

APPROVED

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3
4 **PRIMAXIN I.V.**
5 **(IMIPENEM AND CILASTATIN FOR INJECTION)**

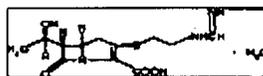
6
7 **(Formerly called IMIPENEM-CILASTATIN SODIUM FOR INJECTION)**

8
9 **For Intravenous Injection Only**

10
11 **DESCRIPTION**

12
13 PRIMAXIN I.V. (Imipenem and Cilastatin for Injection) is a sterile formulation of
14 imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal
15 dipeptidase, dehydropeptidase I), with sodium bicarbonate added as a buffer.
16 PRIMAXIN I.V. is a potent broad spectrum antibacterial agent for intravenous
17 administration.

18
19 Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of
20 thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is
21 (5R,6S)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-
22 azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate. It is an off-white,
23 nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly
24 soluble in water and slightly soluble in methanol. Its empirical formula is
25 $C_{12}H_{17}N_3O_4S \cdot H_2O$, and its structural formula is:



26
27
28 Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name
29 is sodium (Z)-7-[[[(R)-2-amino-2-carboxyethyl]thio]-2-[(S)-2,2-
30 dimethylcyclopropanecarboxamido]-2-heptenoate. It is an off-white to yellowish-white,
31 hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble
32 in water and in methanol. Its empirical formula is $C_{16}H_{25}N_2O_5S Na$, and its structural
33 formula is:



34
35 PRIMAXIN I.V. is buffered to provide solutions in the pH range of 6.5 to 7.5. There is no

36 significant change in pH when solutions are prepared and used as directed. (See
37 **COMPATIBILITY AND STABILITY.**) PRIMAXIN I.V. 250 contains 18.8 mg of sodium
38 (0.8 mEq) and PRIMAXIN I.V. 500 contains 37.5 mg of sodium (1.6 mEq). Solutions of
39 PRIMAXIN I.V. range from colorless to yellow. Variations of color within this range do
40 not affect the potency of the product.

41

42 **CLINICAL PHARMACOLOGY**

43

44 **Adults**

45

46 **Intravenous Administration**

47

48 Intravenous infusion of PRIMAXIN I.V. over 20 minutes results in peak plasma levels of
49 imipenem antimicrobial activity that range from 14 to 24 $\mu\text{g/mL}$ for the 250 mg dose,
50 from 21 to 58 $\mu\text{g/mL}$ for the 500 mg dose, and from 41 to 83 $\mu\text{g/mL}$ for the 1000 mg
51 dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below
52 1 $\mu\text{g/mL}$ or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute
53 intravenous infusion of PRIMAXIN I.V., range from 15 to 25 $\mu\text{g/mL}$ for the 250 mg dose,
54 from 31 to 49 $\mu\text{g/mL}$ for the 500 mg dose, and from 56 to 88 $\mu\text{g/mL}$ for the 1000 mg
55 dose.

56

57 The plasma half-life of each component is approximately 1 hour. The binding of
58 imipenem to human serum proteins is approximately 20% and that of cilastatin is
59 approximately 40%. Approximately, 70% of the administered imipenem is recovered in
60 the urine within 10 hours after which no further urinary excretion is detectable. Urine
61 concentrations of imipenem in excess of 10 $\mu\text{g/mL}$ can be maintained for up to 8 hours
62 with PRIMAXIN I.V. at the 500-mg dose. Approximately, 70% of the cilastatin sodium
63 dose is recovered in the urine within 10 hours of administration of PRIMAXIN I.V.

64

65 No accumulation of imipenem/cilastatin in plasma or urine is observed with regimens
66 administered as frequently as every 6 hours in patients with normal renal function.

67

68 Imipenem, when administered alone, is metabolized in the kidneys by
69 dehydropeptidase I resulting in relatively low levels in urine. Cilastatin sodium, an
70 inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that
71 when imipenem and cilastatin sodium are given concomitantly, fully adequate
72 antibacterial levels of imipenem are achieved in the urine.

73

74 After a 1 gram dose of PRIMAXIN I.V., the following average levels of imipenem were
75 measured (usually at 1 hour post dose except where indicated) in the tissues and fluids
76 listed:

77

Tissue or Fluid	n	Imipenem Level μg/mL or μg/g	Range
Vitreous Humor	3	3.4 (3.5 hours post dose)	2.88-3.6
Aqueous Humor	5	2.99 (2 hours post dose)	2.4-3.9
Lung Tissue	8	5.6 (median)	3.5-15.5
Sputum	1	2.1	-
Pleural	1	22.0	-
Peritoneal	12	23.9 S.D. ± 5.3(2hours post dose)	-
Bile	2	5.3 (2.25 hours post dose)	4.6-6.0
CSF	5	1.0 (4 hours post dose)	0.26-2.0
(uninflamed)	7	2.6 (2 hours post dose)	0.5-5.5
CSF (inflamed)	1	13.6	-
Fallopian Tubes	1	11.1	-
Endometrium	1	5.0	-
Myometrium	10	2.6	0.4-5.4
Bone	12	16.4	10.0-22.6
Interstitial Fluid	12	4.4	NA
Skin	12	4.4	NA
Fascia			

78 Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure
79 in the overdosage setting is questionable. (See **OVERDOSAGE**.)
80

81 Microbiology

82
83 The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its
84 greatest affinity is for penicillin binding proteins (PBPs) 1A, 1B, 2, 4, 5, and 6 of
85 *Escherichia coli*, and 1A, 1B, 2, 4, and 5 of *Pseudomonas aeruginosa*. The lethal effect
86 is related to binding to PBP 2 and PBP 1B.
87

88 Imipenem has a high degree of stability in the presence of beta-lactamases, both
89 penicillinases and cephalosporinases produced by gram-negative and gram-positive
90 bacteria. It is a potent inhibitor of beta-lactamases from certain gram-negative bacteria
91 which are inherently resistant to most beta-lactam antibiotics, e.g., *Pseudomonas*
92 *aeruginosa*, *Serratia* spp., and *Enterobacter* spp.
93

94 Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative
95 organisms. Imipenem is active against most strains of the following microorganisms *in*
96 *vitro* and in clinical infections treated with the intravenous formulation of imipenem-
97 cilastatin sodium. (See **INDICATIONS AND USAGE**.)
98
99

