

## PRESCRIBING INFORMATION

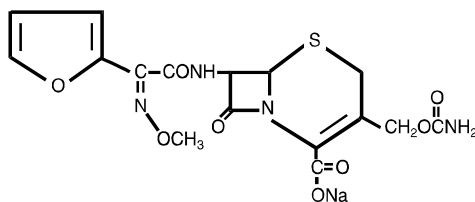
### ZINACEF<sup>®</sup> (cefuroxime for injection)

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To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZINACEF and other antibacterial drugs, ZINACEF should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### DESCRIPTION

Cefuroxime is a semisynthetic, broad-spectrum, cephalosporin antibiotic for parenteral administration. It is the sodium salt of (6R,7R)-3-carbamoyloxymethyl-7-[Z-2-methoxyimino-2-(fur-2-yl)acetamido]ceph-3-em-4-carboxylate, and it has the following chemical structure:



The empirical formula is  $C_{16}H_{15}N_4NaO_8S$ , representing a molecular weight of 446.4.

ZINACEF contains approximately 54.2 mg (2.4 mEq) of sodium per gram of cefuroxime activity.

ZINACEF in sterile crystalline form is supplied in vials equivalent to 750 mg, 1.5 g, or 7.5 g of cefuroxime as cefuroxime sodium and in ADD-Vantage<sup>®</sup> vials equivalent to 750 mg or 1.5 g of cefuroxime as cefuroxime sodium. Solutions of ZINACEF range in color from light yellow to amber, depending on the concentration and diluent used. The pH of freshly constituted solutions usually ranges from 6 to 8.5.

ZINACEF is available as a frozen, iso-osmotic, sterile, nonpyrogenic solution with 750 mg or 1.5 g of cefuroxime as cefuroxime sodium. Approximately 1.4 g of Dextrose Hydrous, USP has been added to the 750-mg dose to adjust the osmolality. Sodium Citrate Hydrous, USP has been added as a buffer (300 mg and 600 mg to the 750-mg and 1.5-g doses, respectively). ZINACEF contains approximately 111 mg (4.8 mEq) and 222 mg (9.7 mEq) of sodium in the 750-mg and 1.5-g doses, respectively. The pH has been adjusted with hydrochloric acid and may have been adjusted with sodium hydroxide. Solutions of premixed ZINACEF range in color from light yellow to amber. The solution is intended for intravenous (IV) use after thawing to room temperature. The osmolality of the solution is approximately 300 mOsmol/kg, and the pH of thawed solutions ranges from 5 to 7.5.

The plastic container for the frozen solution is fabricated from a specially designed multilayer plastic, PL 2040. Solutions are in contact with the polyethylene layer of this container and can leach

38 out certain chemical components of the plastic in very small amounts within the expiration period.  
39 The suitability of the plastic has been confirmed in tests in animals according to USP biological tests  
40 for plastic containers as well as by tissue culture toxicity studies.

41

## 42 **CLINICAL PHARMACOLOGY**

43 After intramuscular (IM) injection of a 750-mg dose of cefuroxime to normal volunteers, the  
44 mean peak serum concentration was 27 mcg/mL. The peak occurred at approximately 45 minutes  
45 (range, 15 to 60 minutes). Following IV doses of 750 mg and 1.5 g, serum concentrations were  
46 approximately 50 and 100 mcg/mL, respectively, at 15 minutes. Therapeutic serum concentrations of  
47 approximately 2 mcg/mL or more were maintained for 5.3 hours and 8 hours or more, respectively.  
48 There was no evidence of accumulation of cefuroxime in the serum following IV administration of  
49 1.5-g doses every 8 hours to normal volunteers. The serum half-life after either IM or IV injections  
50 is approximately 80 minutes.

51 Approximately 89% of a dose of cefuroxime is excreted by the kidneys over an 8-hour period,  
52 resulting in high urinary concentrations.

53 Following the IM administration of a 750-mg single dose, urinary concentrations averaged  
54 1,300 mcg/mL during the first 8 hours. Intravenous doses of 750 mg and 1.5 g produced urinary  
55 levels averaging 1,150 and 2,500 mcg/mL, respectively, during the first 8-hour period.

56 The concomitant oral administration of probenecid with cefuroxime slows tubular secretion,  
57 decreases renal clearance by approximately 40%, increases the peak serum level by approximately  
58 30%, and increases the serum half-life by approximately 30%. Cefuroxime is detectable in  
59 therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, and aqueous humor.

60 Cefuroxime is detectable in therapeutic concentrations in cerebrospinal fluid (CSF) of adults and  
61 pediatric patients with meningitis. The following table shows the concentrations of cefuroxime  
62 achieved in cerebrospinal fluid during multiple dosing of patients with meningitis.

63

64 **Table 1. Concentrations of Cefuroxime Achieved in Cerebrospinal Fluid During Multiple**  
65 **Dosing of Patients with Meningitis**

Patients	Dose	Number of Patients	Mean (Range) CSF Cefuroxime Concentrations (mcg/mL) Achieved Within 8 Hours Post Dose
Pediatric patients (4 weeks to 6.5 years)	200 mg/kg/day, divided q 6 hours	5	6.6 (0.9-17.3)
Pediatric patients (7 months to 9 years)	200 to 230 mg/kg/day, divided q 8 hours	6	8.3 (<2-22.5)
Adults	1.5 grams q 8 hours	2	5.2 (2.7-8.9)
Adults	1.5 grams q 6 hours	10	6.0 (1.5-13.5)

66

67 Cefuroxime is approximately 50% bound to serum protein.

68 **Microbiology:** Cefuroxime has in vitro activity against a wide range of gram-positive and  
69 gram-negative organisms, and it is highly stable in the presence of beta-lactamases of certain  
70 gram-negative bacteria. The bactericidal action of cefuroxime results from inhibition of cell-wall  
71 synthesis.

