

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIMENTIN safely and effectively. See full prescribing information for TIMENTIN.

TIMENTIN (ticarcillin disodium and clavulanate potassium) for Injection

TIMENTIN (ticarcillin disodium and clavulanate potassium) for Injection: Pharmacy Bulk Package

TIMENTIN (ticarcillin disodium and clavulanate potassium) Injection: GALAXY Container

Initial U.S. Approval: 1985

INDICATIONS AND USAGE

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

TIMENTIN is a combination of a β -lactam antibacterial and a β -lactamase inhibitor indicated for the treatment of the following infections due to designated susceptible bacteria:

- Septicemia (1.1)
- Lower respiratory infections (1.2)
- Bone and joint infections (1.3)
- Skin and skin structure infections (1.4)
- Urinary tract infections (1.5)
- Gynecologic infections (1.6)
- Intra-abdominal infections (1.7)

DOSAGE AND ADMINISTRATION

Administer TIMENTIN by intravenous infusion (30 minutes). (2)

Adults:

- Systemic and urinary tract infections: 3.1 g every 4 to 6 hours. (2.1)
- Gynecologic infections: 200 to 300 mg/kg/day in divided doses every 4 to 6 hours depending on severity of infection. (2.1)

Pediatric Patients:

- <60 kg: 200 to 300 mg/kg/day in divided doses every 4 to 6 hours depending on severity of infection. (2.2)
- \geq 60 kg: 3.1 grams every 4 to 6 hours depending on severity of infection. (2.2)

DOSAGE FORMS AND STRENGTHS

- 3.1 gram vial of TIMENTIN for Injection containing ticarcillin disodium equivalent to 3 grams ticarcillin and clavulanate potassium equivalent to 0.1 gram clavulanic acid. (3)

- 31-gram Pharmacy Bulk Package of TIMENTIN for Injection containing ticarcillin disodium equivalent to 30 grams ticarcillin and clavulanate potassium equivalent to 1 gram clavulanic acid. (3)
- 100-mL single-dose GALAXY Container (PL 2040 Plastic) of TIMENTIN Injection containing ticarcillin disodium equivalent to 3.0 grams ticarcillin and clavulanate potassium equivalent to 0.1 gram clavulanic acid as a frozen solution. (3)

CONTRAINDICATIONS

History of a serious hypersensitivity reaction (anaphylaxis or Stevens-Johnson syndrome) to TIMENTIN or to other β -lactams (e.g., penicillins and cephalosporins). (4)

WARNINGS AND PRECAUTIONS

- Serious, including fatal, hypersensitivity (anaphylactic) reactions. Discontinue TIMENTIN and institute appropriate therapy. (5.1)
- *Clostridium difficile* associated diarrhea (CDAD). If diarrhea occurs, evaluate patients for CDAD. (5.2)
- Convulsions may occur when the recommended dose of TIMENTIN is exceeded, especially in the presence of impaired renal function. Institute supportive measures. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (\geq 1%) are rash, nausea, diarrhea, and phlebitis at injection site. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Aminoglycosides: Mixing with TIMENTIN for parenteral administration can inactivate the aminoglycoside. (7.1)
- Probenecid: Interferes with renal tubular secretion of ticarcillin, therefore increases exposure to ticarcillin. (7.2)
- Oral Contraceptives: Effects on gut flora may lower estrogen reabsorption and reduce efficacy of oral contraceptives. (7.3)

USE IN SPECIFIC POPULATIONS

Renal Impairment: Adjust dose based on creatinine clearance and type of dialysis. (2.3, 8.6)

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Revised: 06/2014

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 TIMENTIN[®] is indicated in the treatment of infections caused by susceptible isolates of
4 the designated bacteria in the conditions listed below:

5 **1.1 Septicemia**

6 Septicemia (including bacteremia) caused by β -lactamase-producing isolates of
7 *Klebsiella* spp.^{*}, *Escherichia coli*^{*}, *Staphylococcus aureus*^{*}, or *Pseudomonas aeruginosa*^{*} (or
8 other *Pseudomonas* species^{*})