100 Gram-positive aerobes:
101
102 *Enterococcus faecalis* (formerly *S. faecalis*)
103 (NOTE: Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly
104 *S. faecium*].)
105 *Staphylococcus aureus* including penicillinase-producing strains
106 *Staphylococcus epidermidis* including penicillinase-producing strains
107 (NOTE: Methicillin-resistant staphylococci should be reported as resistant to
108 imipenem.)
109 *Streptococcus agalactiae* (Group B *Streptococcus*)
110 *Streptococcus pneumoniae*
111 *Streptococcus pyogenes*
112
113 Gram-negative aerobes:
114
115 *Acinetobacter* spp.
116 *Citrobacter* spp.
117 *Enterobacter* spp.
118 *Escherichia coli*
119 *Gardnerella vaginalis*
120 *Haemophilus influenzae*
121 *Haemophilus parainfluenzae*
122 *Klebsiella* spp.
123 *Morganella morganii*
124 *Proteus vulgaris*
125 *Providencia rettgeri*
126 *Pseudomonas aeruginosa*
127 (NOTE: Imipenem is inactive *in vitro* against *Xanthomonas* (*Pseudomonas*)
128 *maltophilia* and some strains of *P. cepacia*.)
129 *Serratia* spp., including *S. marcescens*
130
131 Gram-positive anaerobes:
132
133 *Bifidobacterium* spp.
134 *Clostridium* spp.
135 *Eubacterium* spp.
136 *Peptococcus* spp.
137 *Peptostreptococcus* spp.
138 *Propionibacterium* spp.
139
140 Gram-negative anaerobes:
141
142 *Bacteroides* spp., including *B. fragilis*

143 *Fusobacterium spp.*

144

145 The following in vitro data are available, **but their clinical significance is unknown.**
146 Imipenem exhibits in vitro minimum inhibitory concentrations (MIC's) of 4µg/mL or less
147 against most (≥90%) strains of the following microorganisms; however, the safety and
148 effectiveness of imipenem in treating clinical infections due to these microorganisms
149 have not been established in adequate and well-controlled clinical trials.

150

151 Gram-positive aerobes:

152

153 *Listeria monocytogenes*

154 *Nocardia spp.*

155 Group C *Streptococcus*

156 Group G *Streptococcus*

157 Viridans group streptococci

158

159 Gram-negative aerobes:

160

161 *Achromobacter spp.*

162 *Aeromonas hydrophila*

163 *Alcaligenes spp.*

164 *Bordetella bronchiseptica*

165 *Campylobacter spp.*

166 *Hafnia lare*

167 *Klebsiella oxytoca*

168 *Klebsiella pneumoniae*

169 *Moraxella spp.*

170 *Neisseria gonorrhoeae* including penicillinase-producing strains

171 *Pasteurella multocida*

172 *Plesiomonas shigelloides*

173 *Proteus mirabilis*

174 *Providencia stuartii*

175 *Salmonella spp.*

176 *Serratia proteamaculans* (formerly *S. liquefaciens*)

177 *Shigella spp.*

178 *Yersinia spp.*, including *Y. enterocolitica* and *Y. pseudotuberculosis*

179

180 Gram-positive anaerobes:

181

182 *Actinomyces spp.*

183 *Clostridium perfringens*

184 *Propionibacterium acnes*

185

186 Gram-negative anaerobes:

187
188 *Bacteroides* spp., including *B. bivius*, *B. disiens*, *B. distasonis*, *B. intermedius* (formerly
189 *B. melaninogenicus intermedius*), *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgatus*
190 *Porphyromonas asaccharolytica* (formerly *B. asaccharolyticus*)
191 *Veillonella* spp.

192
193 *In vitro* tests show imipenem to act synergistically with aminoglycoside antibiotics
194 against some isolates of *Pseudomonas aeruginosa*.

195
196 Susceptibility Tests:

197
198 *Measurement of MIC or minimum bactericidal concentration (MBC) and achieved*
199 *antimicrobial compound concentrations may be appropriate to guide therapy in some*
200 *infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug*
201 *concentrations achieved in infected body sites and other pharmacokinetic properties of*
202 *this antimicrobial drug product.)*

203
204 Diffusion Techniques:

205
206 Quantitative methods that require measurement of zone diameters provide reproducible
207 estimates of the susceptibility of bacteria to antimicrobial compounds. One such
208 standardized procedure¹ that has been recommended for use with disks to test the
209 susceptibility of microorganisms to imipenem uses the 10-mg imipenem disk.
210 Interpretation involves correlation of the diameter obtained in the disk test with the MIC
211 for imipenem.

212
213 Reports from the laboratory providing results of the standard single-disk susceptibility
214 test with a 10- μ g imipenem disk should be interpreted according to the following
215 criteria:

216

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 16	Susceptible (S)
14-15	Intermediate (I)
≤ 13	Resistant (R)

217 A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually
218 achievable concentrations of the antimicrobial compound in blood. A report of
219 "Intermediate" indicates that the result should be considered equivocal, and, if the
220 microorganism is not fully susceptible to alternative, clinically feasible drugs, the test
221 should be repeated. This category implies possible clinical applicability in body sites
222 where the drug is physiologically concentrated or in situations where high dosage of
223 drug can be used. This category also provides a buffer zone that prevents small

224 uncontrolled technical factors from causing major discrepancies in interpretation. A
225 report of "Resistant" indicates that usually achievable concentrations of the
226 antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy
227 should be selected.

228
229 Standardized susceptibility test procedures require the use of laboratory control
230 microorganisms. The 10- μ g imipenem disk should provide the following diameters in
231 these laboratory test quality control strains:
232

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>E. coli</i> ATCC 25922	26-32
<i>P. aeruginosa</i> ATCC 27853	20-28

233 Dilution Techniques:

234
235 Quantitative methods that are used to determine MIC's provide reproducible estimates
236 of the susceptibility of bacteria to antimicrobial compounds. One such procedure uses a
237 standardized dilution method² (broth, agar, or microdilution) or equivalent with
238 imipenem powder.

239
240 The MIC values obtained should be interpreted according to the following criteria:
241

<u>MIC (μg/mL)</u>	<u>Interpretation</u>
≤ 4	Susceptible (S)
8	Intermediate (I)
≥ 16	Resistant (R)

242 Interpretation should be as stated above for results using diffusion techniques.

243 As with standard diffusion techniques, dilution methods require the use of laboratory
244 control microorganisms. Standard imipenem powder should provide the following MIC
245 values:

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>E. coli</i> ATCC 25922	0.06-0.25
<i>S. aureus</i> ATCC 29213	0.015-0.06
<i>E. faecalis</i> ATCC 29212	0.5-2.0
<i>P. aeruginosa</i> ATCC 7853	1.0-4.0

246
247 Anaerobic techniques:

248
249 For anaerobic bacteria, the susceptibility to imipenem can be determined by the
250 reference agar dilution method or by alternate standardized test methods³.