72 Cefuroxime is usually active against the following organisms in vitro.

73 **Aerobes, Gram-positive:** *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus*  
74 *pneumoniae*, and *Streptococcus pyogenes* (and other streptococci).

75 NOTE: Most strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*),  
76 are resistant to cefuroxime. Methicillin-resistant staphylococci and *Listeria monocytogenes* are  
77 resistant to cefuroxime.

78 **Aerobes, Gram-negative:** *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*,  
79 *Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae*,  
80 *Klebsiella* spp. (including *Klebsiella pneumoniae*), *Moraxella (Branhamella) catarrhalis* (including  
81 ampicillin- and cephalothin-resistant strains), *Morganella morganii* (formerly *Proteus morganii*),  
82 *Neisseria gonorrhoeae* (including penicillinase- and non-penicillinase-producing strains), *Neisseria*  
83 *meningitidis*, *Proteus mirabilis*, *Providencia rettgeri* (formerly *Proteus rettgeri*), *Salmonella* spp.,  
84 and *Shigella* spp.

85 NOTE: Some strains of *Morganella morganii*, *Enterobacter cloacae*, and *Citrobacter* spp. have  
86 been shown by in vitro tests to be resistant to cefuroxime and other cephalosporins. *Pseudomonas*  
87 and *Campylobacter* spp., *Acinetobacter calcoaceticus*, and most strains of *Serratia* spp. and *Proteus*  
88 *vulgaris* are resistant to most first- and second-generation cephalosporins.

89 **Anaerobes:** Gram-positive and gram-negative cocci (including *Peptococcus* and  
90 *Peptostreptococcus* spp.), gram-positive bacilli (including *Clostridium* spp.), and gram-negative  
91 bacilli (including *Bacteroides* and *Fusobacterium* spp.).

92 NOTE: *Clostridium difficile* and most strains of *Bacteroides fragilis* are resistant to cefuroxime.

93 **Susceptibility Tests: Diffusion Techniques:** Quantitative methods that require measurement  
94 of zone diameters give an estimate of antibiotic susceptibility. One such standard procedure<sup>1</sup> that has  
95 been recommended for use with disks to test susceptibility of organisms to cefuroxime uses the  
96 30-mcg cefuroxime disk. Interpretation involves the correlation of the diameters obtained in the disk  
97 test with the minimum inhibitory concentration (MIC) for cefuroxime.

98 A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally  
99 achievable blood levels. A report of "Moderately Susceptible" suggests that the organism would be  
100 susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high  
101 antibiotic levels are attained. A report of "Intermediate" suggests an equivocal or indeterminate  
102 result. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely  
103 to be inhibitory and other therapy should be selected.

104 Reports from the laboratory giving results of the standard single-disk susceptibility test for  
105 organisms other than *Haemophilus* spp. and *Neisseria gonorrhoeae* with a 30-mcg cefuroxime disk  
106 should be interpreted according to the following criteria:

107

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥18	(S) Susceptible
15-17	(MS) Moderately Susceptible
≤14	(R) Resistant

108

109 Results for *Haemophilus* spp. should be interpreted according to the following criteria:

110

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥24	(S) Susceptible
21-23	(I) Intermediate
≤20	(R) Resistant

111

112 Results for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

113

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥31	(S) Susceptible
26-30	(MS) Moderately Susceptible
≤25	(R) Resistant

114

115 Organisms should be tested with the cefuroxime disk since cefuroxime has been shown by in  
116 vitro tests to be active against certain strains found resistant when other beta-lactam disks are used.

117 The cefuroxime disk should not be used for testing susceptibility to other cephalosporins.

118 Standardized procedures require the use of laboratory control organisms. The 30-mcg cefuroxime  
119 disk should give the following zone diameters.

120 1. Testing for organisms other than *Haemophilus* spp. and *Neisseria gonorrhoeae*:

121

<u>Organism</u>	<u>Zone Diameter (mm)</u>
<i>Staphylococcus aureus</i> ATCC 25923	27-35
<i>Escherichia coli</i> ATCC 25922	20-26

122

123 2. Testing for *Haemophilus* spp.:

124

<u>Organism</u>	<u>Zone Diameter (mm)</u>
<i>Haemophilus influenzae</i> ATCC 49766	28-36

125

126 3. Testing for *Neisseria gonorrhoeae*:

127

<u>Organism</u>	<u>Zone Diameter (mm)</u>
<i>Neisseria gonorrhoeae</i> ATCC 49226	33-41
<i>Staphylococcus aureus</i> ATCC 25923	29-33

128

129 **Dilution Techniques:** Use a standardized dilution method<sup>1</sup> (broth, agar, microdilution) or  
130 equivalent with cefuroxime powder. The MIC values obtained for bacterial isolates other than  
131 *Haemophilus* spp. and *Neisseria gonorrhoeae* should be interpreted according to the following  
132 criteria:

133

<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
≤8	(S) Susceptible
16	(MS) Moderately Susceptible
≥32	(R) Resistant

134

135 MIC values obtained for *Haemophilus* spp. should be interpreted according to the following  
136 criteria:

137

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

138

139 MIC values obtained for *Neisseria gonorrhoeae* should be interpreted according to the following  
140 criteria:

141

<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
≤1	(S) Susceptible
2	(MS) Moderately Susceptible
≥4	(R) Resistant

142

143 As with standard diffusion techniques, dilution methods require the use of laboratory control  
144 organisms. Standard cefuroxime powder should provide the following MIC values.