9 **1.2 Lower Respiratory Infections**

10 Lower respiratory infections caused by β -lactamase-producing isolates of *S. aureus*,
11 *Haemophilus influenzae*^{*}, or *Klebsiella* spp.^{*}

12 **1.3 Bone and Joint Infections**

13 Bone and joint infections caused by β -lactamase-producing isolates of *S. aureus*

14 **1.4 Skin and Skin Structure Infections**

15 Skin and skin structure infections caused by β -lactamase-producing isolates of *S. aureus*,
16 *Klebsiella* spp.^{*}, or *E. coli*^{*}

17 **1.5 Urinary Tract Infections**

18 Urinary tract infections (complicated and uncomplicated) caused by β -lactamase-
19 producing isolates of *E. coli*, *Klebsiella* spp., *P. aeruginosa*^{*} (or other *Pseudomonas* spp.^{*}),
20 *Citrobacter* spp.^{*}, *Enterobacter cloacae*^{*}, *Serratia marcescens*^{*}, or *S. aureus*^{*}

21 **1.6 Gynecologic Infections**

22 Endometritis caused by β -lactamase-producing isolates of *Prevotella melaninogenica*^{*},
23 *Enterobacter* spp. (including *E. cloacae*^{*}), *E. coli*, *Klebsiella pneumoniae*^{*}, *S. aureus*, or
24 *Staphylococcus epidermidis*

25 **1.7 Intra-abdominal Infections**

26 Peritonitis caused by β -lactamase-producing isolates of *E. coli*, *K. pneumoniae*, or
27 *Bacteroides fragilis*^{*} group

28 ^{*} Efficacy for this organism in this organ system was studied in fewer than 10 infections.

29 **1.8 Usage**

30 To reduce the development of drug-resistant bacteria and maintain the effectiveness of
31 TIMENTIN and other antibacterial drugs, TIMENTIN should be used only to treat infections
32 that are proven or strongly suspected to be caused by susceptible bacteria. When culture and
33 susceptibility information are available, they should be considered in selecting or modifying
34 antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns
35 may contribute to the empiric selection of therapy.

36 **2 DOSAGE AND ADMINISTRATION**

37 **2.1 Adults**

38 The usual recommended dosage for systemic and urinary tract infections for adults is
39 3.1 grams of TIMENTIN (3 grams ticarcillin and 100 mg clavulanic acid) given every 4 to
40 6 hours.

41 For gynecologic infections, TIMENTIN should be administered as follows (based on
42 ticarcillin content): Moderate infections, 200 mg/kg/day in divided doses every 6 hours; severe
43 infections, 300 mg/kg/day in divided doses every 4 hours.

44 For patients weighing less than 60 kg, the recommended dosage is 200 to 300 mg/kg/day
45 given in divided doses every 4 to 6 hours.

46 The duration of therapy depends upon the severity of infection. The usual duration is 10
47 to 14 days; however, in difficult and complicated infections, more prolonged therapy may be
48 required.

49 **2.2 Pediatric Patients (≥3 Months of Age)**

50 Patients <60 kg: Mild to moderate infections, 200 mg/kg/day based on ticarcillin
51 content in divided doses every 6 hours; severe infections, 300 mg/kg/day in divided doses every
52 4 hours.

53 Patients ≥60 kg: Mild to moderate infections, 3.1 grams every 6 hours; severe
54 infections, 3.1 grams every 4 hours.

55 **2.3 Renal Impairment**

56 For patients with renal insufficiency, an initial loading dose of 3.1 grams should be
57 followed by doses based on creatinine clearance and type of dialysis as indicated in Table 1.
58

59 **Table 1. Dosage Adjustments for Renal Impairment**

Creatinine Clearance (mL/minute) ^a	Dosage ^b
Over 60	3 grams every 4 hours
30 to 60	2 grams every 4 hours
10 to 30	2 grams every 8 hours
Less than 10	2 grams every 12 hours
Less than 10 with hepatic dysfunction	2 grams every 24 hours
Patients on peritoneal dialysis	3 grams every 12 hours
Patients on hemodialysis	2 grams every 12 hours supplemented with 3 grams after each dialysis

60 ^a To calculate creatinine clearance¹ from a serum creatinine value use the following formula:

61
$$C_{cr} = (140 - \text{Age}) (\text{weight in kg}) / 72 \times S_{cr} (\text{mg}/100 \text{ mL})$$

62 This is the calculated creatinine clearance for adult males; for females it is 15% less.

63 ^b Based on ticarcillin content.