251
252 As with other susceptibility techniques, the use of laboratory control microorganisms is
253 required. Standard imipenem powder should provide the following MIC values:

254
255 Reference Agar Dilution Testing:

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>B. fragilis</i> ATCC 25285	0.03-0.12
<i>B. thetaiotaomicron</i> ATCC 29741	0.06-0.25
<i>E. lentum</i> ATCC 43055	0.25-1.0

257
258 Broth Microdilution Testing:

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>B. thetaiotaomicron</i> ATCC 29741	0.06-0.25
<i>E. lentum</i> ATCC 43055	0.12-0.5

259 INDICATIONS AND USAGE

260 PRIMAXIN I.V. is indicated for the treatment of serious infections caused by susceptible
261 strains of the designated microorganisms in the conditions listed below:

- 262
263 (1) **Lower respiratory tract infections.** *Staphylococcus aureus* (penicillinase-
264 producing strains), *Acinetobacter species*, *Enterobacter species*, *Escherichia*
265 *coli*, *Haemophilus influenzae*, *Haemophilus parainfluenzae**, *Klebsiella*
266 *species*, *Serratia marcescens*
- 267
268 (2) **Urinary tract infections** (complicated and uncomplicated). *Enterococcus*
269 *faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)*,
270 *Enterobacter species*, *Escherichia coli*, *Klebsiella species*, *Morganella*
271 *morganii**, *Proteus vulgaris**, *Providencia rettgeri**, *Pseudomonas aeruginosa*

272 **Intra-abdominal infections.** *Enterococcus faecalis*, *Staphylococcus aureus*
273 (penicillinase-producing strains), *Staphylococcus epidermidis*, *Citrobacter*
274 *species*, *Enterobacter species*, *Escherichia coli*, *Klebsiella species*, *Morganella*
275 *morganii**, *Proteus species*, *Pseudomonas aeruginosa*, *Bifidobacterium species*,
276 *Clostridium species*, *Eubacterium species*, *Peptococcus species*,
277 *Peptostreptococcus species*, *Propionibacterium species**, *Bacteroides species*
278 including *B. fragilis*, *Fusobacterium species*

279
280 (4) **Gynecologic infections.** *Enterococcus faecalis*, *Staphylococcus aureus*
281 (penicillinase-producing strains)*, *Staphylococcus epidermidis*, *Streptococcus*
282 *agalactiae* (Group B streptococcus), *Enterobacter species**, *Escherichia coli*,
283 *Gardnerella vaginalis*, *Klebsiella species**, *Proteus species*, *Bifidobacterium*
284 *species**, *Peptococcus species**, *Peptostreptococcus species*, *Propionibacterium*
285 *species**, *Bacteroides species* including *B. fragilis**

286
287 (5) **Bacterial septicemia.** *Enterococcus faecalis*, *Staphylococcus aureus*
288 (penicillinase-producing strains), *Enterobacter species*, *Escherichia coli*, *Klebsiella*
289 *species*, *Pseudomonas aeruginosa*, *Serratia species**, *Bacteroides species*
290 including *B. fragilis**

291
292 (6) **Bone and joint infections.** *Enterococcus faecalis*, *Staphylococcus aureus*
293 (penicillinase-producing strains), *Staphylococcus epidermidis*, *Enterobacter species*,
294 *Pseudomonas aeruginosa*

295
296 (7) **Skin and skin structure infections.** *Enterococcus faecalis*, *Staphylococcus*
297 *aureus* (penicillinase-producing strains), *Staphylococcus epidermidis*, *Acinetobacter*
298 *species*, *Citrobacter species*, *Enterobacter species*, *Escherichia coli*, *Klebsiella*
299 *species*, *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgen**,
300 *Pseudomonas aeruginosa*, *Serratia species*, *Peptococcus species*,
301 *Peptostreptococcus species*, *Bacteroides species* including *B. fragilis*,
302 *Fusobacterium species**

303
304

*Efficacy for this organism in this organ system was studied in fewer than 10
305 infections.

306
307 (8) **Endocarditis.** *Staphylococcus aureus* (penicillinase-producing strains)

308
309 (9) **Polymicrobial infections.** PRIMAXIN I.V. is indicated for polymicrobial infections
310 including those in which *S. pneumoniae* (pneumonia, septicemia), *S. pyogenes*
311 (skin and skin structure), or nonpenicillinase-producing *S. aureus* is one of the
312 causative organisms. However, monobacterial infections due to these organisms
313 are usually treated with narrower spectrum antibiotics, such as penicillin G.

314

315 PRIMAXIN I.V. is not indicated in patients with meningitis because safety and efficacy
316 have not been established.

317

318 For Pediatric Use information, See **PRECAUTIONS**, Pediatric Use, and **DOSAGE AND**
319 **ADMINISTRATION** sections.

320

321 Because of its broad spectrum of bactericidal activity against gram-positive and gram-
322 negative aerobic and anaerobic bacteria, PRIMAXIN I.V. is useful for the treatment of
323 mixed infections and as presumptive therapy prior to the identification of the causative
324 organisms.

325

326 Although clinical improvement has been observed in patients with cystic fibrosis,
327 chronic pulmonary disease, and lower respiratory tract infections caused by
328 *Pseudomonas aeruginosa*, bacterial eradication may not necessarily be achieved.

329

330 As with other beta-lactam antibiotics, some strains of *Pseudomonas aeruginosa* may
331 develop resistance fairly rapidly during treatment with PRIMAXIN I.V. During therapy of
332 *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done
333 when clinically appropriate.

334

335 Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and
336 aminoglycosides, have been shown to respond to treatment with PRIMAXIN I.V.

337

CONTRAINDICATIONS

338 PRIMAXIN I.V. is contraindicated in patients who have shown hypersensitivity to any
339 component of this product.

340

WARNINGS

341 **SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC)**
342 **REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH**
343 **BETA-LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS**
344 **WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.**

345 **THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN**
346 **HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY**
347 **REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE**
348 **INITIATING THERAPY WITH PRIMAXIN I.V., CAREFUL INQUIRY SHOULD BE MADE**
349 **CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS,**
350 **CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN**
351 **ALLERGIC REACTION OCCURS, PRIMAXIN SHOULD BE DISCONTINUED.**

352 **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY**
353 **TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND**
354 **AIRWAY MANAGEMENT, INCLUDING INTUBATION, MAY ALSO BE**

355 **ADMINISTERED AS INDICATED.**

356
357 Seizures and other CNS adverse experiences, such as confusional states and
358 myoclonic activity, have been reported during treatment with PRIMAXIN I.V. (See
359 **PRECAUTIONS.**)

360
361 **Pseudomembranous colitis has been reported with nearly all antibacterial agents,**
362 **including imipenem-cilastatin sodium, and may range in severity from mild to life**
363 **threatening. Therefore, it is important to consider this diagnosis in patients who**
364 **present with diarrhea subsequent to the administration of antibacterial agents.**

365
366 Treatment with antibacterial agents alters the normal flora of the colon and may permit
367 overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is
368 one primary cause of "antibiotic-associated colitis".