145 1. For organisms other than *Haemophilus* spp. and *Neisseria gonorrhoeae*:

146

<u>Organism</u>	<u>MIC (mcg/mL)</u>
<i>Staphylococcus aureus</i> ATCC 29213	0.5-2.0
<i>Escherichia coli</i> ATCC 25922	2.0-8.0

147

148 2. For *Haemophilus* spp.:

149

<u>Organism</u>	<u>MIC (mcg/mL)</u>
<i>Haemophilus influenzae</i> ATCC 49766	0.25-1.0

150

151 3. For *Neisseria gonorrhoeae*:

152

<u>Organism</u>	<u>MIC (mcg/mL)</u>
<i>Neisseria gonorrhoeae</i> ATCC 49226	0.25-1.0
<i>Staphylococcus aureus</i> ATCC 29213	0.25-1.0

153

## 154 **INDICATIONS AND USAGE**

155 ZINACEF is indicated for the treatment of patients with infections caused by susceptible strains  
156 of the designated organisms in the following diseases:

- 157 **1. Lower Respiratory Tract Infections**, including pneumonia, caused by *Streptococcus*  
158 *pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp.,  
159 *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Streptococcus*  
160 *pyogenes*, and *Escherichia coli*.
- 161 **2. Urinary Tract Infections** caused by *Escherichia coli* and *Klebsiella* spp.
- 162 **3. Skin and Skin-Structure Infections** caused by *Staphylococcus aureus* (penicillinase- and non-  
163 penicillinase-producing strains), *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella* spp., and  
164 *Enterobacter* spp.
- 165 **4. Septicemia** caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing  
166 strains), *Streptococcus pneumoniae*, *Escherichia coli*, *Haemophilus influenzae* (including  
167 ampicillin-resistant strains), and *Klebsiella* spp.
- 168 **5. Meningitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including  
169 ampicillin-resistant strains), *Neisseria meningitidis*, and *Staphylococcus aureus* (penicillinase-  
170 and non-penicillinase-producing strains).
- 171 **6. Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria*  
172 *gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
- 173 **7. Bone and Joint Infections** caused by *Staphylococcus aureus* (penicillinase- and non-  
174 penicillinase-producing strains).

175 Clinical microbiological studies in skin and skin-structure infections frequently reveal the growth  
176 of susceptible strains of both aerobic and anaerobic organisms. ZINACEF has been used  
177 successfully in these mixed infections in which several organisms have been isolated.

178 In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients  
179 with other serious infections in which the causative organism has not been identified, ZINACEF  
180 may be used concomitantly with an aminoglycoside (see PRECAUTIONS). The recommended  
181 doses of both antibiotics may be given depending on the severity of the infection and the patient's  
182 condition.

183 To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZINACEF  
184 and other antibacterial drugs, ZINACEF should be used only to treat or prevent infections that are  
185 proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility  
186 information are available, they should be considered in selecting or modifying antibacterial therapy.  
187 In the absence of such data, local epidemiology and susceptibility patterns may contribute to the  
188 empiric selection of therapy.

189 **Prevention:** The preoperative prophylactic administration of ZINACEF may prevent the growth of  
190 susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative  
191 infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified  
192 as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of  
193 antibiotics in surgery depends on the time of administration. ZINACEF should usually be given  
194 one-half to 1 hour before the operation to allow sufficient time to achieve effective antibiotic  
195 concentrations in the wound tissues during the procedure. The dose should be repeated  
196 intraoperatively if the surgical procedure is lengthy.

197 Prophylactic administration is usually not required after the surgical procedure ends and should  
198 be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic  
199 administration of any antibiotic does not reduce the incidence of subsequent infections but will  
200 increase the possibility of adverse reactions and the development of bacterial resistance.

201 The perioperative use of ZINACEF has also been effective during open heart surgery for surgical  
202 patients in whom infections at the operative site would present a serious risk. For these patients it is  
203 recommended that therapy with ZINACEF be continued for at least 48 hours after the surgical  
204 procedure ends. If an infection is present, specimens for culture should be obtained for the  
205 identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

206

## 207 **CONTRAINDICATIONS**

208 ZINACEF is contraindicated in patients with known allergy to the cephalosporin group of  
209 antibiotics.

210

## 211 **WARNINGS**

212 BEFORE THERAPY WITH ZINACEF IS INSTITUTED, CAREFUL INQUIRY SHOULD BE  
213 MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS  
214 HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER  
215 DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE  
216 PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY  
217 PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO  
218 DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG.  
219 SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND  
220 OTHER EMERGENCY MEASURES.

221 **Pseudomembranous colitis has been reported with nearly all antibacterial agents, including**  
222 **cefuroxime, and may range in severity from mild to life threatening. Therefore, it is important**  
223 **to consider this diagnosis in patients who present with diarrhea subsequent to the**  
224 **administration of antibacterial agents.**

225 Treatment with antibacterial agents alters the normal flora of the colon and may permit  
226 overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one  
227 primary cause of “antibiotic-associated colitis.”

228 After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic  
229 measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug  
230 discontinuation alone. In moderate to severe cases, consideration should be given to management

231 with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug  
232 clinically effective against *Clostridium difficile* colitis.