64

65 **2.4 Administration and Directions for Use**

66 TIMENTIN should be administered by intravenous infusion over a 30-minute period.

67 **Directions for Reconstitution and Further Dilution: 3.1-gram Glass Vials:** The
68 3.1-gram vial should be reconstituted by adding approximately 13 mL of Sterile Water for
69 Injection, USP, or Sodium Chloride Injection, USP, and shaking well. When dissolved, the
70 concentration of ticarcillin will be approximately 200 mg/mL with a corresponding concentration
71 of 6.7 mg/mL for clavulanic acid. The color of reconstituted solutions of TIMENTIN normally
72 ranges from light to dark yellow, depending on concentration, duration, and temperature of
73 storage.

74 The dissolved drug should be further diluted to desired volume using the recommended
75 solution listed under Stability [*see Dosage and Administration (2.5)*] to a concentration between
76 10 mg/mL to 100 mg/mL.

77 ***Pharmacy Bulk Package:*** The container closure may be penetrated only one time
78 utilizing a suitable sterile transfer device or dispensing set that allows measured distribution of
79 the contents. A sterile substance that must be reconstituted prior to use may require a separate
80 closure entry.

81 Restrict use of Pharmacy Bulk Packages to an aseptic area such as a laminar flow hood.

82 Reconstituted contents of the vial should be withdrawn immediately. However, if this is
83 not possible, aliquoting operations must be completed within 4 hours of reconstitution. Discard
84 the reconstituted stock solution 4 hours after initial entry.

85 Add 76 mL of Sterile Water for Injection, USP, or Sodium Chloride Injection, USP, to
86 the 31-gram Pharmacy Bulk Package and shake well. For ease of reconstitution, the diluent may
87 be added in 2 portions. Each 1 mL of the resulting concentrated stock solution contains
88 approximately 300 mg of ticarcillin and 10 mg of clavulanic acid.

89 The desired dosage should be withdrawn from the stock solution and further diluted to
90 desired volume using the recommended solution listed under Stability [*see Dosage and*
91 *Administration (2.5)*] to a concentration between 10 mg/mL to 100 mg/mL.

92 **Directions for Intravenous Infusion:** After reconstitution and further dilution and prior
93 to administration, TIMENTIN should be inspected visually for particulate matter. If particulate
94 matter is present, the solution should be discarded.

95 The solution of reconstituted drug may be administered over a 30-minute period by direct
96 infusion or through a Y-type intravenous infusion set. If this method of administration is used, it
97 is advisable to temporarily discontinue the administration of any other solutions during the
98 infusion of TIMENTIN.

99 When TIMENTIN is given in combination with another antimicrobial, such as an
100 aminoglycoside, each drug should be given separately in accordance with the recommended
101 dosage and routes of administration for each drug [*see Drug Interactions (7.1)*].

102 ***GALAXY® Container (PL 2040 Plastic):*** Prior to administration, TIMENTIN
103 should be inspected visually for particulate matter. If particulate matter is present, the solution
104 should be discarded.

105 **Caution:** Do not use plastic containers in series connections. Such use could result in an
106 embolism due to residual air being drawn from the primary container before administration of
107 the fluid from the secondary container is completed.

108 **Preparation for Administration:** See How Supplied/Storage and Handling (16) for
109 thawing and handling instructions:

- 110 • Suspend the container from eyelet support.
- 111 • Remove protector from outlet port at bottom of container.
- 112 • Attach administration set. Refer to complete directions accompanying set.