369
370 After the diagnosis of pseudomembranous colitis has been established, therapeutic
371 measures should be initiated. Mild cases of pseudomembranous colitis usually respond
372 to drug discontinuation alone. In moderate to severe cases, consideration should be
373 given to management with fluids and electrolytes, protein supplementation and
374 treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

375 **PRECAUTIONS**

376 **General**

377
378 CNS adverse experiences such as confusional states, myoclonic activity, and seizures
379 have been reported during treatment with PRIMAXIN I.V., especially when
380 recommended dosages were exceeded. These experiences have occurred most
381 commonly in patients with CNS disorders (e.g., brain lesions or history of seizures)
382 and/or compromised renal function. However, there have been reports of CNS adverse
383 experiences in patients who had no recognized or documented underlying CNS
384 disorder or compromised renal function.

385
386 When recommended doses were exceeded, adult patients with creatinine clearances of
387 ≤ 20 mL/min/1.73 m², whether or not undergoing hemodialysis, had a higher risk of
388 seizure activity than those without impairment of renal function. Therefore, close
389 adherence to the dosing guidelines for these patients is recommended. (See **DOSAGE**
390 **AND ADMINISTRATION.**)

391
392 Patients with creatinine clearances of ≤ 5 mL/min/1.73 m² should not receive
393 PRIMAXIN I.V. unless hemodialysis is instituted within 48 hours.

394
395 For patients on hemodialysis, PRIMAXIN I.V. is recommended only when the benefit
396 outweighs the potential risk of seizures.

397 Close adherence to the recommended dosage and dosage schedules is urged,
398 especially in patients with known factors that predispose to convulsive activity.
399 Anticonvulsant therapy should be continued in patients with known seizure disorders. If
400 focal tremors, myoclonus, or seizures occur, patients should be evaluated
401 neurologically, placed on anticonvulsant therapy if not already instituted, and the
402 dosage of PRIMAXIN I.V. re-examined to determine whether it should be decreased or
403 the antibiotic discontinued.

404
405 As with other antibiotics, prolonged use of PRIMAXIN I.V. may result in overgrowth of
406 nonsusceptible organisms. Repeated evaluation of the patient's condition is essential.
407 If superinfection occurs during therapy, appropriate measures should be taken.

409 **Laboratory Tests**

410
411 While PRIMAXIN I.V. possesses the characteristic low toxicity of the beta-lactam group
412 of antibiotics, periodic assessment of organ system functions, including renal, hepatic,
413 and hematopoietic, is advisable during prolonged therapy.

415 **Drug Interactions**

416
417 Generalized seizures have been reported in patients who received ganciclovir and
418 PRIMAXIN. These drugs should not be used concomitantly unless the potential benefits
419 outweigh the risks.

420
421 Since concomitant administration of PRIMAXIN and probenecid results in only minimal
422 increases in plasma levels of imipenem and plasma half-life, it is not recommended that
423 probenecid be given with PRIMAXIN.

424
425 PRIMAXIN should not be mixed with or physically added to other antibiotics. However,
426 PRIMAXIN may be administered concomitantly with other antibiotics, such as
427 aminoglycosides.

429 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

430
431 Long term studies in animals have not been performed to evaluate carcinogenic
432 potential of imipenem-cilastatin. Genetic toxicity studies were performed in a variety of
433 bacterial and mammalian tests *in vivo* and *in vitro*. The tests used were:
434 V79 mammalian cell mutagenesis assay (imipenem-cilastatin sodium alone and
435 imipenem alone), Ames test (cilastatin sodium alone and imipenem alone),
436 unscheduled DNA synthesis assay (imipenem-cilastatin sodium) and *in vivo* mouse
437 cytogenetics test (imipenem-cilastatin sodium). None of these tests showed any
438 evidence of genetic alterations.

439

440 Reproductive tests in male and female rats were performed with imipenem-cilastatin
441 sodium at dosage levels up to 11 times the usual human dose of the intravenous
442 formulation (on a mg/kg basis). Slight decreases in live fetal body weight were
443 restricted to the highest dosage level. No other adverse effects were observed on
444 fertility, reproductive performance, fetal viability, growth or postnatal development of
445 pups. Similarly, no adverse effects on the fetus or on lactation were observed when
446 imipenem-cilastatin sodium was administered to rats late in gestation.

447 **Pregnancy: Teratogenic Effects**

449
450 Pregnancy Category C: Teratology studies with cilastatin sodium in rabbits and rats at
451 6 to 20 times ^{††} the maximum recommended human dose of the intravenous formulation
452 of imipenem-cilastatin sodium (50 mg/kg/day^{††}), respectively, showed no evidence of
453 adverse effect on the fetus. No evidence of teratogenicity was observed in rabbits and
454 rats given imipenem at doses up to 1 and 18 times the maximum recommended daily
455 human dose of the intravenous formulation of imipenem-cilastatin sodium, respectively.

456
457 Teratology studies with imipenem-cilastatin sodium at doses up to 11 times the usual
458 recommended human dose of the intravenous formulation (30 mg/kg/day^{††}) in pregnant
459 mice and rats during the period of major organogenesis revealed no evidence of
460 teratogenicity.

461
462 Imipenem-cilastatin sodium, when administered to pregnant rabbits at dosages
463 equivalent to the usual human dose of the intravenous formulation and higher, caused
464 body weight loss, diarrhea, and maternal deaths. When comparable doses of
465 imipenem-cilastatin sodium were given to non-pregnant rabbits, body weight loss,
466 diarrhea, and deaths were also observed. This intolerance is not unlike that seen with
467 other beta-lactam antibiotics in this species and is probably due to alteration of gut
468 flora.

