no focus of bacterial infection and no signs or symptoms of systemic infection other than fever. At health-care facilities where gram-positive bacteria are common causes of serious infection and use of vancomycin in the initial empiric regimen is considered necessary, IDSA recommends 2- or 3-drug combination therapy that includes vancomycin and either cefepime, ceftazidime, imipenem, or meropenem given with or without an aminoglycoside; vancomycin should be discontinued 24–48 hours later if a susceptible gram-positive bacterial infection is not identified. At health-care facilities where vancomycin is not indicated in the initial empiric regimen, IDSA recommends monotherapy with a third or fourth generation cephalosporin (ceftazidime, cefepime) or a carbapenem (imipenem, meropenem) for uncomplicated cases; however, for complicated cases or if anti infective resistance is a problem, combination therapy consisting of an aminoglycoside (amikacin, gentamicin, tobramycin) given in conjunction with an antipseudomonal penicillin (ticarcillin and clavulanate, piperacillin and tazobactam), an antipseudomonal cephalosporin (cefepime, ceftazidime), or a carbapenem (imipenem, meropenem) is recommended. Regardless of the initial regimen selected, patients should be reassessed after 3–5 days of treatment and the anti-infective regimen altered (if indicated) based on the presence or absence of fever, identification of the causative organism, and the clinical condition of the patient.

Published protocols for the treatment of infections in febrile neutropenic patients should be consulted for specific recommendations regarding selection of the initial empiric regimen, when to change the initial regimen, possible subsequent regimens, and duration of therapy in these patients.

Dosage and Administration

■ **Administration** Meropenem is administered by IV injection or IV infusion.

Reconstitution and Dilution For direct intermittent IV injection, 10 or 20 mL of sterile water for injection should be added to a vial labeled as containing 500 mg or 1 g, respectively, of meropenem to provide a solution containing approximately 50 mg/mL. The vial should be shaken until dissolution occurs and then allowed to stand until the solution is clear. Reconstituted solutions should be used promptly, but may be stored for up to 2 hours at 15–25°C or up to 12 hours at 4°C.

For IV infusion, vials labeled as containing 500 mg or 1 g of meropenem should be diluted in a compatible IV solution. Alternatively, vials labeled as containing 500 mg or 1 g may be reconstituted as directed for direct intermittent IV injection and the resulting solution added to an IV container and further diluted with a compatible IV solution.

Rate of Administration IV injections of meropenem should be given over a 3- to 5-minute period.

IV infusions of meropenem should be given over approximately 15–30 minutes.

■ **Dosage** Meropenem is commercially available as the trihydrate; potency and dosage of the drug are expressed on the anhydrous basis.

To minimize the risk of seizures, recommended meropenem dosage should not be exceeded, especially in patients with factors known to predispose to seizure activity. (See CNS Effects under Warning/Precautions: Warnings, in Cautions.)

Adult Dosage **Intra-abdominal Infections.** The usual adult dosage of meropenem for the treatment of intra-abdominal infections is 1 g every 8 hours.

Meningitis. For the treatment of bacterial meningitis in adults†, some clinicians recommend a dosage of 6 g daily. A dosage of 40 mg/kg every 8 hours daily (up to 6 g daily) has been used in conjunction with ceftriaxone or cefotaxime in adults with meningitis.

Respiratory Tract Infections. If meropenem is used for the treatment of nosocomial pneumonia† (including hospital-acquired, ventilator-associated, or health-care-associated infections), some clinicians recommend that adults receive a dosage of 1 g every 8 hours.

Skin and Skin Structure Infections. The usual adult dosage of meropenem for the treatment of complicated skin and skin structure infections is 500 mg every 8 hours.

Burkholderia Infections. For the treatment of severe melioidosis† caused by *Burkholderia pseudomallei*, the US Army Medical Research Institute of Infectious Diseases (USAMRIID) and other clinicians recommend a meropenem dosage of 25 mg/kg IV every 8 hours (up to 6 g daily); concomitant co-trimoxazole (8 mg/kg of trimethoprim daily given in 4 divided doses) may be indicated in septicemic individuals. Other clinicians recommend a meropenem dosage of 0.5–1 g every 8 hours with or without co-trimoxazole. The initial parenteral regimen should be continued for at least 14 days and until there is clinical improvement. Although the median time to fever resolution is 9 days, some patients may remain febrile for prolonged periods despite appropriate antimicrobial therapy. When appropriate, treatment may be changed to an oral maintenance regimen (e.g., oral co-trimoxazole with or without oral doxycycline) and continued for at least 3–6 months to prevent recrudence or relapse. More prolonged oral maintenance therapy (up to 12 months) may be necessary, depending on the response to therapy and severity of initial illness.

Although only limited experience is available regarding the treatment of human cases of glanders†, some clinicians suggest that the meropenem regimens recommended for the treatment of severe melioidosis also can be used for the treatment of glanders.

Pediatric Dosage Children weighing more than 50 kg should receive the usually recommended adult dosage of meropenem.

Intra-abdominal Infections. For the treatment of intra abdominal infections, children 3 months of age and older weighing 50 kg or less should receive 20 mg/kg (up to 1 g) every 8 hours.

Meningitis. For the treatment of meningitis, children 3 months of age and older weighing 50 kg or less should receive 40 mg/kg (up to 2 g) every 8 hours.

Skin and Skin Structure Infections. For the treatment of complicated skin and skin structure infections, children 3 months of age and older weighing 50 kg or less should receive 10 mg/kg (up to 500 mg) every 8 hours.

Burkholderia Infections. Some clinicians suggest that children older than 3 months of age can receive meropenem in a dosage of 10–20 mg/kg every 8 hours for the initial treatment of melioidosis† caused by *B. pseudomallei* or glanders† caused by *B. mallei*. Concomitant therapy with co-trimoxazole may be indicated in those with severe illness. These clinicians state that children weighing more than 40 kg may receive the meropenem dosage recommended for adults with these infections. (See Burkholderia Infections under Dosage and Administration: Adult Dosage.)

Geriatric Dosage The manufacturer states that dosage adjustment is not necessary for geriatric patients with creatinine clearances exceeding 50 mL/minute. For geriatric patients with reduced renal function, dosage should be adjusted according to the guidelines for other adults with renal impairment. (See Dosage in Renal and Hepatic Impairment under Dosage and Administration: Dosage.)

■ **Dosage in Renal and Hepatic Impairment** Dosage of meropenem should be modified according to the degree of renal impairment in adults with creatinine clearances of 50 mL/minute or less. The manufacturer and some clinicians recommend that adults with creatinine clearances of 26–50 mL/minute can receive the usual dose every 12 hours, those with creatinine clearances of 10–25 mL/minute can receive half the usual dose every 12 hours, and those with creatinine clearances less than 10 mL/minute can receive half the usual dose every 24 hours. If a measured creatinine clearance is unavailable, the patient's creatinine clearance (Ccr) can be estimated using the following formulas:

$$Ccr\ male = \frac{(140 - age) \times weight}{72 \times serum\ creatinine}$$

$$Ccr\ female = 0.85 \times Ccr\ male$$

where age is in years, weight is in kg, and serum creatinine is in mg/dL.

Because meropenem is removed by hemodialysis, supplemental doses should be given after each hemodialysis session. Meropenem also is removed by various forms of continuous renal replacement therapy, including continuous venovenous hemodiafiltration (CVVHDF), continuous venovenous hemofiltration (CVVHF), and continuous ambulatory peritoneal dialysis (CAPD). Therefore, to avoid inadequate meropenem concentrations in anuric patients undergoing these procedures, dosage adjustments are necessary and should be

based on characteristics of the specific procedure (e.g., filter or membrane type, amount of filtrate produced, dialysate flow rate).

The manufacturer states that there is a lack of experience with use of meropenem in pediatric patients with renal impairment. Some clinicians suggest that pediatric patients undergoing hemodialysis receive meropenem doses after hemodialysis.

Dosage adjustment is not necessary in patients with hepatic impairment.

Cautions

■ **Contraindications** Known hypersensitivity to meropenem, other carbapenems, or any ingredient in the formulation.

History of anaphylactic reaction to β-lactams.

■ **Warnings/Precautions** ***Warnings*** **Superinfection/Clostridium difficile-associated Colitis.** Possible emergence and overgrowth of nonsusceptible organism. Careful observation of the patient is essential. Institute appropriate therapy if superinfection occurs.

Treatment with anti infectives may permit overgrowth of clostridia. Consider *Clostridium difficile*-associated diarrhea and colitis (antibiotic-associated pseudomembranous colitis) if diarrhea develops and manage accordingly.

Some mild cases of *C. difficile* associated diarrhea and colitis may respond to discontinuance alone. Manage moderate to severe cases with fluid, electrolyte, and protein supplementation; appropriate anti-infective therapy (e.g., oral metronidazole or vancomycin) recommended if colitis is severe.

CNS Effects. Seizures and other adverse CNS effects reported during meropenem therapy, especially in those with underlying CNS disorders (e.g., brain lesions, history of seizures), bacterial meningitis, or compromised renal function.

Do not exceed recommended dosage, especially in those with known factors that predispose to seizures. Anticonvulsant therapy should be continued in those with known seizure disorders.

If focal tremors, myoclonus, or seizures occur, evaluate the patient neurologically, initiate anticonvulsant therapy if necessary, and determine whether meropenem dosage should be decreased or the drug discontinued.

Sensitivity Reactions **Hypersensitivity Reactions.** Serious and occasionally fatal hypersensitivity reactions (e.g., anaphylaxis) reported with β-lactams.

If hypersensitivity occurs, discontinue meropenem and institute appropriate therapy as indicated (e.g., epinephrine, corticosteroids, and maintenance of an adequate airway and oxygen).

Cross-hypersensitivity. Partial cross-allergenicity among β-lactam antibiotics, including penicillins, cephalosporins, and other β-lactams.

Prior to initiation of meropenem therapy, make careful inquiry concerning previous hypersensitivity reactions to meropenem, cephalosporins, penicillins, or other drugs.

General Precautions **Selection and Use of Anti-infectives.** To reduce development of drug-resistant bacteria and maintain effectiveness of meropenem and other antibacterials, use only for treatment or prevention of infections proven or strongly suspected to be caused by susceptible bacteria.

When selecting or modifying anti-infective therapy, use results of culture and in vitro susceptibility testing. In the absence of such data, consider local epidemiology and susceptibility patterns when selecting anti-infectives for empiric therapy.

Laboratory Monitoring. Periodically assess organ system functions, including renal, hepatic, and hematopoietic, during prolonged therapy.