113 2.5 Stability

114 **NOTE:** TIMENTIN is incompatible with Sodium Bicarbonate.

115 **3.1-gram Glass Vials:** The concentrated stock solution at 200 mg/mL is stable for up to
116 6 hours at room temperature 21° to 24°C (70° to 75°F) or up to 72 hours under refrigeration 4°C
117 (40°F).

118 If the concentrated stock solution (200 mg/mL) is held for up to 6 hours at room
119 temperature 21° to 24°C (70° to 75°F) or up to 72 hours under refrigeration 4°C (40°F) and
120 further diluted to a concentration between 10 mg/mL and 100 mg/mL with any of the diluents
121 listed below, then the following stability periods apply.

122

STABILITY PERIOD		
(3.1-gram Vials)		
Intravenous Solution (ticarcillin concentrations of 10 mg/mL to 100 mg/mL)	Room Temperature 21° to 24°C (70° to 75°F)	Refrigerated 4°C (40°F)
Dextrose Injection 5%, USP	24 hours	3 days
Sodium Chloride Injection, USP	24 hours	7 days
Lactated Ringer's Injection, USP	24 hours	7 days

123

124 If the concentrated stock solution (200 mg/mL) is stored for up to 6 hours at room
125 temperature and then further diluted to a concentration between 10 mg/mL and 100 mg/mL,
126 solutions of Sodium Chloride Injection, USP, and Lactated Ringer's Injection, USP, may be
127 stored frozen –18°C (0°F) for up to 30 days. Solutions prepared with Dextrose Injection 5%,
128 USP, may be stored frozen –18°C (0°F) for up to 7 days. All thawed solutions should be used
129 within 8 hours or discarded. Once thawed, solutions should not be refrozen.

130 Unused solutions must be discarded after the time periods listed above.

131 **Pharmacy Bulk Package:** Aliquots of the reconstituted stock solution at 300 mg/mL
132 are stable for up to 6 hours between 21° and 24°C (70° and 75°F) or up to 72 hours under
133 refrigeration 4°C (40°F). The reconstituted stock solution should be held under refrigeration 4°C
134 (40°F).

135 If the aliquots of the reconstituted stock solution (300 mg/mL) are held up to 6 hours
136 between 21° and 24°C (70° and 75°F) or up to 72 hours under refrigeration 4°C (40°F) and

137 further diluted to a concentration between 10 mg/mL and 100 mg/mL with any of the diluents
138 listed below, then the following stability periods apply.
139

STABILITY PERIOD		
(31-gram Pharmacy Bulk Package)		
Intravenous Solution (ticarcillin concentrations of 10 mg/mL to 100 mg/mL)	Room Temperature 21° to 24°C (70° to 75°F)	Refrigerated 4°C (40°F)
Dextrose Injection 5%, USP	24 hours	3 days
Sodium Chloride Injection 0.9%, USP	24 hours	4 days
Lactated Ringer's Injection, USP	24 hours	4 days
Sterile Water for Injection, USP	24 hours	4 days

140
141 If an aliquot of concentrated stock solution (300 mg/mL) is stored for up to 6 hours
142 between 21° and 24°C (70° and 75°F) and then further diluted to a concentration between
143 10 mg/mL and 100 mg/mL, solutions of Sodium Chloride Injection, USP, Lactated Ringer's
144 Injection, USP, and Sterile Water for Injection, USP, may be stored frozen –18°C (0°F) for up to
145 30 days. Solutions prepared with Dextrose Injection 5%, USP, may be stored frozen –18°C (0°F)
146 for up to 7 days. All thawed solutions should be used within 8 hours or discarded. Once thawed,
147 solutions should not be refrozen.

148 Unused solutions must be discarded after the time periods listed above.

149 **GALAXY Container (PL 2040 Plastic):** Do not add supplementary medication to the
150 container. The thawed solution is stable for 24 hours at room temperature 22°C (72°F) or for
151 7 days under refrigeration at 4°C (39°F).