233 When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is  
234 the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *Clostridium*  
235 *difficile*. Other causes of colitis should also be considered.

236

## 237 **PRECAUTIONS**

238 **General:** Although ZINACEF rarely produces alterations in kidney function, evaluation of renal  
239 status during therapy is recommended, especially in seriously ill patients receiving the maximum  
240 doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with  
241 potent diuretics as these regimens are suspected of adversely affecting renal function.

242 The total daily dose of ZINACEF should be reduced in patients with transient or persistent renal  
243 insufficiency (see DOSAGE AND ADMINISTRATION), because high and prolonged serum  
244 antibiotic concentrations can occur in such individuals from usual doses.

245 As with other antibiotics, prolonged use of ZINACEF may result in overgrowth of nonsusceptible  
246 organisms. Careful observation of the patient is essential. If superinfection occurs during therapy,  
247 appropriate measures should be taken.

248 Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of  
249 gastrointestinal disease, particularly colitis.

250 Nephrotoxicity has been reported following concomitant administration of aminoglycoside  
251 antibiotics and cephalosporins.

252 As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing  
253 loss has been reported in a few pediatric patients treated with cefuroxime. Persistence of positive  
254 CSF (cerebrospinal fluid) cultures at 18 to 36 hours has also been noted with cefuroxime injection,  
255 as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

256 Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include  
257 patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a  
258 protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant  
259 therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K  
260 administered as indicated.

261 Prescribing ZINACEF in the absence of a proven or strongly suspected bacterial infection or a  
262 prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the  
263 development of drug-resistant bacteria.

264 **Information for Patients:** Patients should be counseled that antibacterial drugs, including  
265 ZINACEF, should only be used to treat bacterial infections. They do not treat viral infections (e.g.,  
266 the common cold). When ZINACEF is prescribed to treat a bacterial infection, patients should be  
267 told that although it is common to feel better early in the course of therapy, the medication should  
268 be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1)  
269 decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria  
270 will develop resistance and will not be treatable by ZINACEF or other antibacterial drugs in the  
271 future.

272 **Drug/Laboratory Test Interactions:** A false-positive reaction for glucose in the urine may  
273 occur with copper reduction tests (Benedict's or Fehling's solution or with CLINITEST<sup>®</sup> tablets) but  
274 not with enzyme-based tests for glycosuria. As a false-negative result may occur in the ferricyanide  
275 test, it is recommended that either the glucose oxidase or hexokinase method be used to determine  
276 blood plasma glucose levels in patients receiving ZINACEF.

277 Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate  
278 method.

279 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Although lifetime studies in animals  
280 have not been performed to evaluate carcinogenic potential, no mutagenic activity was found for  
281 cefuroxime in the mouse lymphoma assay and a battery of bacterial mutation tests. Positive results  
282 were obtained in an in vitro chromosome aberration assay, however, negative results were found in  
283 an in vivo micronucleus test at doses up to 10 g/kg. Reproduction studies in mice at doses up to  
284 3,200 mg/kg/day (3.1 times the recommended maximum human dose based on mg/m<sup>2</sup>) have  
285 revealed no impairment of fertility.

286 Reproductive studies revealed no impairment of fertility in animals.

287 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been  
288 performed in mice at doses up to 6,400 mg/kg/day (6.3 times the recommended maximum human  
289 dose based on mg/m<sup>2</sup>) and rabbits at doses up to 400 mg/kg/day (2.1 times the recommended  
290 maximum human dose based on mg/m<sup>2</sup>) and have revealed no evidence of impaired fertility or harm  
291 to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in  
292 pregnant women. Because animal reproduction studies are not always predictive of human response,  
293 this drug should be used during pregnancy only if clearly needed.

294 **Nursing Mothers:** Since cefuroxime is excreted in human milk, caution should be exercised when  
295 ZINACEF is administered to a nursing woman.

296 **Pediatric Use:** Safety and effectiveness in pediatric patients below 3 months of age have not been  
297 established. Accumulation of other members of the cephalosporin class in newborn infants (with  
298 resulting prolongation of drug half-life) has been reported.

299 **Geriatric Use:** Of the 1,914 subjects who received cefuroxime in 24 clinical studies of ZINACEF,  
300 901 (47%) were 65 and over while 421 (22%) were 75 and over. No overall differences in safety or  
301 effectiveness were observed between these subjects and younger subjects, and other reported clinical  
302 experience has not identified differences in responses between the elderly and younger patients, but  
303 greater susceptibility of some older individuals to drug effects cannot be ruled out. This drug is  
304 known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be  
305 greater in patients with impaired renal function. Because elderly patients are more likely to have  
306 decreased renal function, care should be taken in dose selection, and it may be useful to monitor  
307 renal function (see DOSAGE AND ADMINISTRATION).

308

## 309 **ADVERSE REACTIONS**

310 ZINACEF is generally well tolerated. The most common adverse effects have been local  
311 reactions following IV administration. Other adverse reactions have been encountered only rarely.

312 **Local Reactions:** Thrombophlebitis has occurred with IV administration in 1 in 60 patients.

313 **Gastrointestinal:** Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea  
314 (1 in 220 patients) and nausea (1 in 440 patients). The onset of pseudomembranous colitis may occur  
315 during or after antibacterial treatment (see WARNINGS).