Sodium Content. Each g of meropenem contains 3.92 mEq (90.2 mg) of sodium as sodium carbonate.

Specific Populations **Pregnancy.** Category B. (See Users Guide)

Lactation. Not known whether meropenem is distributed into milk. Use with caution.

Pediatric Use. Safety and efficacy not established in children younger than 3 months of age.

Geriatric Use. No substantial differences in safety and efficacy relative to younger adults, but increased sensitivity cannot be ruled out.

Substantially eliminated by kidneys; risk of toxicity may be greater in patients with impaired renal function. Select dosage with caution and assess renal function periodically since geriatric patients are more likely to have renal impairment.

No dosage adjustments except those related to renal function. (See Dosage in Renal and Hepatic Impairment under Dosage and Administration: Dosage.)

Hepatic Impairment. Pharmacokinetics not affected by hepatic impairment; dosage adjustments not required.

Renal Impairment. Decreased clearance. Dosage adjustments recommended in patients with creatinine clearance less than 50 mL/minute. (See Dosage in Renal and Hepatic Impairment under Dosage and Administration: Dosage.)

■ **Common Adverse Effects** Adverse effects reported in 1% or more of patients receiving meropenem including GI effects (diarrhea, nausea, vomiting, constipation), local reactions (pain and inflammation at injection site, phlebitis/thrombophlebitis), headache, anemia, rash, pruritus, sepsis, apnea, shock, glossitis, and oral candidiasis.

Drug Interactions

■ **Aminoglycosides** Potential pharmacologic interaction (synergistic antibacterial effects against *Pseudomonas aeruginosa*).

■ **Probenecid** Pharmacokinetic interaction (decreased renal tubular secretion of meropenem; increased systemic exposure and prolonged meropenem half-life). Concomitant use not recommended.

■ **Valproic Acid** Pharmacokinetic interaction (valproic acid serum concentrations may be decreased to subtherapeutic concentrations; possible increased risk of seizures). Use concomitantly with caution.

Description

Meropenem is a synthetic carbapenem antibiotic structurally and pharmacologically related to other carbapenems (e.g., imipenem, ertapenem). Unlike imipenem, meropenem has a methyl group at position 1 of the 5-membered ring, which confers stability against hydrolysis by dehydropeptidase 1 (DHP 1) present on the brush border of proximal renal tubular cells and therefore does not require concomitant administration with a DHP-1 inhibitor such as cilastatin.

Meropenem usually is bactericidal in action. Like other β-lactam antibiotics, the antibacterial activity of meropenem results from inhibition of bacterial cell wall synthesis. Meropenem has a broad spectrum of antibacterial activity and is active against many gram-positive and -negative bacteria and some anaerobic bacteria. The spectrum of activity of meropenem resembles that of imipenem; however, meropenem generally is more active in vitro against Enterobacteriaceae and less active against gram-positive bacteria. Like imipenem, meropenem is highly resistant to hydrolysis by a variety of β-lactamases (including penicillinases, cephalosporinases, and extended-spectrum β-lactamases) but appears to be more susceptible to hydrolysis by metallo-β-lactamases.

Meropenem is active in vitro and in clinical infections against many gram-positive aerobic and facultatively aerobic bacteria, including *Streptococcus pneumoniae* (penicillin-susceptible strains only), *S. pyogenes* (group A β-hemolytic streptococci), *S. agalactiae* (group B streptococci), *Staphylococcus aureus* (including β-lactamase-producing strains, but not oxacillin-resistant [methicillin-resistant] strains), *Enterococcus faecalis* (not vancomycin-resistant strains), and viridans streptococci. The drug also is active in vitro against *S. epidermidis* (including β-lactamase-producing strains, but not oxacillin-resistant strains).

Meropenem is active in vitro and in clinical infections against many gram-negative aerobic and facultatively aerobic bacteria, including *Escherichia coli*, *Haemophilus influenzae* (including β-lactamase-producing strains), *Klebsiella pneumoniae*, *Neisseria meningitidis*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. The drug also is active in vitro against *Acinetobacter*, *Aeromonas hydrophila*, *Campylobacter jejuni*, *Citrobacter diversus*, *C. freundii*, *Enterobacter cloacae*, *H. influenzae* (ampicillin-resistant, non-β-lactamase-producing strains; BLNAR), *Havnia alvei*, *K. oxytoca*, *Moraxella catarrhalis* (including β-lactamase-producing strains), *Morganella morganii*, *Pasteurella multocida*, *P. vulgaris*, *Salmonella*, *Shigella*, *Serratia marcescens*, and *Yersinia enterocolitica*.

Meropenem is active in vitro and in clinical infections against some anaerobic bacteria, including *Bacteroides fragilis*, *B. thetaiotaomicron*, and *Peptostreptococcus*. The drug also is active in vitro against *B. distasonis*, *B. ovatus*, *B. uniformis*, *B. ureolyticus*, *B. vulgatus*, *Clostridium difficile*, *C. perfringens*, *Eubacterium lentum*, *Fusobacterium*, *Prevotella bivia*, *P. intermedia*, *P. melaninogenica*, *Porphyromonas asaccharolytica*, and *Propionibacterium acnes*.

Cross resistance may occur between meropenem and other carbapenems (e.g., imipenem).

Meropenem is distributed into most body tissues and fluids, including bronchial mucosa, lung, bile, gynecologic tissue (endometrium, myometrium, ovary, cervix, fallopian tube), muscle, heart valves, skin, interstitial and peritoneal fluid, and CSF. Plasma protein binding is approximately 2%. The drug is partially metabolized to at least one microbiologically inactive metabolite. About 70% of an IV dose is eliminated in urine as unchanged drug by tubular secretion and glomerular filtration. The plasma half-life of meropenem is approximately 1 hour in adults with normal renal function and 1.5 hours in children 3 months to 2 years of age. Plasma half-life is increased and clearance of the drug is decreased in patients with renal impairment.

Advice to Patients

Advise patients that antibacterials (including meropenem) should only be used to treat bacterial infections and not used to treat viral infections (e.g., the common cold).

Importance of completing full course of therapy, even if feeling better after a few days.

Advise patients that skipping doses or not completing the full course of therapy may decrease effectiveness and increase the likelihood that bacteria will develop resistance and will not be treatable with meropenem or other antibacterials in the future.

Importance of informing clinicians of other medical conditions, including history of seizures.

Importance of discontinuing therapy and informing clinician if an allergic or hypersensitivity reaction occurs.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, and any concomitant illnesses.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview† (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Meropenem (Trihydrate)

Parenteral

For injection, for IV use only	500 mg (of anhydrous meropenem)	**Merrem® I.V.**, AstraZeneca
	1 g (of anhydrous meropenem)	**Merrem® I.V.**, AstraZeneca

†Use is not currently included in the labeling approved by the US Food and Drug Administration

CEPHAMYCINS 8:12.07.12

cefoTEtan Disodium

■ Cefotetan is a semisynthetic cephamycin β-lactam antibiotic.

Uses

Cefotetan is used for treatment of urinary tract, lower respiratory tract, skin and skin structure, bone and joint, gynecologic, and intra-abdominal infections caused by susceptible bacteria and also is used for perioperative prophylaxis. Cefotetan should not be used for treatment of meningitis or other CNS infections.

Prior to initiation of cefotetan therapy, appropriate specimens should be obtained for identification of the causative organism and in vitro susceptibility tests. Cefotetan therapy may be started pending results of susceptibility tests, but should be discontinued if the organism is found to be resistant to the drug. In certain serious infections, including confirmed or suspected gram-positive or gram-negative sepsis, when the causative organism is unknown, cefotetan and concomitant therapy with an aminoglycoside may be indicated initially pending results of susceptibility tests. If an aminoglycoside is used concomitantly with cefotetan, renal function should be monitored. (See Drug Interactions: Aminoglycosides.)

■ **Gram-positive Aerobic Bacterial Infections** Cefotetan is used in

■ **Anaerobic an**
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LAMPIRAN 2

(untuk minggu ke IV)

Monografi obat di *Stockley's herbal medicine interactions*

of talinolol, which is considered to be of little or no clinically relevance.

1. Fan L, Tao G-Y, Wang G, Chen Y, He Y-J, Li Q, Lei H-P, Jiang F, Hu D-L, Huang Y-F, Zhou H-H. Effects of ginkgo biloba extract ingestion on the pharmacokinetics of talinolol in healthy Chinese volunteers. *Am Pharmacother* (2009) 43, 944–9.
2. Fan L, Mao X-Q, Tao G-Y, Wang G, Jiang F, Chen Y, Li Q, Zhang W, Lei H-P, Hu D-L, Huang Y-F, Wang D, Zhou H-H. Effect of *Schisandra chinensis* extract and *Ginkgo biloba* extract on the pharmacokinetics of talinolol in healthy volunteers. *Xenobiotica* (2009) 39, 249–54.
3. Hellum BH, Nilsen OG. *In vitro* inhibition of CYP3A4 metabolism and P-glycoprotein-mediated transport by trade herbal products. *Basic Clin Pharmacol Toxicol* (2008) 102, 466–75.

Ginkgo + Theophylline

The interaction between ginkgo and theophylline is based on experimental evidence only.

Clinical evidence

No interactions found.

Experimental evidence

In an experimental study in *rats* pretreated with oral ginkgo extract 100 mg/kg daily for 5 days, the serum levels and AUC of a single 10 mg/kg oral dose of theophylline given on day 6 were reduced by about 20% and 40%, respectively. The clearance was increased by 70%. A less marked effect was seen with ginkgo 10 mg/kg (30% increase in clearance). Similar results were seen with intravenous theophylline 10 mg/kg.[1]

Mechanism

This interaction is thought to be due to the induction of the cytochrome P450 isoenzyme CYP1A2 by ginkgo. Theophylline is a substrate of CYP1A2 and by inducing the activity of this isoenzyme, theophylline is more readily metabolised and cleared from the body. However, ginkgo had no relevant effect on another CYP1A2 substrate, caffeine, in humans. See Ginkgo + Caffeine, page 242.

Importance and management

The evidence for this interaction is limited to experimental data and the dose of ginkgo used is far higher than the most common clinical dose. A human study using caffeine as a CYP1A2 probe substrate, found that ginkgo does not affect CYP1A2 to a clinically relevant extent. Therefore an interaction with theophylline based on this mechanism is unlikely to be clinically important.

1. Tang J, Sun J, Zhang Y, Li L, Cui F, He Z. Herb-drug interactions: Effect of *Ginkgo biloba* extract on the pharmacokinetics of theophylline in rats. *Food Chem Toxicol* (2007) 45, 2441–5.