152 **3 DOSAGE FORMS AND STRENGTHS**

153 The 3.1-gram glass vial of TIMENTIN for Injection is a white to pale yellow sterile
154 powder for reconstitution containing ticarcillin disodium equivalent to 3 grams ticarcillin and
155 clavulanate potassium equivalent to 0.1 gram clavulanic acid.

156 The 31-gram Pharmacy Bulk Package of TIMENTIN for Injection is a white to pale
157 yellow sterile powder for reconstitution containing ticarcillin disodium equivalent to 30 grams
158 ticarcillin and clavulanate potassium equivalent to 1 gram clavulanic acid.

159 The 100-mL single-dose GALAXY Container (PL 2040 Plastic) of TIMENTIN is a
160 frozen solution containing ticarcillin disodium equivalent to 3.0 grams ticarcillin and clavulanate
161 potassium equivalent to 0.1 gram clavulanic acid.

162 **4 CONTRAINDICATIONS**

163 TIMENTIN is contraindicated in patients who have a history of hypersensitivity reaction
164 (e.g., anaphylaxis or erythema multiforme) to TIMENTIN or to other β-lactam antibacterials
165 (e.g., penicillins and cephalosporins).

166 **5 WARNINGS AND PRECAUTIONS**

167 **5.1 Anaphylactic Reactions**

168 Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been
169 reported in patients receiving beta-lactam antibacterials. These reactions are more likely to occur
170 in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to
171 multiple allergens. Before initiating therapy with TIMENTIN, inquire about previous
172 hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction
173 occurs, discontinue TIMENTIN and institute appropriate therapy.

174 **5.2 Clostridium difficile Associated Diarrhea**

175 *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all
176 antibacterial agents, including TIMENTIN, and may range in severity from mild diarrhea to fatal
177 colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to
178 overgrowth of *C. difficile*.

179 *C. difficile* produces toxins A and B, which contribute to the development of CDAD.
180 Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these
181 infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be
182 considered in all patients who present with diarrhea following antibacterial use. Careful medical
183 history is necessary since CDAD has been reported to occur over 2 months after the
184 administration of antibacterial agents.

185 If CDAD is suspected or confirmed, ongoing antibacterial use not directed against
186 *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein
187 supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be
188 instituted as clinically indicated.

189 **5.3 Convulsions**

190 Patients may experience convulsions when the dose of TIMENTIN exceeds the
191 recommended dose, especially in the presence of impaired renal function [*see Adverse Reactions*
192 (6.2), *Overdosage (10)*].

193 **5.4 Risk of Bleeding**

194 Some patients receiving β -lactam antibacterials have experienced bleeding associated
195 with abnormalities in coagulation tests. These adverse reactions are more likely to occur in
196 patients with renal impairment. If bleeding manifestations appear, treatment with TIMENTIN
197 should be discontinued and appropriate therapy instituted.

198 **5.5 Potential for Microbial Overgrowth or Bacterial Resistance**

199 The possibility of superinfections with fungal or bacterial pathogens should be
200 considered during therapy. If superinfections occur, appropriate measures should be taken.

201 **5.6 Development of Drug-Resistant Bacteria**

202 Prescribing TIMENTIN in the absence of a proven or strongly suspected bacterial
203 infection is unlikely to provide benefit to the patient and increases the risk of the development of
204 drug-resistant bacteria.

205 **5.7 Interference with Laboratory Tests**

206 High urine concentrations of ticarcillin may produce false-positive protein reactions
207 (pseudoproteinuria) [*see Drug Interactions (7.4)*].

208 Clavulanic acid may cause a nonspecific binding of IgG and albumin by red cell
209 membranes, leading to a false-positive Coombs test [*see Drug Interactions (7.4)*].

210 **5.8 Electrolyte Imbalance**

211 Hypokalemia has been reported during treatment with TIMENTIN. Serum potassium
212 should be monitored in patients with fluid and electrolyte imbalance and in patients receiving
213 prolonged therapy. The theoretical sodium content is 4.51 mEq (103.6 mg) per gram of
214 TIMENTIN. This should be considered when treating patients requiring restricted salt intake.