316 **Hypersensitivity Reactions:** Hypersensitivity reactions have been reported in fewer than 1% of  
317 the patients treated with ZINACEF and include rash (1 in 125). Pruritus, urticaria, and positive  
318 Coombs' test each occurred in fewer than 1 in 250 patients, and, as with other cephalosporins, rare  
319 cases of anaphylaxis, drug fever, erythema multiforme, interstitial nephritis, toxic epidermal  
320 necrolysis, and Stevens-Johnson syndrome have occurred.

321 **Blood:** A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and  
322 transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia  
323 (fewer than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence  
324 were seen with other cephalosporins used in controlled studies. As with other cephalosporins, there  
325 have been rare reports of thrombocytopenia.

326 **Hepatic:** Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in  
327 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

328 **Kidney:** Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine  
329 clearance have been observed, but their relationship to cefuroxime is unknown.

330 **Postmarketing Experience with ZINACEF Products:** In addition to the adverse events  
331 reported during clinical trials, the following events have been observed during clinical practice in  
332 patients treated with ZINACEF and were reported spontaneously. Data are generally insufficient to  
333 allow an estimate of incidence or to establish causation.

334 **Neurologic:** Seizure.

335 **Non-site specific:** Angioedema.

336 **Cephalosporin-class Adverse Reactions:** In addition to the adverse reactions listed above  
337 that have been observed in patients treated with cefuroxime, the following adverse reactions and  
338 altered laboratory tests have been reported for cephalosporin-class antibiotics:

339 **Adverse Reactions:** Vomiting, abdominal pain, colitis, vaginitis including vaginal  
340 candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia,  
341 hemolytic anemia, hemorrhage.

342 Several cephalosporins, including ZINACEF, have been implicated in triggering seizures,  
343 particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE  
344 AND ADMINISTRATION). If seizures associated with drug therapy should occur, the drug should  
345 be discontinued. Anticonvulsant therapy can be given if clinically indicated.

346 **Altered Laboratory Tests:** Prolonged prothrombin time, pancytopenia, agranulocytosis.

347

## 348 **OVERDOSAGE**

349 Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels  
350 of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

351

## 352 **DOSAGE AND ADMINISTRATION**

353 **Dosage: Adults:** The usual adult dosage range for ZINACEF is 750 mg to 1.5 grams every  
354 8 hours, usually for 5 to 10 days. In uncomplicated urinary tract infections, skin and skin-structure

355 infections, disseminated gonococcal infections, and uncomplicated pneumonia, a 750-mg dose every  
356 8 hours is recommended. In severe or complicated infections, a 1.5-gram dose every 8 hours is  
357 recommended.

358 In bone and joint infections, a 1.5-gram dose every 8 hours is recommended. In clinical trials,  
359 surgical intervention was performed when indicated as an adjunct to therapy with ZINACEF. A  
360 course of oral antibiotics was administered when appropriate following the completion of parenteral  
361 administration of ZINACEF.

362 In life-threatening infections or infections due to less susceptible organisms, 1.5 grams every  
363 6 hours may be required. In bacterial meningitis, the dosage should not exceed 3 grams every  
364 8 hours. The recommended dosage for uncomplicated gonococcal infection is 1.5 grams given  
365 intramuscularly as a single dose at 2 different sites together with 1 gram of oral probenecid. For  
366 preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5-gram  
367 dose administered intravenously just before surgery (approximately one-half to 1 hour before the  
368 initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every  
369 8 hours when the procedure is prolonged.

370 For preventive use during open heart surgery, a 1.5-gram dose administered intravenously at the  
371 induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

372 **Impaired Renal Function:** A reduced dosage must be employed when renal function is  
373 impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of  
374 the causative organism (see Table 2).

375

376 **Table 2. Dosage of ZINACEF in Adults With Reduced Renal Function**

Creatinine Clearance (mL/min)	Dose	Frequency
>20	750 mg-1.5 grams	q8h
10-20	750 mg	q12h
<10	750 mg	q24h*

377 \*Since ZINACEF is dialyzable, patients on hemodialysis should be given a further dose at the end  
378 of the dialysis.

379

380 When only serum creatinine is available, the following formula<sup>2</sup> (based on sex, weight, and age of  
381 the patient) may be used to convert this value into creatinine clearance. The serum creatinine should  
382 represent a steady state of renal function.

383

384 Males: Creatinine clearance (mL/min) =  $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$

385  
386 Females: 0.85 x male value

387

388 **Note:** As with antibiotic therapy in general, administration of ZINACEF should be continued for a  
389 minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial  
390 eradication has been obtained; a minimum of 10 days of treatment is recommended in infections

391 caused by *Streptococcus pyogenes* in order to guard against the risk of rheumatic fever or  
392 glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of  
393 chronic urinary tract infection and may be required for several months after therapy has been  
394 completed; persistent infections may require treatment for several weeks; and doses smaller than  
395 those indicated above should not be used. In staphylococcal and other infections involving a  
396 collection of pus, surgical drainage should be carried out where indicated.

397 **Pediatric Patients Above 3 Months of Age:** Administration of 50 to 100 mg/kg/day in  
398 equally divided doses every 6 to 8 hours has been successful for most infections susceptible to  
399 cefuroxime. The higher dosage of 100 mg/kg/day (not to exceed the maximum adult dosage) should  
400 be used for the more severe or serious infections.

401 In bone and joint infections, 150 mg/kg/day (not to exceed the maximum adult dosage) is  
402 recommended in equally divided doses every 8 hours. In clinical trials, a course of oral antibiotics  
403 was administered to pediatric patients following the completion of parenteral administration of  
404 ZINACEF.