Ginkgo + Tolbutamide

Gingko does not appear to have a clinically relevant effect on the metabolism or blood-glucose-lowering effects of tolbutamide.

Clinical evidence

In healthy subjects, ginkgo extract (*Ginkgold*) 120 mg twice daily for 7 days had no effect on the urinary metabolic ratio of tolbutamide.[1] Similarly, in another 18 healthy subjects, another ginkgo extract, EGb 761, at a dose of 120 mg twice daily or 240 mg daily for 8 days, had no effect on the metabolism of a single 125-mg dose of tolbutamide.[2]

In another study in 10 healthy subjects, ginkgo 360 mg daily for 28 days slightly reduced the AUC of a single 125-mg oral dose of tolbutamide by about 16%, with no significant changes in other pharmacokinetic parameters. The ginkgo product used was *Ginkgold*, which contained 24% flavone glycosides and 6% terpene lactones. The pharmacodynamics of tolbutamide were not significantly altered although there was a tendency towards the attenuation of its hypoglycaemic effects by ginkgo (14% reduction).[3]

Experimental evidence

In an experimental study, ginkgo 32 mg/kg given daily for 5 days before a single 40-mg/kg dose of tolbutamide significantly reduced its blood-glucose-lowering effects in aged *rats*. However, when a single 100-mg/kg dose of ginkgo was given with a single 40-mg/kg dose of tolbutamide, the blood-glucose levels were significantly lower, when compared with tolbutamide alone, suggesting that ginkgo potentiated the blood-glucose-lowering effects of tolbutamide.[4]

Mechanism

It was suggested that ginkgo might induce the cytochrome P450 isoenzyme CYP2C9, by which tolbutamide is metabolised. However, the clinical study shows that ginkgo has little or no clinically relevant effect on CYP2C9. The disparate effects between single and multiple dose administration in the *animal* study are not understood.

Importance and management

From the clinical evidence, it is clear that ginkgo has little, if any, effect on the metabolism and blood-glucose-lowering effects of tolbutamide. A clinically relevant interaction therefore seems unlikely.

Tolbutamide is used as a probe drug for CYP2C9 activity, and therefore these results also suggest that a clinically relevant pharmacokinetic interaction between ginkgo and other CYP2C9 substrates is unlikely.

1. Mohutsky MA, Anderson GA, Miller JW, Elmer GW. *Ginkgo biloba*: evaluation of CYP2C9 drug interactions in vitro and in vivo. *Am J Ther* (2006) 13, 24–31.
2. Zadoyan G, Rokitta D, Klement S, Dienel A, Hoerr R, Gramatté T, Fuhr U. Effect of *Ginkgo biloba* special extract EGb 761® on human cytochrome P450 activity: a cocktail interaction study in healthy volunteers. *Eur J Clin Pharmacol* (2012) 68, 553–60.
3. Uchida S, Yamada H, Li DX, Maruyama S, Ohmori Y, Oki T, Watanabe H, Umegaki K, Ohashi K, Yamada S. Effects of Ginkgo biloba extract on pharmacokinetics and pharmacodynamics of tolbutamide and midazolam in healthy volunteers. *J Clin Pharmacol* (2006) 46, 1290–1298.
4. Sugiyama T, Kubota Y, Shinozuka K, Yamada S, Wu J, Umegaki K. Ginkgo biloba extract modifies hypoglycemic action of tolbutamide via hepatic cytochrome P450 mediated mechanism in aged rats. *Life Sci* (2004) 75, 1113–22.

Ginkgo + Trazodone

Coma developed in an elderly patient with Alzheimer's disease after she took trazodone and ginkgo.

Clinical evidence

An 80-year-old woman with Alzheimer's disease became comatose a few days after starting to take low-dose trazodone 20 mg twice daily and ginkgo. The patient woke immediately after being given flumazenil 1 mg intravenously.[1]

Experimental evidence

No relevant data found.

Mechanism

It was suggested that the flavonoids in the ginkgo had a subclinical direct effect on the benzodiazepine receptor. In addition, it was suggested that ginkgo increased the metabolism of trazodone to its active metabolite, 1-(m-chlorophenyl)piperazine (mCPP) by the cytochrome P450 isoenzyme CYP3A4. The increased levels of the metabolite were thought to have enhanced the release of GABA (gamma-amino butyric acid). Flumazenil may have blocked the direct effect of the flavonoids, thus causing the GABA activity to fall below the level required to have a clinical effect. However, note that clinically relevant CYP3A4 induction has not been seen

Monografi obat di *Drug Interaction and Analysis*

1 = Avoid Combination 2 = Usually Avoid Combination 3 = Minimize Risk
4 = No Action Needed 5 = No Interaction

Amiodarone (eg, *Cordarone*) 3

Theophylline (eg, *Theo-24*)

SUMMARY: Amiodarone may increase the concentration of theophylline, resulting in toxicity.

RISK FACTORS: No specific risk factors are known.

MECHANISM: Amiodarone is known to be an enzyme inhibitor and may inhibit the metabolism of theophylline.

CLINICAL EVALUATION: The theophylline serum concentration in an 86-year-old man taking sustained-release theophylline 300 mg twice daily increased from 93.2 mmol/L (normal range, 55 to 110 mmol/L) to 194.2 mmol/L after amiodarone 600 mg/day was started.[1] Symptoms included tachycardia, nervousness, and tremors that resolved 2 days after theophylline was discontinued. The patient expired from a cardiorespiratory arrest before this potential interaction could be further evaluated.

RELATED DRUGS: No information is available.

MANAGEMENT OPTIONS:

➥ ***Monitor.*** Carefully observe patients maintained on theophylline for the development of theophylline toxicity (eg, nausea, tachycardia, nervousness, tremor, seizures) following the addition of amiodarone. One or more weeks may be required for the onset and offset of this interaction because of the long half-life of amiodarone.

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1. Soto J, et al. Possible theophylline-amiodarone interaction. *DICP*. 1990;24:1115.

Amiodarone (eg, *Cordarone*) 1

Thioridazine AVOID

SUMMARY: Amiodarone may increase thioridazine serum concentrations and produce additive prolongation of the QT interval, thus increasing the risk of ventricular arrhythmias; avoid concurrent use.

RISK FACTORS:

➥ ***Pharmacogenetics.*** Only patients with the extensive metabolizer CYP2D6 phenotype would be expected to experience increased thioridazine serum concentrations. Poor metabolizers do not have the gene for production of CYP2D6 and would likely already have high serum concentrations of thioridazine. Approximately 8% of whites are deficient in CYP2D6, but the deficiency is rare in Asians (usually 1% or less).

➥ ***Hypokalemia.*** The corrected QT interval (QTc) may be prolonged in patients with hypokalemia, thus increasing the risk of this interaction. Any other factor that may prolong the QTc interval increases the risk of this interaction.

MECHANISM: Amiodarone is an inhibitor of CYP2D6 and probably inhibits the hepatic metabolism of thioridazine. Also, amiodarone and thioridazine prolong the QT interval, and additive effects may be seen.

Monografi obat (meropenem) di *Drug Interaction Analysis and Management*

frequency), bone marrow exam (to evaluate marrow status), liver function tests (weekly initially, then monthly; monitor more frequently if on concomitant hepatotoxic agents), renal function, urinalysis; consider TPMT genotyping to identify TPMT defect (if severe toxicity occurs)

For use in inflammatory bowel disease, monitor CBC with differential weekly for 1 month, then biweekly for 1 month, followed by monitoring every 1-2 months throughout the course of therapy. LFTs should be assessed every 3 months. Monitor for signs/symptoms of malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss) (Sandhu, 2010).

Test Interactions TPMT testing: Recent transfusions may result in a misinterpretation of the actual TPMT activity. Concomitant drugs may influence TPMT activity in the blood.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Purinethol: 50 mg [scored]

Generic: 50 mg

Extemporaneous Preparations Hazardous agent: Use appropriate precautions for handling and disposal.

A 50 mg/mL oral suspension may be prepared in a vertical flow hood with tablets and a mixture of sterile water for injection (SWFI), simple syrup, and cherry syrup. Crush thirty 50 mg tablets in a mortar and reduce to a fine powder. Add ~5 mL SWFI and mix to a uniform paste; then add ~10 mL simple syrup; mix while continuing to add cherry syrup to make a final volume of 30 mL; transfer to a calibrated bottle. Label "shake well" and "caution chemotherapy". Stable for 35 days at room temperature.

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◆ **6-Mercaptopurine (error-prone abbreviation)** see Mercaptopurine *on page 1216*

◆ **Mercapturic Acid** *see* Acetylcysteine *on page 54*

Meropenem (mer oh PEN em)

Medication Safety Issues

Sound-alike/look-alike issues:

Meropenem may be confused with ertapenem, imipenem, metroNIDAZOLE

Brand Names: U.S. Merrem

Brand Names: Canada Merrem®

Therapeutic Category Antibiotic, Carbapenem

Generic Availability (U.S.) Yes

Use Treatment of multidrug-resistant infection caused by gram-negative and gram-positive aerobic and anaerobic pathogens documented or suspected to be susceptible to meropenem; used in treatment of meningitis (FDA approved in pediatric patients ages ≥3 months), intra-abdominal infections and complicated skin and skin structure infections caused by susceptible *S. aureus*, *S. pyogenes*, *S. agalactiae*, *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, *M. catarrhalis*, *E. coli*, *Klebsiella*, *Enterobacter*, *Serratia*, *P. aeruginosa*, *B. cepacia*, and *B. fragilis* (FDA approved in ages ≥3 months and adults); has been used for treatment of lower respiratory tract infections, acute pulmonary exacerbations in cystic fibrosis, urinary tract infections, empiric treatment of febrile neutropenia, and sepsis

Pregnancy Risk Factor B

Pregnancy Considerations Adverse events were not observed in animal reproduction studies. Incomplete transplacental transfer of meropenem was found using an ex *vivo* human perfusion model.

Lactation Excreted in breast milk/use caution

Breast-Feeding Considerations Small amounts of meropenem are excreted into breast milk (case report). The manufacturer recommends that caution be exercised when administering meropenem to breast-feeding women. Non-dose-related effects could include modification of bowel flora

Contraindications Hypersensitivity to meropenem, any component, other carbapenems, or in patients who have experienced anaphylactic reactions to beta-lactams

Warnings Serious and occasionally fatal hypersensitivity reactions have been reported in patients receiving beta-lactam therapy; careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other beta-lactams before initiating meropenem. Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment; use with caution in patients with a history of colitis. Seizures and other CNS adverse events have been reported, most commonly in patients with renal impairment and/or underlying neurologic disorders. Valproic acid (VPA) serum concentrations may be significantly decreased by concurrent carbapenem use leading to breakthrough seizures; serum VPA concentrations should be closely monitored after initiation of meropenem. VPA dosage adjustment may not adequately compensate for this interaction. Thrombocytopenia has been reported in patients with renal dysfunction who are receiving meropenem.