469
470 A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium
471 at doses of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous
472 injection) resulted in maternal toxicity including emesis, inappetence, body weight loss,
473 diarrhea, abortion, and death in some cases. In contrast, no significant toxicity was
474 observed when non-pregnant cynomolgus monkeys were given doses of imipenem-
475 cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When doses of
476 imipenem-cilastatin sodium (approximately 100 mg/kg/day or approximately 2 times the
477 maximum recommended daily human dose of the intravenous formulation) were
478 administered to pregnant cynomolgus monkeys at an intravenous infusion rate which
479 mimics human clinical use, there was minimal maternal intolerance (occasional
480 emesis), no maternal deaths, no evidence of teratogenicity, but an increase in
481 embryonic loss relative to control groups.

483 There are, however, no adequate and well-controlled studies in pregnant women.
484 PRIMAXIN I.V. should be used during pregnancy only if the potential benefit justifies
485 the potential risk to the mother and fetus.

486
487 ^{††} Based on patient weight of 70 kg.

488 489 **Nursing Mothers**

490
491 It is not known whether imipenem-cilastatin sodium is excreted in human milk. Because
492 many drugs are excreted in human milk, caution should be exercised when
493 PRIMAXIN I.V. is administered to a nursing woman.

494 495 **Pediatric Use**

496 Use of PRIMAXIN I.V. in pediatric patients neonates to 16 years of age is supported by
497 evidence from adequate and well-controlled studies of PRIMAXIN I.V. in adults and by
498 the following clinical studies and published literature in pediatric patients: Based on
499 published studies of 178** pediatric patients ≥3 months of age (with non-CNS
500 infections), the recommended dose of PRIMAXIN I.V. is 15-25mg/kg/dose administered
501 every six hours. Doses of 25 mg/kg/dose in patients 3 months to <3 years of age, and
502 15mg/kg/dose in patients 3-12 years of age were associated with mean trough plasma
503 concentrations of imipenem of 1.1±0.4 µg /mL and 0.6±0.2µg /mL following multiple 60-
504 minute infusions, respectively; trough urinary concentrations of imipenem were in
505 excess of 10 µg/mL for both doses. These doses have provided adequate plasma and
506 urine concentrations for the treatment of non-CNS infections. Based on studies in
507 adults, the maximum daily dose for treatment of infections with fully susceptible
508 organisms is 2.0 g per day, and of infections with moderately susceptible organisms
509 (primarily some strains of *P. aeruginosa*) is 4.0 g/day. (See Table 1 **DOSAGE AND**
510 **ADMINISTRATION.**) Higher doses (up to 90 mg/kg/day in older children) have been
511 used in patients with cystic fibrosis. (See **DOSAGE AND ADMINISTRATION.**)

512
513 Based on studies of 135*** pediatric patients ≤3 months of age (weighing ≥1,500 gms),
514 the following dosage schedule is recommended for non-CNS infections:

515 < 1 wk of age: 25 mg/kg every 12 hrs

516 1-4 wks of age: 25 mg/kg every 8 hrs

517 4 wks-3 mos. of age: 25 mg/kg every 6 hrs.

518
519 In a published dose-ranging study of smaller premature infants (670-1,890 gms) in the
520 first week of life, a dose of 20 mg/kg q12h by 15-30 minutes infusion was associated
521 with mean peak and trough plasma imipenem concentrations of 43 µg/mL and 1.7
522 µg/mL after multiple doses, respectively. However, moderate accumulation of cilastatin
523 in neonates may occur following multiple doses of PRIMAXIN I.V. The safety of this
524 accumulation is unknown.

525 PRIMAXIN I.V. is not recommended in pediatric patients with CNS infections because
526 of the risk of seizures.

527
528 PRIMAXIN I.V. is not recommended in pediatric patients <30 kg with impaired renal
529 function, as no data are available.

530
531 ** Two patients were less than 3 months of age.
532 *** One patient was greater than 3 months of age.

533 **ADVERSE REACTIONS**

534 **Adults**

535
536 PRIMAXIN I.V. is generally well tolerated. Many of the 1,723 patients treated in clinical
537 trials were severely ill and had multiple background diseases and physiological
538 impairments, making it difficult to determine causal relationship of adverse experiences
539 to therapy with PRIMAXIN I.V.

540 541 **Local Adverse Reactions**

542
543 Adverse local clinical reactions that were reported as possibly, probably, or definitely
544 related to therapy with PRIMAXIN I.V. were:

545
546 Phlebitis/thrombophlebitis — 3.1%
547 Pain at the injection site — 0.7%
548 Erythema at the injection site — 0.4%
549 Vein induration — 0.2%
550 Infused vein infection — 0.1%

551 552 **Systemic Adverse Reactions**

553
554 The most frequently reported systemic adverse clinical reactions that were reported as
555 possibly, probably, or definitely related to PRIMAXIN I.V. were nausea (2.0%), diarrhea
556 (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures
557 (0.4%) (see **PRECAUTIONS**), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%),
558 somnolence (0.2%).

559
560 Additional adverse systemic clinical reactions reported as possibly, probably, or
561 definitely drug related occurring in less than 0.2% of the patients or reported since the
562 drug was marketed are listed within each body system in order of decreasing severity:

563
564 Gastrointestinal — pseudomembranous colitis (the onset of pseudomembranous colitis
565 symptoms may occur during or after antibacterial treatment, see **WARNINGS**),
566 hemorrhagic colitis, hepatitis, jaundice, gastroenteritis, abdominal pain, glossitis,

567 tongue papillar hypertrophy, staining of the teeth and/or tongue, heartburn, pharyngeal
568 pain, increased salivation; Hematologic — pancytopenia, bone marrow depression,
569 thrombocytopenia, neutropenia, leukopenia, hemolytic anemia; CNS —
570 encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache,
571 psychic disturbances including hallucinations; Special Senses — hearing loss, tinnitus,
572 taste perversion; Respiratory — chest discomfort, dyspnea, hyperventilation, thoracic
573 spine pain; Cardiovascular — palpitations, tachycardia; Skin — Stevens-Johnson
574 syndrome, toxic epidermal necrolysis, erythema multiforme, angioneurotic edema,
575 flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae;
576 Body as a whole — polyarthralgia, asthenia/weakness, drug fever; Renal — acute renal
577 failure, oliguria/anuria, polyuria, urine discoloration. The role of PRIMAXIN I.V. in
578 changes in renal function is difficult to assess, since factors predisposing to pre-renal
579 azotemia or to impaired renal function usually have been present.