215 **6 ADVERSE REACTIONS**

216 The following are discussed in more detail in other sections of the labeling:

- 217 • Anaphylactic Reactions [*see Warnings and Precautions (5.1)*]
- 218 • *Clostridium difficile* Associated Diarrhea [*see Warnings and Precautions (5.2)*]

219 **6.1 Clinical Trials Experience**

220 Because clinical trials are conducted under widely varying conditions, adverse reaction
221 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
222 trials of another drug and may not reflect the rates observed in practice.

223 Adverse reactions occurring in $\geq 1\%$ of 867 patients receiving TIMENTIN 3.1 grams in
224 clinical studies included rash, nausea, diarrhea, and phlebitis at the injection site. The most
225 common laboratory abnormalities ($\geq 3\%$) were elevations in eosinophils, serum aspartate
226 aminotransferase (AST), and serum alanine aminotransferase (ALT).

227 Available safety data for pediatric patients treated with TIMENTIN demonstrate a similar
228 adverse event profile to that observed in adult patients.

229 **6.2 Postmarketing Experience**

230 In addition to adverse reactions reported from clinical trials, the following adverse
231 reactions have been identified during postmarketing use of TIMENTIN. Because they are
232 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
233 These adverse reactions have been chosen for inclusion due to a combination of their
234 seriousness, frequency of reporting, or potential causal connection to TIMENTIN.

235 Hypersensitivity Reactions: Skin rash, pruritus, urticaria, arthralgia, myalgia, drug
236 fever, chills, chest discomfort, anaphylactic reactions, and bullous reactions (including erythema
237 multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome).

238 Central Nervous System: Headache, giddiness, neuromuscular hyperirritability, or
239 convulsive seizures.

240 Gastrointestinal Disturbances: Disturbances of taste and smell, stomatitis, flatulence,
241 nausea, vomiting and diarrhea, epigastric pain, and pseudomembranous colitis have been
242 reported. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial
243 treatment [*see Warnings and Precautions (5.2)*].

244 Hemic and Lymphatic Systems: Thrombocytopenia, leukopenia, neutropenia,
245 eosinophilia, reduction of hemoglobin or hematocrit, and prolongation of prothrombin time and
246 bleeding time.

247 Abnormalities of Hepatic Function Tests: Elevation of AST, ALT, serum alkaline
248 phosphatase, serum LDH, and serum bilirubin. There have been reports of transient hepatitis and
249 cholestatic jaundice, as with some other penicillins and some cephalosporins.

250 Renal and Urinary Effects: Hemorrhagic cystitis, elevation of serum creatinine and/or
251 BUN, hyponatremia, reduction in serum potassium, and uric acid.

252 Local Reactions: Pain, burning, swelling, and induration at the injection site and
253 thrombophlebitis with intravenous administration.

254 **7 DRUG INTERACTIONS**

255 **7.1 Aminoglycosides**

256 The mixing of TIMENTIN with an aminoglycoside in solutions for parenteral
257 administration can result in substantial inactivation of the aminoglycoside.

258 **7.2 Probenecid**

259 Probenecid interferes with the renal tubular secretion of ticarcillin, thereby increasing
260 serum concentrations and prolonging serum half-life of ticarcillin. Probenecid does not affect the
261 serum levels of clavulanic acid.

262 **7.3 Oral Contraceptives**

263 Ticarcillin disodium/clavulanate potassium may affect the gut flora, leading to lower
264 estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone
265 contraceptives.

266 **7.4 Effects on Laboratory Tests**

267 High urine concentrations of ticarcillin may produce false-positive protein reactions
268 (pseudoproteinuria) with certain methods. The bromphenol blue reagent strip test has been
269 reported to be a reliable method for testing protein reactions [*see Warnings and Precautions*
270 (5.7)].

271 Clavulanic acid in TIMENTIN may cause a nonspecific binding of IgG and albumin by
272 red cell membranes, leading to a false-positive Coombs test. A positive Coombs test should be
273 interpreted with caution during treatment with TIMENTIN [*see Warnings and Precautions*
274 (5.7)].