Precautions Use with caution in patients with a history of seizures. CNS disease, CNS infection, and/or compromised renal function; dosage adjustment required in patients with renal impairment

Adverse Reactions

Central nervous system: Headache, pain

Dermatologic: Pruritus, rash (includes diaper-area moniliasis in infants)

Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Constipation, diarrhea, glossitis, nausea, oral moniliasis, vomiting

Hematologic: Anemia

Local: Inflammation at the injection site, injection site reaction, phlebitis/thrombophlebitis

Respiratory: Apnea, pharyngitis, pneumonia

Miscellaneous: Sepsis, shock

Rare but important or life-threatening: Abdominal enlargement, abdominal pain, agitation/delirium, agranulocytosis, alkaline phosphatase increased, ALT increased, AST increased, anemia (hypochromic), angioedema, anorexia, anxiety, aPTT decreased, asthma, back pain, bilirubin increased, bradycardia, BUN increased, cardiac arrest, chest pain, chills, cholestatic jaundice/jaundice, confusion, cough, creatinine increased, depression, diaphoresis, dizziness, dyspepsia, dyspnea, dysuria, eosinophilia, epistaxis, erythema multiforme, fever, flatulence, gastrointestinal hemorrhage, hallucinations, heart failure, hematuria, hemoglobin/hematocrit decreased, hemolytic anemia, hemoperitoneum, hepatic failure, hyper-/hypotension, hypervolemia, hypokalemia, hypoxia, ileus, injection site edema, injection site pain, insomnia, intestinal obstruction, LDH increased, leukocytosis, leukopenia, melena, MI, nervousness, neutropenia, paresthesia, pelvic pain, peripheral edema, platelets decreased/increased, pleural effusion, PT decreased, pulmonary edema, positive Coombs test, pulmonary embolism, renal failure, respiratory disorder, seizure, skin ulcer, somnolence, Stevens-Johnson syndrome, syncope, tachycardia, toxic epidermal necrolysis, urinary incontinence, urticaria, vaginal moniliasis, weakness, WBC decreased, whole body pain

Drug Interactions

Metabolism/Transport Effects None known.

Avoid Concomitant Use

Avoid concomitant use of Meropenem with any of the following: BCG; Probenecid

Increased Effect/Toxicity

The levels/effects of Meropenem may be increased by: Probenecid

Decreased Effect

Meropenem may decrease the levels/effects of: BCG; Sodium Picosulfate; Typhoid Vaccine; Valproic Acid and Derivatives

Stability Store intact vials at 20°C to 25°C (68°F to 77°F); meropenem reconstituted with SWI is stable for up to 2 hours at room temperature or for up to 12 hours when refrigerated; when diluted with NS to a final concentration between 2.5-50 mg/mL, the solution is stable for up to 2 hours at room temperature or 18 hours when refrigerated; when diluted with D_5W to a final concentration between 1-50 mg/mL, the solution is stable for up to 1 hour at room temperature or 8 hours when refrigerated; solutions prepared for infusion in plastic I.V. bags with NS at concentrations ranging from 1-20 mg/mL are stable for 4 hours at room temperature or 24 hours when refrigerated

Mechanism of Action Inhibits cell wall synthesis by binding to penicillin-binding proteins (PBPs) with its strongest affinities for PBPs 2, 3 and 4 of *E. coli* and *P. aeruginosa* and PBPs 1, 2 and 4 of *S. aureus*

Pharmacokinetics (Adult data unless noted)

Distribution: Penetrates into most tissues and body fluids including urinary tract, peritoneal fluid, bone, bile, lung, bronchial mucosa, muscle tissue, heart valves, and CSF (CSF penetration: Neonates and Infants ≤3 months: 70%)

V_d:

Neonates and Infants ≤3 months: Median: ~0.47 L/kg (Smith, 2011)

Children: 0.3-0.4 L/kg (Blumer, 1995)

Adults: 15-20 L

Protein binding: 2%

Metabolism: 20% is hydrolyzed in plasma to an inactive metabolite

Half-life:

Neonates and Infants ≤3 months: Median: 2.7 hours; range: 1.6- 3.8 hours (Smith, 2011)

Infants and Children 3 months to 2 years: 1.5 hours

Children 2-12 years and Adults: 1 hour

Time to peak tissue and fluid concentrations: 1 hour after the start of infusion except in bile, lung, muscle, and CSF which peak at 2-3 hours

Elimination: Cleared by the kidney with 70% excreted unchanged in urine

Clearance:

Neonates and Infants ≤3 months: 0.12 L/hour/kg (Smith, 2011)

Infants and Children: 0.26-0.37 L/hour/kg (Blumer, 1995)

Dosing: Neonatal

General dosing:

Susceptible infection (non-CNS), treatment: For organisms highly susceptible to meropenem, MIC <4 mcg/mL:

Age-directed dosing (Smith, 2011):

GA <32 weeks:

PNA <14 days: 20 mg/kg/dose every 12 hours

PNA ≥14 days: 20 mg/kg/dose every 8 hours

GA ≥32 weeks:

PNA <14 days: 20 mg/kg/dose every 8 hours

PNA ≥14 days: 30 mg/kg/dose every 8 hours

Weight-directed dosing (*Red Book*, 2012):

Body weight <1 kg:

PNA ≤14 days: 20 mg/kg/dose every 12 hours

PNA 15-28 days: 20 mg/kg/dose every 8 hours

Body weight 1-2 kg:

PNA ≤7 days: 20 mg/kg/dose every 12 hours

PNA 8-28 days: 20 mg/kg/dose every 8 hours

Body weight >2 kg: 20 mg/kg/dose every 8 hours

Moderately resistant infection (non-CNS), treatment: For organisms with MIC 4-8 mcg/mL: Limited data available; further studies needed: GA >30 weeks, PNA >7 days: 40 mg/kg/dose every 8 hours, some suggest as a 4-hour infusion; dosing based on a single-dose pharmacokinetic study (n=38) (van den Anker, 2009)

Meningitis: Limited data available; dose not established; further studies are needed. An evaluation of CSF

concentrations in six patients using the dosing for susceptible infection [see Susceptible infection (non-CNS) dosing] reported levels to be above the target of 4 mcg/mL and highly variable (4.1-34.6 mcg/mL) at 0.3-7.9 hours (Smith, 2011); other suggest using the upper end of the dosing range (van den Anker, 2009); recommended duration of therapy dependent upon pathogen: *N. meningitides, H. influenza:* 7 days; *S. pneumoniae:* 10-14 days; *Listeria monocytogenes:* ≥ 21 days; aerobic gram-negative bacilli: Either 2 weeks beyond the first sterile CSF culture or >3 weeks, whichever is longer (Tunkel, 2004)

Dosing: Usual

Infants, Children, and Adolescents:

General dosing, susceptible infection (*Red Book*, 2012): I.V.:

Severe infections (non-CNS): 10-20 mg/kg/dose every 8 hours; maximum single dose: 2000 mg

Alternate dosing for infants <3 months (non-CNS): For organisms highly susceptible to meropenem, MIC <4 mcg/mL: 20-30 mg/kg/dose every 8 hours (Smith, 2011); maximum single dose: 200 mg

Cystic fibrosis, pulmonary exacerbation: I.V.: 40 mg/kg/dose every 8 hours; maximum single dose: 2000 mg (Zobell, 2012)

Fever/neutropenia empiric treatment: I.V.: 20 mg/kg/dose every 8 hours; maximum single dose: 1000 mg

Intra-abdominal infection, complicated: I.V.: 20 mg/kg/dose every 8 hours for 4-7 days; maximum single dose: 1000 mg (Solomkin, 2010)

Meningitis: I.V.: 40 mg/kg/dose every 8 hours; maximum single dose: 2000 mg; duration of therapy dependent upon pathogen: *N. meningitides, H. influenza:* 7 days; *S. pneumoniae:* 10-14 days; aerobic gram-negative bacilli: 21 days (Tunkel, 2004)

Skin and skin structure infection, complicated: Infants ≥3 months, Children, and Adolescents: I.V.: 10 mg/kg/dose every 8 hours; maximum dose: 500 mg

Adults:

General dosing, susceptible infection: I.V.: 500-2000 mg every 8 hours

Intra-abdominal infection: I.V.: 1000 mg every 8 hours

Meningitis: I.V.: 2000 mg every 8 hours; duration of therapy dependent upon pathogen: *N. meningitides, H. influenza:* 7 days; *S. pneumoniae:* 10-14 days; aerobic gram-negative bacilli: 21 days (Tunkel, 2004)

Skin and skin structure infection, complicated: I.V.: 500 mg every 8 hours

Dosing adjustment in renal impairment:

Infants, Children, and Adolescents: There are no dosage adjustments provided in the manufacturer's labeling. Some clinicians have used the following (Aronoff, 2007): **Note:** Renally adjusted dose recommendations are based on doses of 20-40 mg/kg/dose every 8 hours:

GFR >50 mL/minute/1.73 m^2: No adjustment required.

GFR 30-50 mL/minute/1.73 m^2: Administer 20-40 mg/kg/dose every 12 hours

GFR 10-29 mL/minute/1.73 m^2: Administer 10-20 mg/kg/dose every 12 hours

GFR <10 mL/minute/1.73 m^2: Administer 10-20 mg/kg/dose every 24 hours

Intermittent hemodialysis (IHD): Meropenem and metabolite are readily dialyzable: 10-20 mg/kg/dose every 24 hours; on dialysis days give dose **after** hemodialysis

Peritoneal dialysis (PD): 10-20 mg/kg/dose every 24 hours

Continuous renal replacement therapy (CRRT): 20-40 mg/kg/dose every 12 hours

Adults:

Cl_{cr} >50 mL/minute: No adjustment required.

Cl_{cr} 26-50 mL/minute: Standard dose every 12 hours

Cl_{cr} 10-25 mL/minute: One-half dose every 12 hours

Cl_{cr} <10 mL/minute: One-half dose every 24 hours

Intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): Meropenem and its metabolites are readily dialyzable: 500 mg every 24 hours. **Note:** Dosing dependent on the assumption of 3 times weekly, complete IHD sessions (Heintz, 2009).