405 In cases of bacterial meningitis, a larger dosage of ZINACEF is recommended, 200 to  
406 240 mg/kg/day intravenously in divided doses every 6 to 8 hours.

407 In pediatric patients with renal insufficiency, the frequency of dosing should be modified  
408 consistent with the recommendations for adults.

409 **Preparation of Solution and Suspension:** The directions for preparing ZINACEF for both IV  
410 and IM use are summarized in Table 3.

411 **For Intramuscular Use:** Each 750-mg vial of ZINACEF should be constituted with 3.0 mL of  
412 Sterile Water for Injection. Shake gently to disperse and withdraw completely the resulting  
413 suspension for injection.

414 **For Intravenous Use:** Each 750-mg vial should be constituted with 8.0 mL of Sterile Water  
415 for Injection. Withdraw completely the resulting solution for injection.

416 Each 1.5-gram vial should be constituted with 16.0 mL of Sterile Water for Injection, and the  
417 solution should be completely withdrawn for injection.

418 The 7.5-gram pharmacy bulk vial should be constituted with 77 mL of Sterile Water for Injection;  
419 each 8 mL of the resulting solution contains 750 mg of cefuroxime.

420 Each 750-mg and 1.5-gram infusion pack should be constituted with 100 mL of Sterile Water for  
421 Injection, 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or any of the solutions listed  
422 under the Intravenous portion of the COMPATIBILITY AND STABILITY section.

423

424 **Table 3. Preparation of Solution and Suspension**

Strength	Amount of Diluent to Be Added (mL)	Volume to Be Withdrawn	Approximate Cefuroxime Concentration (mg/mL)
750-mg Vial	3.0 (IM)	Total*	220
750-mg Vial	8.0 (IV)	Total	90
1.5-gram Vial	16.0 (IV)	Total	90
750-mg Infusion pack	100 (IV)	-----	7.5
1.5-gram Infusion pack	100 (IV)	-----	15
7.5-gram Pharmacy bulk package	77 (IV)	Amount Needed†	95

425 \***Note:** ZINACEF is a suspension at IM concentrations.

426 †8 mL of solution contains 750 mg of cefuroxime; 16 mL of solution contains 1.5 grams of cefuroxime.

427

428 **Administration:** After constitution, ZINACEF may be given intravenously or by deep IM injection  
429 into a large muscle mass (such as the gluteus or lateral part of the thigh). Before injecting  
430 intramuscularly, aspiration is necessary to avoid inadvertent injection into a blood vessel.

431 **Intravenous Administration:** The IV route may be preferable for patients with bacterial  
432 septicemia or other severe or life-threatening infections or for patients who may be poor risks  
433 because of lowered resistance, particularly if shock is present or impending.

434 **For direct intermittent IV administration,** slowly inject the solution into a vein over a  
435 period of 3 to 5 minutes or give it through the tubing system by which the patient is also receiving  
436 other IV solutions.

437 **For intermittent IV infusion with a Y-type administration set,** dosing can be  
438 accomplished through the tubing system by which the patient may be receiving other IV solutions.  
439 However, during infusion of the solution containing ZINACEF, it is advisable to temporarily  
440 discontinue administration of any other solutions at the same site.

441 ADD-Vantage vials are to be constituted only with 50 or 100 mL of 5% Dextrose Injection, 0.9%  
442 Sodium Chloride Injection, or 0.45% Sodium Chloride Injection in Abbott ADD-Vantage flexible  
443 diluent containers (see Instructions for Constitution). ADD-Vantage vials that have been joined to  
444 Abbott ADD-Vantage diluent containers and activated to dissolve the drug are stable for 24 hours at  
445 room temperature or for 7 days under refrigeration. Joined vials that have not been activated may be  
446 used within a 14-day period; this period corresponds to that for use of Abbott ADD-Vantage  
447 containers following removal of the outer packaging (overwrap).

448 Freezing solutions of ZINACEF in the ADD-Vantage system is not recommended.

449 **For continuous IV infusion,** a solution of ZINACEF may be added to an IV infusion pack  
450 containing one of the following fluids: 0.9% Sodium Chloride Injection; 5% Dextrose Injection;  
451 10% Dextrose Injection; 5% Dextrose and 0.9% Sodium Chloride Injection; 5% Dextrose and 0.45%  
452 Sodium Chloride Injection; or 1/6 M Sodium Lactate Injection.

453 Solutions of ZINACEF, like those of most beta-lactam antibiotics, should not be added to  
454 solutions of aminoglycoside antibiotics because of potential interaction.

455 However, if concurrent therapy with ZINACEF and an aminoglycoside is indicated, each of these  
456 antibiotics can be administered separately to the same patient.

457 **Directions for Use of ZINACEF Frozen in GALAXY<sup>®</sup> Plastic Containers:** ZINACEF  
458 supplied as a frozen, sterile, iso-osmotic, nonpyrogenic solution in plastic containers is to be  
459 administered after thawing either as a continuous or intermittent IV infusion. The thawed solution of  
460 the premixed product is stable for 28 days if stored under refrigeration (5°C) or for 24 hours if stored  
461 at room temperature (25°C). **Do not refreeze.**

462 Thaw container at room temperature (25°C) or under refrigeration (5°C). Do not force thaw by  
463 immersion in water baths or by microwave irradiation. Components of the solution may precipitate  
464 in the frozen state and will dissolve upon reaching room temperature with little or no agitation.  
465 Potency is not affected. Mix after solution has reached room temperature. Check for minute leaks by  
466 squeezing bag firmly. Discard bag if leaks are found as sterility may be impaired. Do not add  
467 supplementary medication. Do not use unless solution is clear and seal is intact.