580

581 Adverse Laboratory Changes

582

583 Adverse laboratory changes without regard to drug relationship that were reported
584 during clinical trials or reported since the drug was marketed were:

585

586 Hepatic: Increased ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, and
587 LDH

588

589 Hemic: Increased eosinophils, positive Coombs test, increased WBC, increased
590 platelets, decreased hemoglobin and hematocrit, agranulocytosis, increased
591 monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils

592

593 Electrolytes: Decreased serum sodium, increased potassium, increased chloride

594

595 Renal: Increased BUN, creatinine

596

597 Urinalysis: Presence of urine protein, urine red blood cells, urine white blood cells,
598 urine casts, urine bilirubin, and urine urobilinogen

599 Pediatric Patients

600

601 In studies of 178 pediatric patients, ≥ 3 months of age the following adverse events
602 were noted:

603

604 The Most Common Clinical Adverse Experiences Without Regard
605 to Drug Relationship
606 (Patient Incidence $>1\%$)

607

608 Adverse Experience No. of Patients (%)

609

610 Digestive System

611 Diarrhea 7* (3.9)

612 Gastroenteritis 2 (1.1)

613 Vomiting 2* (1.1)

614

615 Skin

616 Rash 4 (2.2)

617 Irritation, I.V. site 2 (1.1)

618

619 Urogenital System

620 Urine discoloration 2 (1.1)

621

622 Cardiovascular System

623 Phlebitis 4 (2.2)

624

625 *One patient had both vomiting and diarrhea and is counted in each category.

626 In studies of 135 patients (newborn to 3 months of age), the following adverse events
627 were noted:

628
629 **The Most Common Clinical Adverse Experiences**
630 **Without Regard to Drug Relationship**
631 **(Patient Incidence >1%)**

632	Adverse Experience	No. of Patients (%)
633		
634		
635	Digestive System	
636	Diarrhea	4 (3.0%)
637	Oral Candidiasis	2 (1.5%)
638		
639	Skin	
640	Rash	2 (1.5%)
641		
642	Urogenital System	
643	Oliguria/anuria	3 (2.2%)
644		
645	Cardiovascular System	
646	Tachycardia	2 (1.5%)
647		
648	Nervous System	
649	Convulsions	8 (5.9%)
650		

651 Patients \geq 3 months of age With Normal Pretherapy But Abnormal During Therapy
 652 Laboratory Values

654 Laboratory Parameter	655 Abnormality	656 No. of Patients with Abnormalities/ No. of Patients with Lab Done (%)	
657 Hemoglobin	658 Age < 4-5 mos.: <10 gm % 6 mos.-12 yrs.: <11.5 gm%	19/129	(14.7)
660 Hematocrit	661 Age < 4-5 mos.: <30 vol % 6 mos.-12 yrs.: <34.5 vol %	23/129	(17.8)
662 Neutrophils	663 $\leq 1000/\text{mm}^3$ (absolute)	4/123	(3.3)
663 Eosinophils	664 $\geq 7\%$	15/117	(12.8)
664 Platelet Count	665 $\geq 500 \text{ ths}/\text{mm}^3$	16/119	(13.4)
665 Urine Protein	666 ≥ 1	8/97	(8.2)
666 Serum Creatinine	667 >1.2 mg/dl	0/105	(0)
667 BUN	668 >22 mg/dl	0/108	(0)
668 AST (SGOT)	669 >36 IU/L	14/78	(17.9)
669 ALT (SGPT)	>30 IU/L	10/93	(10.8)

671 Examination of published literature and spontaneous adverse event reports suggested a
 672 similar spectrum of adverse events in adult and pediatric patients.

674 Patients (<3 months of age) With Normal Pretherapy But Abnormal During Therapy
 675 Laboratory Values

677 Laboratory Parameter	678 No. of Patients with Abnormalities* (%)
679 Eosinophil Count \uparrow	11 (9.0%)
680 Hematocrit \downarrow	3 (2.0%)
681 Hematocrit \uparrow	1 (1.0%)
682 Platelet Count \uparrow	5 (4.0%)
683 Platelet Count \downarrow	2 (2.0%)
684 Serum Creatinine \uparrow	5 (5.0%)
685 Bilirubin \uparrow	3 (3.0%)
686 Bilirubin \downarrow	1 (1.0%)
687 AST (SGOT) \uparrow	5 (6.0%)
688 ALT (SGPT) \uparrow	3 (3.0%)
689 Serum Alkaline Phosphate \uparrow	2 (3.0%)

691 * The denominator used for percentages was the number of patients for whom the test
 692 was performed during or post treatment and, therefore, varies by test.

693

OVERDOSAGE

694 The acute intravenous toxicity of imipenem-cilastatin sodium in a ratio of 1:1 was studied
695 in mice at doses of 751 to 1359 mg/kg. Following drug administration, ataxia was rapidly
696 produced and clonic convulsions were noted in about 45 minutes. Deaths occurred within
697 4-56 minutes at all doses.

698

699 The acute intravenous toxicity of imipenem-cilastatin sodium was produced within
700 5-10 minutes in rats at doses of 771 to 1583 mg/kg. In all dosage groups, females had
701 decreased activity, bradypnea, and ptosis with clonic convulsions preceding death; in
702 males, ptosis was seen at all dose levels while tremors and clonic convulsions were seen
703 at all but the lowest dose (771 mg/kg). In another rat study, female rats showed ataxia,
704 bradypnea, and decreased activity in all but the lowest dose (550 mg/kg); deaths were
705 preceded by clonic convulsions. Male rats showed tremors at all doses and clonic
706 convulsions, and ptosis were seen at the two highest doses (1130 and 1734 mg/kg).
707 Deaths occurred between 6 and 88 minutes with doses of 771 to 1734 mg/kg.

708

709 In the case of overdosage, discontinue PRIMAXIN I.V., treat symptomatically, and institute
710 supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable.
711 However, usefulness of this procedure in the overdosage setting is questionable.

712

DOSAGE AND ADMINISTRATION

713 Adults

714

715 The dosage recommendations for PRIMAXIN I.V. represent the quantity of imipenem to be
716 administered. An equivalent amount of cilastatin is also present in the solution. Each
717 125 mg, 250 mg, or 500 mg dose should be given by intravenous administration over 20
718 to 30 minutes. Each 750 mg or 1000 mg dose should be infused over 40 to 60 minutes. In
719 patients who develop nausea during the infusion, the rate of infusion may be slowed.

720

721 The total daily dosage for PRIMAXIN I.V. should be based on the type or severity of
722 infection and given in equally divided doses based on consideration of degree of
723 susceptibility of the pathogen(s), renal function, and body weight. Adult patients with
724 impaired renal function, as judged by creatinine clearance ≤ 70 mL/min/1.73 m², require
725 adjustment of dosage as described in the succeeding section of these guidelines.