Peritoneal dialysis: Administer recommended dose (based on indication) every 24 hours (Aronoff, 2007).

Continuous renal replacement therapy (CRRT) (Heintz, 2009; Trotman, 2005): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug concentrations in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1-2 L/hour and minimal residual renal function) and should not supersede clinical judgment:

CVVH: Loading dose of 1000 mg followed by either 500 mg every 8 hours or 1000 mg every 12 hours

CVVHD/CVVHDF: Loading dose of 1000 mg followed by either 500 mg every 6-8 hours or 1000 mg every 8-12 hours

Note: Consider giving patients receiving CVVHDF dosages of 750 mg every 8 hours or 1500 mg every 12 hours (Heintz, 2009). Substantial variability exists in various published recommendations, ranging from 1000-3000 mg/**day** in 2-3 divided doses. One gram every 12 hours achieves a target trough of ~4 mg/L.

Dosing adjustment in hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling; pharmacokinetics of meropenem are not altered in hepatic impairment so adjustment should not be necessary; use with caution.

Administration Administer by I.V. push or I.V. intermittent infusion; infuse I.V. push injection over 3-5 minutes at a final concentration not to exceed 50 mg/mL; intermittent infusion dose should be administered over 15-30 minutes at a final concentration ranging from 1-50 mg/mL in D_5W or NS; some studies have demonstrated enhanced pharmacodynamic effects when extending intermittent infusions to 4 hours (van den Anker, 2009)

Monitoring Parameters Periodic renal, hepatic, and hematologic function tests. Observe for changes in bowel frequency. Monitor for signs of anaphylaxis during first dose.

Test Interactions Positive Coombs' [direct]

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution Reconstituted, Intravenous:

Merrem: 500 mg (1 ea); 1 g (1 ea)

Generic: 500 mg (1 ea); 1 g (1 ea)

References

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Monografi obat (meropenem) di *Geriatric Dosage Handbook*

Renal Impairment The manufacturer's labeling recommends starting with reduced doses (starting at the low end of the dosing range) or increasing the dosing interval to every 36 to 48 hours in patients with renal impairment to avoid accumulation; however, no specific dosage adjustment is provided. The following adjustments have also been recommended (Aronoff, 2007): Children:
CrCl <50 mL/minute/1.73 m^2: Administer every 48 hours
Hemodialysis: Administer every 48 hours
Continuous ambulatory peritoneal dialysis (CAPD): Administer every 48 hours
Continuous renal replacement therapy (CRRT): Administer every 48 hours

Hepatic Impairment The manufacturer's labeling recommends considering a reduced dose (starting at the low end of the dosing range) with close monitoring for toxicity dose in patients with baseline hepatic impairment; however, no specific dosage adjustment is provided.

Obesity *ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer:* Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Administration Preferably on an empty stomach (1 hour before or 2 hours after meals)

Administration in the evening has demonstration superior outcome; administration with food did not significantly affect outcome.

Hazardous agent; use appropriate precautions for handling and disposal (NIOSH, 2012).

Monitoring Parameters CBC with differential (weekly initially, although clinical status may require increased frequency), bone marrow exam (to evaluate marrow status), liver function tests (transaminases, alkaline phosphatase, and bilirubin; weekly initially, then monthly; monitor more frequently if on concomitant hepatotoxic agents or in patients with preexisting hepatic impairment), renal function, urinalysis; consider TPMT genotyping to identify TPMT defect (if severe hematologic toxicity occurs)
For use as immunomodulatory therapy in CD or UC, monitor CBC with differential weekly for 1 month, then biweekly for 1 month, followed by monitoring every 1 to 2 months throughout the course of therapy. LFTs should be assessed every 3 months. Monitor for signs/symptoms of malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss).

Test Interactions TPMT testing: Recent transfusions may result in a misinterpretation of the actual TPMT activity. Concomitant drugs may influence TPMT activity in the blood.

Special Geriatric Considerations Toxicity to immunosuppressives is increased in the elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and WBC rise, may not occur. Lethargy and confusion may be more prominent signs of infection.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.
Suspension, Oral:
Purixan: 2000 mg/100 mL (100 mL) [contains aspartame, methylparaben, propylparaben]
Tablet, Oral:
Purinethol: 50 mg [scored]
Generic: 50 mg

◆ **6-Mercaptopurine (error-prone abbreviation)** *see* Mercaptopurine *on page 910*

Meropenem (mer oh PEN em)

Related Information
Antimicrobial Drugs of Choice *on page 1647*
Community-Acquired Pneumonia in Adults *on page 1653*

Medication Safety Issues
Sound-alike/look-alike issues:
Meropenem may be confused with ertapenem, imipenem, metroNIDAZOLE

Brand Names: U.S. Merrem

Brand Names: Canada Meropenem For Injection; Merrem

Generic Availability (U.S.) Yes

Pharmacologic Category Antibiotic, Carbapenem

Use
Treatment of intra-abdominal infections (complicated appendicitis and peritonitis); treatment of complicated skin and skin structure infections caused by susceptible organisms

Canadian labeling: Additional indications (not in U.S. labeling): Treatment of lower respiratory tract infections (community-acquired and nosocomial pneumonias), complicated urinary tract infections, gynecologic infections (excluding chlamydia), and septicemia; treatment of bacterial meningitis in adults caused by *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* (use in adult meningitis based on pediatric data)

Unlabeled Use *Burkholderia pseudomallei* (melioidosis), catheter-related blood stream infections; cystic fibrosis pulmonary exacerbation; febrile neutropenia; pneumonia (hospital-acquired, healthcare-associated, or ventilator-associated); treatment of prosthetic joint infection

Contraindications Hypersensitivity to meropenem, any component of the formulation, or other carbapenems (eg, doripenem, ertapenem, imipenem); patients who have experienced anaphylactic reactions to other beta-lactams

Warnings/Precautions Serious hypersensitivity reactions, including anaphylaxis, have been reported (some without a history of previous allergic reactions to beta-lactams). Carbapenems have been associated with CNS adverse effects, including confusional states and seizures (myoclonic); use caution with CNS disorders (eg, brain lesions and history of seizures) and adjust dose in renal impairment to avoid drug accumulation, which may increase seizure risk. Outpatient use may result in paresthesias, seizures, or headaches that can impair neuromotor function and alertness; patients should not operate machinery or drive until it is established that meropenem is well tolerated. Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. Use with caution in patients with renal impairment; dosage adjustment required in patients with moderate-to-severe renal dysfunction. Thrombocytopenia has been reported in patients with renal dysfunction. Lower doses (based upon renal function) are often required in the elderly. May decrease divalproex sodium/valproic acid concentrations leading to breakthrough seizures; concomitant use not recommended. Alternative antimicrobial agents should be considered; if concurrent meropenem is necessary, consider additional antiseizure medication.

Adverse Reactions (Reflective of adult population; not specific for elderly) 1% to 10%:
Central nervous system: Headache (2% to 8%), pain (≤5%)
Dermatologic: Rash (2% to 3%, includes diaper-area moniliasis in infants), pruritus (1%)
Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Diarrhea (4% to 7%), nausea/vomiting (1% to 8%), constipation (1% to 7%), oral moniliasis (up to 2% in pediatric patients), glossitis (1%)
Hematologic: Anemia (≤6%)
Local: Inflammation at the injection site (2%), phlebitis/thrombophlebitis (1%), injection site reaction (1%)
Respiratory: Apnea (1%), pharyngitis, pneumonia
Miscellaneous: Sepsis (2%), shock (1%)

Drug Interactions

Metabolism/Transport Effects None known.

Avoid Concomitant Use

Avoid concomitant use of Meropenem with any of the following: BCG; Probenecid

Increased Effect/Toxicity

The levels/effects of Meropenem may be increased by: Probenecid

Decreased Effect

Meropenem may decrease the levels/effects of: BCG; Sodium Picosulfate; Typhoid Vaccine; Valproic Acid and Derivatives

Preparation for Administration Meropenem infusion vials may be reconstituted with SWFI. The 500 mg vials should be reconstituted with 10 mL, and 1 g vials with 20 mL. May be further diluted with compatible solutions for infusion. Consult detailed reference/product labeling for compatibility.

Storage/Stability Freshly prepared solutions should be used. However, constituted solutions maintain satisfactory potency under the conditions described below. Solutions should not be frozen.

Dry powder should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F).

Injection reconstitution: Stability in vial when constituted (up to 50 mg/mL) with:

SWFI: Stable for up to 3 hours at up to 25°C (77°F) or for up to 13 hours at up to 5°C (41°F).

Infusion admixture (1-20 mg/mL): Solution is stable when diluted in NS for 1 hour at up to 25°C (77°F) or 15 hours at up to 5°C (41°F). Solutions constituted with dextrose injection 5% should be used immediately. **Note:** Meropenem stability (admixed with NS at a concentration of 20 mg/mL) at room temperature for >1 hour or under refrigeration for >15 hours is not supported by the manufacturer. Data exist supporting stability (admixed with NS at a concentration of 20 mg/mL) at room temperature for ≤4 hours and under refrigeration ≤24 hours (Patel, 1997).

Mechanism of Action Inhibits bacterial cell wall synthesis by binding to several of the penicillin-binding proteins, which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis; bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested

Pharmacodynamics/Kinetics

Distribution: V_d: Adults: 15-20 L; penetrates well into most body fluids and tissues; CSF concentrations approximate those of the plasma
Protein binding: ~2%
Metabolism: Hepatic; metabolized to open beta-lactam form (inactive)
Half-life elimination:
Normal renal function: 1-1.5 hours
CrCl 30-80 mL/minute: 1.9-3.3 hours
CrCl 2-30 mL/minute: 3.82-5.7 hours
Time to peak, tissue: 1 hour following infusion
Excretion: Urine (~70% as unchanged drug)

Dosage

Geriatric & Adult

Usual dosage range: I.V.: 1.5-6 g daily divided every 8 hours

Extended infusion method (unlabeled dosing): I.V.: 0.5-2 g over 3 hours every 8 hours (Crandon, 2011; Dandekar, 2003). **Note:** Dosing used at some centers and is based on pharmacokinetic/pharmacodynamic modeling and not clinical efficacy data. Meropenem stability (admixed with NS at a concentration of 20 mg/mL) at room temperature for >1 hour or under refrigeration for >15 hours is not supported by the manufacturer. Data exist supporting stability (admixed with NS at a concentration of 20 mg/mL) at room temperature for ≤4 hours and under refrigeration ≤24 hours (Patel, 1997).