468 Use sterile equipment.

469 **Caution:** Do not use plastic containers in series connections. Such use could result in air  
470 embolism due to residual air being drawn from the primary container before administration of the  
471 fluid from the secondary container is complete.

472 **Preparation for Administration:**

- 473 1. Suspend container from eyelet support.
- 474 2. Remove protector from outlet port at bottom of container.
- 475 3. Attach administration set. Refer to complete directions accompanying set.

476

477 **COMPATIBILITY AND STABILITY**

478 **Intramuscular:** When constituted as directed with Sterile Water for Injection, suspensions of  
479 ZINACEF for IM injection maintain satisfactory potency for 24 hours at room temperature and for  
480 48 hours under refrigeration (5°C).

481 After the periods mentioned above any unused suspensions should be discarded.

482 **Intravenous:** When the 750-mg, 1.5-g, and 7.5-g pharmacy bulk vials are constituted as directed  
483 with Sterile Water for Injection, the solutions of ZINACEF for IV administration maintain  
484 satisfactory potency for 24 hours at room temperature and for 48 hours (750-mg and 1.5-g vials) or  
485 for 7 days (7.5-g pharmacy bulk vial) under refrigeration (5°C). More dilute solutions, such as  
486 750 mg or 1.5 g plus 100 mL of Sterile Water for Injection, 5% Dextrose Injection, or 0.9% Sodium  
487 Chloride Injection, also maintain satisfactory potency for 24 hours at room temperature and for  
488 7 days under refrigeration.

489 These solutions may be further diluted to concentrations of between 1 and 30 mg/mL in the  
490 following solutions and will lose not more than 10% activity for 24 hours at room temperature or for  
491 at least 7 days under refrigeration: 0.9% Sodium Chloride Injection; 1/6 M Sodium Lactate  
492 Injection; Ringer's Injection, USP; Lactated Ringer's Injection, USP; 5% Dextrose and 0.9% Sodium  
493 Chloride Injection; 5% Dextrose Injection; 5% Dextrose and 0.45% Sodium Chloride Injection; 5%  
494 Dextrose and 0.225% Sodium Chloride Injection; 10% Dextrose Injection; and 10% Invert Sugar in  
495 Water for Injection.

496 Unused solutions should be discarded after the time periods mentioned above.

497 ZINACEF has also been found compatible for 24 hours at room temperature when admixed in IV  
498 infusion with heparin (10 and 50 U/mL) in 0.9% Sodium Chloride Injection and Potassium Chloride  
499 (10 and 40 mEq/L) in 0.9% Sodium Chloride Injection. Sodium Bicarbonate Injection, USP is not  
500 recommended for the dilution of ZINACEF.

501 The 750-mg and 1.5-g ZINACEF ADD-Vantage vials, when diluted in 50 or 100 mL of 5%  
502 Dextrose Injection, 0.9% Sodium Chloride Injection, or 0.45% Sodium Chloride Injection, may be  
503 stored for up to 24 hours at room temperature or for 7 days under refrigeration.

504 **Frozen Stability:** Constitute the 750-mg, 1.5-g, or 7.5-g vial as directed for IV administration in  
505 Table 3. Immediately withdraw the total contents of the 750-mg or 1.5-g vial or 8 or 16 mL from the  
506 7.5-g bulk vial and add to a Baxter VIAFLEX<sup>®</sup> MINI-BAG<sup>™</sup> containing 50 or 100 mL of 0.9%  
507 Sodium Chloride Injection or 5% Dextrose Injection and freeze. Frozen solutions are stable for  
508 6 months when stored at -20°C. Frozen solutions should be thawed at room temperature and not  
509 refrozen. Do not force thaw by immersion in water baths or by microwave irradiation. Thawed  
510 solutions may be stored for up to 24 hours at room temperature or for 7 days in a refrigerator.

511 **Note:** Parenteral drug products should be inspected visually for particulate matter and discoloration  
512 before administration whenever solution and container permit.

513 As with other cephalosporins, ZINACEF powder as well as solutions and suspensions tend to  
514 darken, depending on storage conditions, without adversely affecting product potency.

515 **Directions for Dispensing: Pharmacy Bulk Package—Not for Direct Infusion:** The  
516 pharmacy bulk package is for use in a pharmacy admixture service only under a laminar flow hood.  
517 Entry into the vial must be made with a sterile transfer set or other sterile dispensing device, and the  
518 contents dispensed in aliquots using aseptic technique. The use of syringe and needle is not  
519 recommended as it may cause leakage (see DOSAGE AND ADMINISTRATION). AFTER  
520 INITIAL WITHDRAWAL USE ENTIRE CONTENTS OF VIAL PROMPTLY. ANY UNUSED  
521 PORTION MUST BE DISCARDED WITHIN 24 HOURS.

522

## 523 HOW SUPPLIED

524 ZINACEF in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected  
525 from light. ZINACEF is a dry, white to off-white powder supplied in vials and infusion packs as  
526 follows:

527 NDC 0173-0352-31 750-mg\* Vial (Tray of 25)

528 NDC 0173-0354-35 1.5-g\* Vial (Tray of 25)

529 NDC 0173-0353-32 750-mg\* Infusion Pack (Tray of 10)

530 NDC 0173-0356-32 1.5-g\* Infusion Pack (Tray of 10)

531 NDC 0173-0400-00 7.5-g\* Pharmacy Bulk Package (Tray of 6)

532 NDC 0173-0436-00 750-mg ADD-Vantage Vial (Tray of 25)

533 NDC 0173-0437-00 1.5-g ADD-Vantage Vial (Tray of 10)

534 (The above ADD-Vantage vials are to be used only with Abbott ADD-Vantage diluent containers.)