726

727 Intravenous Dosage Schedule for Adults with Normal Renal Function and Body Weight
728 ≥ 70 kg.

729

730 Doses cited in Table I are based on a patient with normal renal function and a body
731 weight of 70 kg. These doses should be used for a patient with a creatinine clearance of
732 ≥ 71 mL/min/1.73 m² and a body weight of ≥ 70 kg. A reduction in dose must be made for a
733 patient with a creatinine clearance of ≤ 70 mL/min/1.73 m² and/or a body weight less than

734 70 kg. (See Tables II and III.)

735

736 Dosage regimens in column A of Table I are recommended for infections caused by fully
737 susceptible organisms which represent the majority of pathogenic species. Dosage
738 regimens in column B of Table I are recommended for infections caused by organisms
739 with moderate susceptibility to imipenem, primarily some strains of *P. aeruginosa*.

TABLE I
INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH
NORMAL RENAL FUNCTION AND BODY WEIGHT ≥ 70 kg

Type or Severity of Infection	A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately susceptible organisms, primarily some strains of <i>P. aeruginosa</i>
Mild	250 mg q6h (TOTAL DAILY DOSE = 1.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g)
Moderate	500 mg q8h (TOTAL DAILY DOSE = 1.5g) or 500 mg q6h (TOTAL DAILY DOSE = 2.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g) or 1 g q8h (TOTAL DAILY DOSE = 3.0g)
Severe, life threatening only	500 mg q6h (TOTAL DAILY DOSE = 2.0g)	1 g q8h (TOTAL DAILY DOSE = 3.0g) or 1 g q6h (TOTAL DAILY DOSE = 4.0g)
Uncomplicated urinary tract infection	250 mg q6h (TOTAL DAILY DOSE = 1.0g)	250 mg q6h (TOTAL DAILY DOSE = 1.0g)
Complicated urinary tract infection	500 mg q6h (TOTAL DAILY DOSE = 2.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g)

741
742 Due to the high antimicrobial activity of PRIMAXIN I.V., it is recommended that the
743 maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.
744 There is no evidence that higher doses provide greater efficacy. However, patients over
745 twelve years of age with cystic fibrosis and normal renal function have been treated with
746 PRIMAXIN I.V. at doses up to 90 mg/kg/day in divided doses, not exceeding 4.0 g/day.

747 **Reduced Intravenous Schedule for Adults with Impaired Renal Function and/or Body**
748 **Weight <70 kg**

749
750 Patients with creatinine clearance of ≤ 70 mL/min/1.73 m² and/or body weight less than
751 70 kg require dosage reduction of PRIMAXIN I.V. as indicated in the tables below.
752 Creatinine clearance may be calculated from serum creatinine concentration by the
753 following equation:
754

$$T_{cc} \text{ (Males)} = \frac{(\text{wt. in kg}) (140 - \text{age})}{(72) (\text{creatinine in mg/dL})}$$

$$T_{cc} = 0.85 \times \text{above value}$$

755
756 To determine the dose for adults with impaired renal function and/or reduced body
757 weight:

- 758
- 759 1. Choose a total daily dose from Table I based on infection characteristics.
 - 760
 - 761 2. a) If the total daily dose is 1.0 g, 1.5 g, or 2.0 g, use the appropriate
762 subsection of Table II and continue with step 3.
763
764 b) If the total daily dose is 3.0 g or 4.0 g, use the appropriate subsection of Table III
765 and continue with step 3.
766
 - 767 3. From Table II or III:
768
769 a) Select the body weight on the far left which is closest to the patient's body
770 weight (kg).
771
772 b) Select the patient's creatinine clearance category.
773
774 c) Where the row and column intersect is the reduced dosage regimen.

TABLE II
REDUCED INTRAVENOUS DOSAGE OF PRIMAXIN I.V. IN ADULT PATIENTS WITH
IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT <70 kg

		If TOTAL DAILY DOSE from TABLE I is:											
		1.0 g/day				1.5 g/day				2.0 g/day			
and Body Weight (kg) is:	and creatinine clearance (mL/min/1.73 m ²) is:				and creatinine clearance (mL/min/1.73 m ²) is:				and creatinine clearance (mL/min/1.73 m ²) is:				
	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20	
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:				
≥ 70	250 q6h	250 q8h	250 q12h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h	
60	250 q8h	125 q6h	250 q12h	125 q12h	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h	
50	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h	250 q6h	250 q6h	250 q8h	250 q12h	
40	125 q6h	125 q8h	125 q12h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h	
30	125 q8h	125 q8h	125 q12h	125 q12h	125 q6h	125 q8h	125 q8h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h	

TABLE III
REDUCED INTRAVENOUS DOSAGE OF PRIMAXIN I.V. IN ADULT PATIENTS WITH
IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT <70 kg

		If TOTAL DAILY DOSE from TABLE I is:							
		3.0 g/day				4.0 g/day			
and Body Weight (kg) is:		and creatinine clearance (mL/min/1.73 m ²) is:				and creatinine clearance (mL/min/1.73 m ²) is:			
		≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20
		then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥70		1000 q8h	500 q6h	500 q8h	500 q12h	1000 q6h	750 q8h	500 q6h	500 q12h
60		750 q8h	500 q8h	500 q8h	500 q12h	1000 q8h	750 q8h	500 q8h	500 q12h
50		500 q6h	500 q8h	250 q6h	250 q12h	750 q8h	500 q6h	500 q8h	500 q12h
40		500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
30		250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h

759 Patients with creatinine clearances of 6 to 20 mL/min/1.73 m² should be treated with
760 PRIMAXIN I.V. 125 mg or 250 mg every 12 hours for most pathogens. There may be an
761 increased risk of seizures when doses of 500 mg every 12 hours are administered to
762 these patients.

763

764 Patients with creatinine clearance ≤ 5 mL/min/1.73 m² should not receive PRIMAXIN I.V.
765 unless hemodialysis is instituted within 48 hours. There is inadequate information to
766 recommend usage of PRIMAXIN I.V. for patients undergoing peritoneal dialysis.