Indication-specific dosing:

***Burkholderia pseudomallei* (melioidosis) (unlabeled use):** 1 g every 8 hours (Cheng, 2004; Inglis, 2006)

Catheter-related bloodstream infections (unlabeled use): 1 g every 8 hours (Mermel, 2009)

Cholangitis, intra-abdominal infections, complicated: 1 g every 8 hours. **Note:** 2010 IDSA guidelines recommend treatment duration of 4-7 days (provided source controlled). Not recommended for mild-to-moderate, community-acquired intra-abdominal infections due to risk of toxicity and the development of resistant organisms (Solomkin, 2010).

Cystic fibrosis, pulmonary exacerbation (unlabeled use): 40 mg/kg every 8 hours; maximum single dose: 2 g (Zobell, 2012)

Febrile neutropenia (unlabeled use): 1 g every 8 hours (Ohata, 2011; Paul, 2010)

Gynecologic and pelvic inflammatory disease: Adults: Canadian labeling (not in U.S. labeling): I.V.: 500 mg every 8 hours

Meningitis:

Unlabeled use [U.S.]: 2 g every 8 hours; duration of therapy dependent upon pathogen: *N. meningitides*, *H. influenza*: 7 days; *S. pneumoniae*: 10-14 days; aerobic gram-negative bacilli: 21 days (Tunkel, 2004)

Canadian labeling (not in U.S. labeling): 2 g every 8 hours

Pneumonia (community-acquired): Canadian labeling (not in U.S. labeling): 500 mg every 8 hours

Pneumonia (hospital-acquired, healthcare-associated, or ventilator-associated) (unlabeled use): 1 g every 8 hours (ATS/IDSA, 2005)

Pneumonia (nosocomial): Adults: Canadian labeling (not in U.S. labeling): I.V.: 1 g every 8 hours

Prosthetic joint infection, *Pseudomonas aeruginosa* (unlabeled use): 1 g every 8 hours for 4-6 weeks (consider addition of aminoglycoside) (Osmon, 2013)

Septicemia: Adults: Canadian labeling (not in U.S. labeling): I.V.: 1 g every 8 hours

Skin and skin structure infections:

Complicated: U.S. labeling:

Pseudomonas aeruginosa-suspected or confirmed: 1 g every 8 hours

Pseudomonas aeruginosa not suspected: 500 mg every 8 hours

Uncomplicated: Canadian labeling (not in U.S. labeling): 500 mg every 8 hours

Urinary tract infections (complicated): Canadian labeling (not in U.S. labeling): 500 mg every 8 hours. **Note:** Up to 1 g every 8 hours may be administered (Pallett, 2010).

Renal Impairment

Adults:

CrCl 26-50 mL/minute: Administer recommended dose based on indication every 12 hours

CrCl 10-25 mL/minute: Administer one-half recommended dose based on indication every 12 hours

CrCl <10 mL/minute: Administer one-half recommended dose based on indication every 24 hours

Alternative dosing recommendations: (unlabeled dosing; Aronoff, 2007):
GFR 10-50 mL/minute: Administer recommended dose (based on indication) every 12 hours
GFR <10 mL/minute: Administer recommended dose (based on indication) every 24 hours
Intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): Meropenem and its metabolite are readily dialyzable: 500 mg every 24 hours. **Note:** Dosing dependent on the assumption of 3 times/week, complete IHD sessions.
Peritoneal dialysis (unlabeled dose): Administer recommended dose (based on indication) every 24 hours (Aronoff, 2007).
Continuous renal replacement therapy (CRRT) (Heintz, 2009; Trotman, 2005): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug concentrations in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1-2 L/hour and minimal residual renal function) and should not supersede clinical judgment:
CVVH: Loading dose of 1 g followed by either 0.5 g every 8 hours **or** 1 g every 12 hours
CVVHD/CVVHDF: Loading dose of 1 g followed by either 0.5 g every 6-8 hours **or** 1 g every 8-12 hours
Note: Consider giving patients receiving CVVHDF dosages of 750 mg every 8 hours **or** 1500 mg every 12 hours (Heintz, 2009). Substantial variability exists in various published recommendations, ranging from 1-3 g/day in 2-3 divided doses. One gram every 12 hours achieves a target trough of ~4 mg/L.

Hepatic Impairment No dosage adjustment necessary.

Administration Administer I.V. infusion over 15-30 minutes; I.V. bolus injection (5-20 mL) over 3-5 minutes
Extended infusion administration (unlabeled dosing): Administer over 3 hours (Crandon 2011; Dandekar, 2003). **Note:** Must consider meropenem's limited room temperature stability if using extended infusions

Monitoring Parameters Perform culture and sensitivity testing prior to initiating therapy. Monitor for signs of anaphylaxis during first dose. During prolonged therapy, monitor renal function, liver function, CBC.

Test Interactions Positive Coombs' [direct]

Special Geriatric Considerations Adjust dose based on renal function.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.
Solution Reconstituted, Intravenous:
Merrem: 500 mg (1 ea); 1 g (1 ea)
Generic: 500 mg (1 ea); 1 g (1 ea)

◆ **Merrem** *see* Meropenem *on page 912*

Mesalamine (me SAL a meen)

Related Information
Oral Medications That Should Not Be Crushed or Altered *on page 1694*

Brand Names: Canada Asacol; Asacol 800; Mezavant; Novo-5 ASA; Pentasa; Salofalk
Index Terms 5-Aminosalicylic Acid; 5-ASA; Mesalazine
Generic Availability (U.S.) May be product dependent
Pharmacologic Category 5-Aminosalicylic Acid Derivative
Use
U.S. labeling:
Oral:
Apriso: Maintenance of remission of ulcerative colitis in patients ≥18 years
Asacol HD: Treatment of moderately active ulcerative colitis in adults
Lialda, Pentasa: Treatment and maintenance of remission of mildly to moderately active ulcerative colitis
Delzicol: Treatment of mildly to moderately active ulcerative colitis in patients ≥12 years; maintenance of remission of ulcerative colitis in adults
Rectal: Treatment of active mild to moderate distal ulcerative colitis (suspension only), proctosigmoiditis (suspension only), or proctitis (suspension and suppository)
Canadian labeling:
Oral:
Asacol, Mezavant: Treatment and maintenance of remission of mildly- to moderately-active ulcerative colitis
Asacol 800: Treatment of moderately active ulcerative colitis
Mesasal: Treatment and maintenance of remission of ulcerative colitis
Pentasa: Treatment and maintenance of remission of mildly to moderately active ulcerative colitis; treatment and maintenance of remission of mild to moderate Crohn disease
Rectal: Treatment and maintenance of remission of ulcerative colitis (extending to splenic flexure) as adjunctive therapy in more extensive disease (suspension only); treatment and maintenance of ulcerative proctitis (suppository only)

Contraindications
U.S. labeling: Hypersensitivity to mesalamine, amino salicylates, salicylates, or any component of the formulation (including suppository vehicle of vegetable fatty esters)
Canadian labeling: Hypersensitivity to mesalamine, salicylates, or any component of the formulation; severe renal impairment (GFR <30 mL/minute/1.73 m^2); severe hepatic impairment
Additional contraindications per specific Canadian product labeling: Existing gastric or duodenal ulcer, GI tract obstruction, use in children <2 years (Asacol, Asacol 800, Mesasal, Pentasa, Salofalk); hemorrhagic diathesis (Mesasal); patients unable to swallow intact tablet (Asacol, Asacol 800); renal parenchymal disease (Pentasa)

Warnings/Precautions May cause an acute intolerance syndrome (cramping, acute abdominal pain, bloody diarrhea; sometimes fever, headache, rash); discontinue if occurs. Use caution in patients with active peptic ulcer. Patients with pyloric stenosis or other gastrointestinal obstructive disorders may have prolonged gastric retention of mesalamine in the

LAMPIRAN 3
(untuk minggu ke V)

Monografi obat (meropenem) di *Handbook on Injectable Drugs*

MEPIVACAINE HYDROCHLORIDE
AHFS 72:00

Products — Mepivacaine hydrochloride is available in concentrations of 1, 1.5, and 2.0%. Methylparaben is incorporated into multiple-dose containers, but single-dose containers may be preservative free. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid. (1; 4)

pH — From 4.5 to 6.8. (1; 4)

Osmolality — Mepivacaine hydrochloride injections are isotonic. (1)

Trade Name(s) — Carbocaine, Polocaine, Polocaine-MPF.

Administration — Mepivacaine hydrochloride may be administered by infiltration and by peripheral or sympathetic nerve block. Mepivacaine hydrochloride *without* preservatives may be administered by epidural block, including caudal anesthesia; forms containing preservatives should not be administered by this route (4).

Stability — Mepivacaine hydrochloride in intact containers should be stored at controlled room temperature and protected from temperatures above 40 °C and from freezing. Mepivacaine hydrochloride is resistant to hydrolysis and may be autoclaved repeatedly. (1; 4) However, mepivacaine hydrochloride in dental cartridges should not be subjected to autoclaving because of breakdown of the dental cartridge closures. (4)

Syringes — The stability of mepivacaine (salt form unspecified) 10 mg/mL repackaged in polypropylene syringes was evaluated. Little change in concentration was found after four weeks of storage at room temperature not exposed to direct light. (2164)

Compatibility Information

Drugs in Syringe Compatibility

Mepivacaine HCl

Drug (in syringe)	*Mfr*	*Amt*	*Mfr*	*Amt*	*Remarks*	*Ref*	*C/I*
Sodium bicarbonate	AB	4%; 1, 2, 4 mL	AST, WI	1 and 1.5%/ 20 mL	Precipitate forms within approximately 1 hr	1724	I
	AST	8.4%; 0.5, 1, 2 mL	AST, WI	1 and 1.5%/ 20 mL	Precipitate forms within approximately 1 hr	1724	I

MEROPENEM
AHFS 8:12.07.08

Products — Meropenem is available in dosage forms containing 500 mg and 1 g of drug along with sodium carbonate. (1)

Reconstitute the 500-mg vials with 10 mL and the 1-g vials with 20 mL of sterile water for injection, shake the vial, and allow it to stand until the solution is clear. Each milliliter of the resultant solution contains 50 mg of meropenem. (1)

pH — The reconstituted solution has a pH from 7.3 to 8.3. (1)

Sodium Content — Each gram of meropenem provides 3.92 mEq (90.2 mg) of sodium from the sodium carbonate present in the formulation. (1)

Trade Name(s) — Merrem.