535 ZINACEF frozen as a premixed solution of cefuroxime injection should not be stored above  
536 -20°C. ZINACEF is supplied frozen in 50-mL, single-dose, plastic containers as follows:

537 NDC 0173-0424-00 750-mg\* Plastic Container (Carton of 24)

538 NDC 0173-0425-00 1.5-g\* Plastic Container (Carton of 24)

539 \*Equivalent to cefuroxime.

540

541 **REFERENCES**

- 542 1. National Committee for Clinical Laboratory Standards. *Performance Standards for*  
543 *Antimicrobial Susceptibility Testing*. Third Informational Supplement. NCCLS Document  
544 M100-S3, Vol. 11, No. 17. Villanova, Pa: NCCLS; 1991.
- 545 2. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*.  
546 1976;16:31-41.

547

548



549

550 GlaxoSmithKline

551 Research Triangle Park, NC 27709

552

553 ZINACEF<sup>®</sup> (cefuroxime for injection):

554 GlaxoSmithKline

555 Research Triangle Park, NC 27709

556

557 ZINACEF<sup>®</sup> (cefuroxime injection):

558 Manufactured for GlaxoSmithKline

559 Research Triangle Park, NC 27709

560 by Baxter Healthcare Corporation, Deerfield, IL 60015

561

562 ZINACEF is a registered trademark of GlaxoSmithKline.

563 ADD-Vantage is a registered trademark of Abbott Laboratories.

564 CLINITEST is a registered trademark of Ames Division, Miles Laboratories, Inc.

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568 October 2003

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*Tear Away*

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573

**ZINACEF<sup>®</sup>**

574

**(cefuroxime for injection)**

575

576

**Instructions for Constitution**

577

**of ADD-Vantage<sup>®</sup> Vials**

578

579 **To Open Diluent Container:**

580 Peel the corner of the ADD-Vantage diluent overwrap and remove flexible diluent container. Some  
581 opacity of the plastic flexible container due to moisture absorption during the sterilization process  
582 may be observed. This is normal and does not affect the solution quality or safety. The opacity will  
583 diminish gradually.

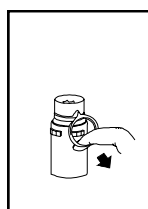
584

585 **To Assemble Vial and Flexible Diluent Container (Use Aseptic Technique):**

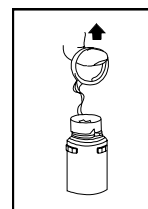
586 1. Remove the protective covers from the top of the vial and the vial port on the diluent container as  
587 follows:

588 a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down  
589 far enough to start the opening (see Figure 1), then pull straight up to remove the cap (see Figure  
590 2). **Note:** Once the breakaway cap has been removed, do not access vial with syringe.

591



592 Figure 1



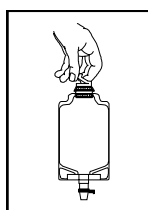
593 Figure 2

594

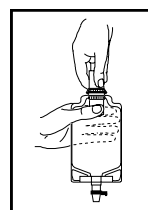
595 b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the 3 tie strings,  
596 then pull back to remove the cover (see Figure 3).

597 2. Screw the vial into the vial port until it will go no further. **THE VIAL MUST BE SCREWED IN**  
598 **TIGHTLY TO ASSURE A SEAL.** This occurs approximately one-half turn (180°) after the first  
599 audible click (see Figure 4). The clicking sound does not assure a seal; the vial must be turned as  
600 far as it will go. **Note:** Once vial is seated, do not attempt to remove (see Figure 4).

601



602 Figure 3



603 Figure 4

604

605 3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.

606 4. Label appropriately.

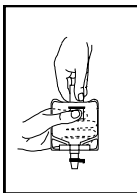
607

608 **To Prepare Admixture:**

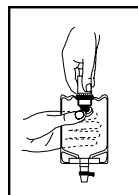
609 1. Squeeze the bottom of the diluent container gently to inflate the portion of the container  
610 surrounding the end of the drug vial.

611 2. With the other hand, push the drug vial down into the container, telescoping the walls of the  
612 container. Grasp the inner cap of the vial through the walls of the container (see Figure 5).

- 613 3. Pull the inner cap from the drug vial (see Figure 6). Verify that the rubber stopper has been  
614 pulled out, allowing the drug and diluent to mix.  
615



616  
617 Figure 5



618 Figure 6

- 619 4. Mix container contents thoroughly and use within the specified time.  
620

621 **Preparation for Administration (Use Aseptic Technique):**

- 622 1. Confirm the activation and admixture of vial contents.  
623 2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be  
624 impaired.  
625 3. Close flow control clamp of administration set.  
626 4. Remove cover from outlet port at bottom of container.  
627 5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly  
628 seated. **Note:** See full directions on administration set carton.  
629 6. Lift the free end of the hanger loop on the bottom of the vial, breaking the 2 tie strings. Bend the  
630 loop outward to lock it in the upright position, then suspend container from hanger.  
631 7. Squeeze and release drip chamber to establish proper fluid level in chamber.  
632 8. Open flow control clamp and clear air from set. Close clamp.  
633 9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.  
634 10. Regulate rate of administration with flow control clamp.  
635

636 **WARNING: Do not use flexible container in series connections.**  
637  
638



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