767

768 Hemodialysis

769

770 When treating patients with creatinine clearances of ≤ 5 mL/min/1.73 m² who are
771 undergoing hemodialysis, use the dosage recommendations for patients with creatinine
772 clearances of 6-20 mL/min/1.73 m². (See Reduced Intravenous Dosage Schedule for
773 Adults with Impaired Renal Function and/or Body Weight <70 kg.) Both imipenem and
774 cilastatin are cleared from the circulation during hemodialysis. The patient should
775 receive PRIMAXIN I.V. after hemodialysis and at 12 hour intervals timed from the end of
776 that hemodialysis session. Dialysis patients, especially those with background CNS
777 disease, should be carefully monitored; for patients on hemodialysis, PRIMAXIN I.V. is
778 recommended only when the benefit outweighs the potential risk of seizures. (See
779 **PRECAUTIONS.**)

780

781 Pediatric Patients

782 See **PRECAUTIONS**, Pediatric Patients.

783 For pediatric patients ≥ 3 months of age, the recommended dose for non-CNS infections
784 is 15-25 mg/kg/dose administered every six hours. Based on studies in adults, the
785 maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g
786 per day, and of infections with moderately susceptible organisms (primarily some strains
787 of *P. aeruginosa*) is 4.0 g/day. Higher doses (up to 90 mg/kg/day in older children) have
788 been used in patients with cystic fibrosis. (See **DOSAGE AND ADMINISTRATION.**)

789

790 For pediatric patients ≤ 3 months of age (weighing $\geq 1,500$ gms), the following dosage
791 schedule is recommended for non-CNS infections:

792 < 1 wk of age: 25 mg/kg every 12 hrs

793 1-4 wks of age: 25 mg/kg every 8 hrs

794 4 wks-3 mos. of age: 25 mg/kg every 6 hrs.

795

796 Doses less than or equal to 500 mg should be given by intravenous infusion over 15-30
797 minutes. Doses greater than 500 mg should be given by intravenous infusion over 40-60
798 minutes.

799

800

801 PRIMAXIN I.V. is not recommended in pediatric patients with CNS infections because of
802 the risk of seizures.

803

804 PRIMAXIN I.V. is not recommended in pediatric patients <30 kg with impaired renal
805 function, as no data are available.

806 PREPARATION OF SOLUTION

807 Infusion Bottles

808

809 Contents of the infusion bottles of PRIMAXIN I.V. Powder should be restored with
810 100 mL of diluent (see list of diluents under **COMPATIBILITY AND STABILITY**) and
811 shaken until a clear solution is obtained.

812 *Vials*

813

814 Contents of the vials must be suspended and transferred to 100 mL of an appropriate
815 infusion solution.

816

817 A suggested procedure is to add approximately 10 mL from the appropriate infusion
818 solution (see list of diluents under **COMPATIBILITY AND STABILITY**) to the vial. Shake
819 well and transfer the resulting suspension to the infusion solution container.

820

821 **Benzyl alcohol as a preservative has been associated with toxicity in neonates.**
822 **While toxicity has not been demonstrated in pediatric patients greater than three**
823 **months of age, small pediatric patients in this age range may also be at risk for**
824 **benzyl alcohol toxicity. Therefore, diluents containing benzyl alcohol should not**
825 **be used when PRIMAXIN I.V. is constituted for administration to pediatric patients**
826 **in this age range.**

827

828 **CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.**

829

830 Repeat with an additional 10 mL of infusion solution to ensure complete transfer of vial
831 contents to the infusion solution. **The resulting mixture should be agitated until clear.**

832 *ADD-Vantage[®] ^{†††} Vials*

833

834 ^{†††} Registered trademark of Abbott Laboratories, Inc.

835

836 See separate INSTRUCTIONS FOR USE OF 'PRIMAXIN I.V.' IN ADD-Vantage[®] VIALS.

837

838 PRIMAXIN I.V. in ADD-Vantage[®] vials should be reconstituted with ADD-Vantage[®]
839 diluent containers containing 100 mL of either 0.9% Sodium Chloride Injection or 100 mL
840 5% Dextrose Injection.

841

842

COMPATIBILITY AND STABILITY

843

Before Reconstitution:

844

The dry powder should be stored at a temperature below 25°C (77°F).

845

Reconstituted Solutions:

847

Solutions of PRIMAXIN I.V. range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

848

849

850

PRIMAXIN I.V., as supplied in infusion bottles and vials and reconstituted as above with the following diluents, maintains satisfactory potency for four hours at room temperature or for 24 hours under refrigeration (5°C). Solutions of PRIMAXIN I.V. should not be frozen.

851

852

853

854

0.9% Sodium Chloride Injection

855

5% or 10% Dextrose Injection

856

5% Dextrose and 0.9% Sodium Chloride Injection

857

5% Dextrose Injection with 0.225% or 0.45% saline solution

858

5% Dextrose Injection with 0.15% potassium chloride solution

859

Mannitol 5% and 10%

860

861

PRIMAXIN I.V. is supplied in single dose ADD-Vantage® vials and should be prepared as directed in the accompanying INSTRUCTIONS FOR USE OF 'PRIMAXIN I.V.' IN ADD-Vantage® VIALS using ADD-Vantage® diluent containers containing 100 mL of either 0.9% Sodium Chloride Injection or 5% Dextrose Injection. When prepared with either of these diluents, PRIMAXIN I.V. maintains satisfactory potency for 4 hours at room temperature.

862

863

864

865

866

867

868

PRIMAXIN I.V. should not be mixed with or physically added to other antibiotics.

869

However, PRIMAXIN I.V. may be administered concomitantly with other antibiotics, such as aminoglycosides.

870

871

HOW SUPPLIED

872

PRIMAXIN I.V. is supplied as a sterile powder mixture in vials and infusion bottles containing imipenem (anhydrous equivalent) and cilastatin sodium as follows:

873

874

875

No. 3514 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer

876

877

NDC 0006-3514-58 in trays of 25 vials

878

(6505-01-332-4793 250 mg, 25's).

879

880

No. 3516 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer

881

882

NDC 0006-3516-59 in trays of 25 vials

883 (6505-01-332-4794 500 mg, 25's).

884

385 No. 3515 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg
386 sodium bicarbonate as a buffer

887 **NDC 0006-3515-74** in trays of 10 infusion bottles

888 (6505-01-246-4126 infusion bottle, 10's).

889

890 No. 3517 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg
891 sodium bicarbonate as a buffer

892 **NDC 0006-3517-75** in trays of 10 infusion bottles

893 (6505-01-234-0240 infusion bottle, 10's).

894

895 No. 3551 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg
896 sodium bicarbonate as a buffer

897 **NDC 0006-3551-58** in trays of 25 ADD-Vantage[®] vials.

898

899 No. 3552 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg
900 sodium bicarbonate as a buffer

901 **NDC 0006-3552-59** in trays of 25 ADD-Vantage[®] vials

902 (6505-01-279-9627 500 mg ADD-Vantage[®], 25's).

903

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908

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