Administration — Meropenem is administered by direct intravenous injection of 5 to 20 mL over three to five minutes or by intravenous infusion diluted in a compatible infusion solution over 15 to 30 minutes. (1)

Stability — Intact vials should be stored at controlled room temperature between 20 and 25 °C. The drug is a white to pale yellow powder that yields a colorless to yellow solution on reconstitution. (1)

The manufacturer indicates that reconstituted solutions in vials of meropenem up to 50 mg/mL in sterile water for injection are stable for two hours at room temperature and up to 12 hours under refrigeration. The infusion vials diluted in sodium chloride 0.9% to a meropenem concentration of 2.5 to 50 mg/mL are stated to be stable for two hours at room temperature and 18 hours under refrigeration; in dextrose 5% at these concentrations, stability is only one hour at room temperature and eight hours under refrigeration. (1)

Meropenem 50 mg/mL reconstituted with sodium chloride 0.9% is reported to reach 10% loss in 4.8 hours at 25 °C. (2697)

Solutions of meropenem 2.5 to 20 mg/mL in sodium chloride 0.9% in the Minibag Plus (Baxter) are stable for up to four hours at room temperature and up to 24 hours under refrigeration. In dextrose 5% in the same concentration range, the drug is stable for only one hour at room temperature and up to six hours under refrigeration. (1)

In addition, the manufacturer notes that meropenem 1 to 20 mg/mL in sterile water for injection or sodium chloride 0.9% is stable for up to four hours and in dextrose 5% for up to two hours at room

temperature in plastic administration set tubing, drip chambers, and volume control devices. (1)

The manufacturer notes that meropenem 1 to 20 mg/mL in sterile water for injection or sodium chloride 0.9% is stable for up to 48 hours and in dextrose 5% for up to six hours in plastic syringes stored under refrigeration. (1)

Central Venous Catheter — Meropenem (Zeneca) 5 mg/mL in sodium chloride 0.9% was found to be compatible with the ARROWg+ard Blue Plus (Arrow International) chlorhexidine-bearing triple-lumen central catheter. Essentially complete delivery of the drug was found with little or no drug loss occurring. Furthermore, chlorhexidine delivered from the catheter remained at trace amounts with no substantial increase due to the delivery of the drug through the catheter. (2335)

Compatibility Information

Solution Compatibility

Meropenem

Solution	*Mfr*	*Mfr*	*Conc/L*	*Remarks*	*Ref*	*C/I*
Dextrose 5% with potassium chloride 0.15%	BA[a]	ZEN	1 g	10 to 11% loss in 4 hr at 24 °C and in 18 hr at 4 °C	2089	I[c]
	BA[a]	ZEN	20 g	8 to 10% loss in 3 hr at 24 °C and in 18 hr at 4 °C	2089	I[c]
Dextrose 5% in Ringer's injection, lactated	BA[a]	ZEN	1 g	11% loss in 8 hr at 24 °C and 4 to 10% loss in 48 hr at 4 °C	2089	I[c]
	BA[a]	ZEN	20 g	15% loss in 4 hr at 24 °C and 10% loss in 18 hr at 4 °C	2089	I[c]
Dextrose 5% with sodium bicarbonate 0.02%	BA[a]	ZEN	1 g	11% loss in 4 hr at 24 °C and 9% in 18 hr at 4 °C	2089	I[c]
	BA[a]	ZEN	20 g	10 to 12% loss in 3 hr at 24 °C and 10% loss in 20 hr at 4 °C	2089	I[c]
Dextrose 2.5% in sodium chloride 0.45%	BA[a]	ZEN	1 g	10% loss in 6 hr at 24 °C and 7% loss in 24 hr at 4 °C	2089	I[c]
	BA[a]	ZEN	20 g	8% loss in 4 hr at 24 °C and 7% loss in 24 hr at 4 °C	2089	I[c]
Dextrose 5% in sodium chloride 0.2%	BA[a]	ZEN	1 g	10 to 11% loss in 4 hr at 24 °C and in 16 hr at 4 °C	2089	I[c]
	BA[a]	ZEN	20 g	Up to 10% loss in 3 hr at 24 °C and 9% loss in 18 hr at 4 °C	2089	I[c]
Dextrose 5% in sodium chloride 0.9%	BA[a]	ZEN	1 g	11 to 13% loss in 4 hr at 24 °C and in 14 hr at 4 °C	2089	I[c]
	BA[a]	ZEN	20 g	9 to 11% loss in 3 hr at 24 °C and in 14 hr at 4 °C	2089	I[c]
Dextrose 5%	BA[a]	ZEN	1 g	9% loss in 4 hr at 24 °C and in 14 hr at 4 °C	2089	I[c]
	BA[b]	ZEN	2.5 g	6 to 7% loss in 4 hr at 24 °C and 8 to 10% in 24 hr at 4 °C	2089	I[c]
	BA[a]	ZEN	20 g	11 to 12% loss in 4 hr at 24 °C and in 18 hr at 4 °C	2089	I[c]
	BA[b]	ZEN	50 g	9 to 10% loss in 3 hr at 24 °C and in 24 hr at 4 °C	2089	I[c]
	[a]	ZEN	1 g	Visually compatible. Calculated time to 10% loss in 4.5 hr at 23 °C, 1.8 days at 4 °C, and 1.2 days at −20 °C	2492	I
	[a]	ZEN	22 g	Visually compatible. Calculated time to 10% loss in 8 hr at 23 °C, 2.1 days at 4 °C, and 7.8 days at −20 °C	2492	I
Dextrose 10%	BA[a]	ZEN	1 g	10 to 12% loss in 3 hr at 24 °C and in 8 hr at 4 °C	2089	I[c]
	BA[a]	ZEN	20 g	9 to 10% loss in 2 hr at 24 °C and in 8 hr at 4 °C	2089	I[c]
Normosol M with dextrose 5%	AB[a]	ZEN	1 g	5% loss in 8 hr at 24 °C and 4% loss in 48 hr at 4 °C	2089	I[c]
	AB[a]	ZEN	20 g	10% loss in 3 hr at 24 °C and 7 to 8% loss in 24 hr at 4 °C	2089	I[c]
Ringer's injection	BA[a]	ZEN	1 g	6% loss in 10 hr at 24 °C and 4 to 5% loss in 48 hr at 4 °C	2089	I[c]

Solution Compatibility (Cont.)

Meropenem

Solution	*Mfr*	*Mfr*	*Conc/L*	*Remarks*	*Ref*
	BA[a]	ZEN	20 g	7% loss in 8 hr at 24 °C and 7% loss in 48 hr at 4 °C	2089
Ringer's injection, lactated	BA[a]	ZEN	1 g	10 to 12% loss in 10 hr at 24 °C and 9% loss in 48 hr at 4 °C	2089
	BA[a]	ZEN	20 g	9% loss in 8 hr at 24 °C and 7% loss in 48 hr at 4 °C	2089
Sodium chloride 0.45%	AB[d]	ZEN	5 g	9 to 10% loss in 22 hr at 24 °C and 3% loss in 48 hr at 4 °C	2089
	AB[d]	ZEN	20 g	6 to 8% loss in 10 hr at 24 °C and 5 to 6% loss in 48 hr at 4 °C	2089
Sodium chloride 0.9%	BA[a]	ZEN	1 g	8 to 10% loss in 20 hr at 24 °C and 3 to 4% loss in 48 hr at 4 °C	2089
	BA[b]	ZEN	2.5 g	10% loss in 24 hr at 24 °C and 2% loss in 48 hr at 4 °C	2089
	BA[a]	ZEN	20 g	8% loss in 10 hr at 24 °C and 5 to 7% loss in 48 hr at 4 °C	2089
	BA[b]	ZEN	50 g	9 to 10% loss in 8 hr at 24 °C and in 48 hr at 4 °C	2089
	[c]	ZEN	20 and 30 g	Less than 3% loss in 24 hr when kept at less than 5 °C	2261
	[h]	ZEN	5 g	Visually compatible. Calculated times to 10% loss were 34 hr at 24 °C and 120 hr at 5 °C	2151
	[h]	ZEN	10 g	Visually compatible. Calculated times to 10% loss were 20 hr at 24 °C and 120 hr at 5 °C	215
	[a]	ZEN	1 g	Visually compatible. Calculated time to 10% loss in 22 hr at 23 °C, 10.7 days at 4 °C, and 33.4 days at −20 °C	249
	[a]	ZEN	22 g	Visually compatible. Calculated time to 10% loss in 17 hr at 23 °C, 4.9 days at 4 °C, and 11.4 days at −20 °C	249
		ASZ	5 g	6% loss in 8 hr at 20 °C; 12% loss in 8 hr at 37 °C	25
	[f]	ASZ	30 g	No loss in 24 hr kept in a cold pouch with two freezer packs	25
	[a,g]	ZEN	4 g	3 to 4% loss in 168 hr at 5 °C	25
	[a,g]	ZEN	10 g	2 to 5% loss in 120 hr at 5 °C	25
	[a,g]	ZEN	20 g	7% loss in 120 hr at 5 °C	25
Sodium lactate ⅙ M	BA[a]	ZEN	1 g	7% loss in 8 hr at 24 °C and 6 to 7% loss in 48 hr at 4 °C	2
	BA[a]	ZEN	20 g	9% loss in 8 hr at 24 °C and 4 to 5% loss in 24 hr at 4 °C	2

[a] *Tested in PVC containers.*
[b] *Tested in glass containers.*
[c] *Incompatible by conventional standards but recommended for dilution of meropenem with use in shorter periods of time.*
[d] *Tested in Abbott ADD-Vantage system.*
[e] *Tested in CADD-Plus medication cassettes.*
[f] *Tested in Deltec medication cassettes.*
[g] *Tested in Homepump Eclipse elastomeric pump reservoirs.*
[h] *Tested in Intermate SV elastomeric pump reservoirs.*

Additive Compatibility

Meropenem

Drug	*Mfr*	*Conc/L*	*Mfr*	*Conc/L*	*Test Soln*	*Remarks*	*Ref*	*C/I*
Acyclovir sodium	BW	5 g	ZEN	1 g	NS	Visually compatible for 4 hr at room temperature	1994	C
	BW	5 g	ZEN	20 g	NS	Precipitates immediately	1994	I
Aminophylline	AMR	1 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Amphotericin B	SQ	200 mg	ZEN	1 and 20 g	NS	Precipitate forms	2068	I
Atropine sulfate	ES	40 mg	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Dexamethasone sodium phosphate	MSD	4 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Dobutamine HCl	LI	1 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Dopamine HCl	DU	800 mg	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Doxycycline hyclate	RR	200 mg	ZEN	1 g	NS	Visually compatible for 4 hr at room temperature	1994	C
	RR	200 mg	ZEN	20 g	NS	Brown discoloration forms in 1 hr at room temperature	1994	I
Enalaprilat	MSD	50 mg	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Fluconazole	RR	2 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Furosemide	HO	1 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Gentamicin sulfate	SC	800 mg	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Heparin sodium	ES	20,000 units	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Insulin, regular	LI	1000 units	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Magnesium sulfate	AST	1 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Mannitol	BA[a]	2.5%	ZEN	1 g		7 to 8% meropenem loss in 8 hr at 24 °C and in 24 hr at 4 °C	2089	I[b]
	BA[a]	2.5%	ZEN	20 g		7 to 9% meropenem loss in 4 hr at 24 °C and 6% loss in 20 hr at 4 °C	2089	I[b]
	BA[a]	10%	ZEN	1 g		10 to 11% meropenem loss in 4 hr at 24 °C and in 20 hr at 4 °C	2089	I[b]
	BA[a]	10%	ZEN	20 g		10% meropenem loss in 3 hr at 24 °C and in 20 hr at 4 °C	2089	I[b]
Metoclopramide HCl	RB	100 mg	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Morphine sulfate	ES	1 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Multivitamins	AST	50 mL	ZEN	1 and 20 g	NS	Color darkened in 4 hr at room temperature	1994	I

Additive Compatibility (Cont.)

Meropenem

Drug	*Mfr*	*Conc/L*	*Mfr*	*Conc/L*	*Test Soln*	*Remarks*	*Ref*	*C/I*
Norepinephrine bitartrate	WI	8 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Ondansetron HCl	GL	1 g	ZEN	1 g	NS	Visually compatible for 4 hr at room temperature	1994	C
	GL	1 g	ZEN	20 g	NS	White precipitate forms immediately	1994	I
Phenobarbital sodium	ES	200 mg	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Ranitidine HCl	GL	100 mg	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Sodium bicarbonate	BA	5%	ZEN	1 g		10% meropenem loss in 4 hr at 24 °C and 18 hr at 4 °C	2089	I[b]
	BA	5%	ZEN	20 g		9 to 10% meropenem loss in 3 hr at 24 °C and 18 hr at 4 °C	2089	I[b]
Vancomycin HCl	LI	1 g	ZEN	1 and 20 g	NS	Visually compatible for 4 hr at room temperature	1994	C
Zidovudine	BW	4 g	ZEN	1 g	NS	Visually compatible for 4 hr at room temperature	1994	C
	BW	4 g	ZEN	20 g	NS	Dark yellow discoloration forms in 4 hr at room temperature	1994	I

[a]*Tested in PVC containers.*
[b]*Incompatible by conventional standards but may be used in shorter periods of time.*

Drugs in Syringe Compatibility

Meropenem

Drug (in syringe)	*Mfr*	*Amt*	*Mfr*	*Amt*	*Remarks*	*Ref*	*C/I*
Pantoprazole sodium	[a]	4 mg/1 mL		50 mg/1 mL	Precipitates within 15 min	2574	I

[a]*Test performed using the formulation WITHOUT edetate disodium.*

Y-Site Injection Compatibility (1:1 Mixture)

Meropenem

Drug	*Mfr*	*Conc*	*Mfr*	*Conc*	*Remarks*	*Ref*	*C/I*
Acyclovir sodium	BW	5 mg/mL[c]	ZEN	1 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
	BW	5 mg/mL[c]	ZEN	50 mg/mL[b]	Precipitate forms	2068	I
Aminophylline	AMR	25 mg/mL	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Amphotericin B	SQ	5 mg/mL	ZEN	1 and 50 mg/mL[b]	Precipitate forms	2068	I
Anidulafungin	VIC	0.5 mg/mL[a]	ASZ	2.5 mg/mL[b]	Physically compatible for 4 hr at 23 °C	2617	C
Atropine sulfate	ES	0.4 mg/mL	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Calcium gluconate	AMR	4 mg/mL[c]	ZEN	1 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C

Y-Site Injection Compatibility (1:1 Mixture) (Cont.)

Meropenem

Drug	*Mfr*	*Conc*	*Mfr*	*Conc*	*Remarks*	*Ref*	*Cl*
	AMR	4 mg/mL[c]	ZEN	50 mg/mL[b]	Yellow discoloration forms in 4 hr at room temperature	1994	I
Caspofungin acetate	ME	0.7 mg/mL[b]	ASZ	2.5 mg/mL[b]	Physically compatible for 4 hr at room temperature	2758	C
	ME	0.5 mg/mL[b]	ASZ	10 mg/mL[b]	Physically compatible over 30 min	2766	C
Cyclosporine	BED	1 mg/mL[a]	ASZ	10 mg/mL[b]	Physically compatible	2794	C
Dexamethasone sodium phosphate	MSD	10 mg/mL[c]	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Diazepam	RC	5 mg/mL	ZEN	1 and 50 mg/mL[b]	White precipitate forms immediately	1994	I
Digoxin	BW	0.25 mg/mL	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Diphenhydramine HCl	PD	50 mg/mL	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Docetaxel	RPR	0.9 mg/mL[a]	ZEN	20 mg/mL[b]	Physically compatible for 4 hr at 23 °C	2224	C
Doxycycline hyclate	RR	1 mg/mL[c]	ZEN	1 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
	RR	1 mg/mL[c]	ZEN	50 mg/mL[b]	Amber discoloration forms within 30 min	1994	I
Enalaprilat	MSD	0.05 mg/mL[c]	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Fluconazole	RR	2 mg/mL	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Furosemide	HO	10 mg/mL	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Gentamicin sulfate	SC	4 mg/mL[c]	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
	AMS	30 mg/mL[c]	ASZ	10 mg/mL[b]	Physically compatible	2794	C
Heparin sodium	ES	1 unit/mL[c]	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Insulin, regular	LI	0.2 unit/mL[c]	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Linezolid	PHU	2 mg/mL	ZEN	2.5 mg/mL[b]	Physically compatible for 4 hr at 23 °C	2264	C
Metoclopramide HCl	RB	5 mg/mL	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Milrinone lactate	SS	0.2 mg/mL[a]	ZEN	50 mg/mL[a]	Visually compatible for 4 hr at 25 °C	2381	C
Morphine sulfate	ES	1 mg/mL[c]	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Norepinephrine bitartrate	WI	1 mg/mL	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Ondansetron HCl	GL	1 mg/mL[c]	ZEN	1 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
	GL	1 mg/mL[c]	ZEN	50 mg/mL[b]	White precipitate forms immediately	1994	I
Phenobarbital sodium	ES	0.32 mg/mL[c]	ZEN	1 and 50 mg/mL[b]	Visually compatible for 4 hr at room temperature	1994	C
Potassium chloride		10 and 40 mEq/L[a]	ZEN	1 mg/mL[a]	Visually compatible. Calculated 10% meropenem loss in 3.3 hr at 23 °C	2492	C

Monografi obat (meropenem) di Pedoman Pemberian Obat Injeksi edisi 2

M-O

Meropenem Trihydrate
Meronem® (AstraZeneca UK Limited), Merofen™ (Dankos Farma), Simpenem® (Lapi Laboratories), Tripenem® (Dexa Medica)
Vial 500mg (Meronem®, AstraZeneca; Merofen™, Dankos Farma; Tripenem®, Dexa Medica)
vial 1g (Meronem®, AstraZeneca; Merofen™, Dankos Farma; Simpenem®, Lapi Laboratories; Tripenem®, Dexa Medica)

Rute	Instruksi pengenceran dan pelarut yang digunakan	Lama Pemberian	Keterangan	Ketercampuran/ketidakcampuran
IV infus[1-3,5,6,9]	Larutkan dalam 50-200mL larutan infus yang sesuai.[1,4-7,9] Cara lain: larutkan seperti untuk IV intermittent langsung, kemudian encerkan dengan larutan infus yang sesuai. **Dosis ≤500mg**: tambahkan 50-100 mL NS atau D5W.[6,8,9] **Dosis >500mg**: tambahkan 50-250 mL NS atau D5W.[6,8,9]	15-30 menit.[1-3]	**Kejadian yang dapat menyertai pemberian obat**: nyeri dan bengkak pada saat pemberian, ruam kulit, sakit kepala, mual.[1,4,6,8] **pH**: 7,3-8,3.[5,8] **Stabilitas**: sediaan berupa serbuk berwarna putih sampai kuning pucat.[1-5] Larutan rekonstitusi jernih dan tak berwarna atau berwarna kuning pucat.[1,5,8] Simpan vial yang belum dibuka pada suhu 20-25°C dan hindarkan dari suhu beku.[3,5,7,8] Larutan rekonstitusi harus segera digunakan.[1] Setiap vial hanya untuk satu kali penggunaan.[1] Larutan rekonstitusi dengan konsentrasi: • 1-20mg/mL dalam NS dan aqua pro injeksi stabil selama 8 jam pada suhu 15-25°C dan selama 48 jam pada suhu 4°C. Sedangkan dalam D5W stabil selama 3 jam pada suhu 15-25°C dan stabil 14 jam pada suhu 4°C.[1-3,7] • 2,5-50mg/mL stabil selama 2 jam pada suhu kamar dan 18 jam pada suhu kulkas, dalam NS.[7] **Bilas**: NS.[6,8] **Informasi lain**: kandungan sodium: tiap 1g meropenem (anhidrat) mengandung 90mg (3,9mmol) sodium.[1,5,8,9]	Ketercampuran: Larutan infus:[1,2,7] NS, D5W, D10W. **Ketidakcampuran:** larutan infus:[1] D5W, RL, D5S, D5RL, D10W, mannitol 2,5%, mannitol 10%. **dalam syringe**:[1] pantoprazole sodium. **Y-site**:[1] amphotericin B[4], diazepam[3]. **aditif**:[1] amphotericin B[4], multivitamin[4], sodium bicarbonate.
IV bolus[1-9]	Larutkan tiap 250mg sediaan dengan 5mL aqua pro-injeksi untuk mencapai konsentrasi 50mg/mL.[1,3] ATAU **Vial 500mg**: larutkan dalam 10mL aqua pro injeksi untuk mencapai konsentrasi 50mg/mL. Kocok vial sampai serbuk terlarut, lalu diamkan sampai diperoleh larutan jernih.[4,5] **Vial 1g**: larutkan dalam 20mL aqua pro injeksi untuk mencapai konsentrasi 50mg/mL. Kocok vial sampai serbuk terlarut, lalu diamkan sampai diperoleh larutan jernih.[4,6,9]	3-5 menit.[1,3,7,9]		

Pustaka
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