275 **8 USE IN SPECIFIC POPULATIONS**

276 **8.1 Pregnancy**

277 Pregnancy Category B.

278 Reproduction studies have been performed in rats given doses up to 1,050 mg/kg/day
279 (approximately half of the recommended human dose based on body surface area) and have
280 revealed no evidence of harm to the fetus due to TIMENTIN. There are, however, no adequate
281 and well-controlled studies in pregnant women. Because animal reproduction studies are not

282 always predictive of human response, this drug should be used during pregnancy only if clearly
283 needed.

284 **8.3 Nursing Mothers**

285 It is not known whether ticarcillin or clavulanic acid is excreted in human milk. Because
286 many drugs are excreted in human milk, caution should be exercised when TIMENTIN is
287 administered to a nursing woman.

288 **8.4 Pediatric Use**

289 The safety and effectiveness of TIMENTIN have been established in the age group of
290 3 months to 16 years. Use of TIMENTIN in these age groups is supported by evidence from
291 adequate and well-controlled studies of TIMENTIN in adults with additional efficacy, safety,
292 and pharmacokinetic data from both comparative and non-comparative studies in pediatric
293 patients. There are insufficient data to support the use of TIMENTIN in pediatric patients under
294 3 months of age.

295 If meningitis is suspected or documented, an alternative agent with demonstrated clinical
296 efficacy in this setting should be used.

297 **8.5 Geriatric Use**

298 An analysis of clinical studies of TIMENTIN was conducted to determine whether
299 subjects aged 65 and older respond differently from younger subjects. Of the 1,078 subjects
300 treated with at least one dose of TIMENTIN, 67.5% were <65 years old, and 32.5% were
301 ≥65 years old. No overall differences in safety or efficacy were observed between older and
302 younger subjects, and other reported clinical experience have not identified differences in
303 responses between the elderly and younger patients, but a greater sensitivity of some older
304 individuals cannot be ruled out.

305 This drug is known to be substantially excreted by the kidney, and the risk of toxic
306 reactions to this drug may be greater in patients with impaired renal function. Because elderly
307 patients are more likely to have decreased renal function, care should be taken in dose selection,
308 and it may be useful to monitor renal function [*see Dosage and Administration (2.3)*].

309 TIMENTIN contains 103.6 mg (4.51 mEq) of sodium per gram of TIMENTIN. At the
310 usual recommended doses, patients would receive between 1,285 and 1,927 mg/day (56 and
311 84 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt
312 loading. This may be clinically important with regard to such diseases as congestive heart failure.

313 **8.6 Renal Impairment**

314 Ticarcillin is predominantly excreted by the kidney [*see Clinical Pharmacology (12.3)*].
315 Dosage adjustments should be made for patients with renal impairment [*see Dosage and*
316 *Administration (2.3)*].

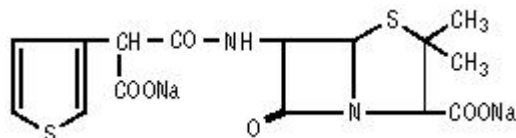
317 **10 OVERDOSAGE**

318 In case of overdosage, discontinue TIMENTIN, treat symptomatically, and institute
319 supportive measures as required. Ticarcillin and clavulanic acid may be removed from
320 circulation by hemodialysis.

321 **11 DESCRIPTION**

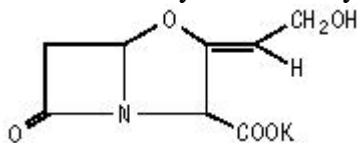
322 TIMENTIN (ticarcillin disodium and clavulanate potassium) for Injection, 3.1-gram glass
323 vial, 31-gram Pharmacy Bulk Package, and TIMENTIN (ticarcillin disodium and clavulanate
324 potassium) Injection in the GALAXY Container (PL 2040 Plastic) are a combination of
325 ticarcillin disodium and the β -lactamase inhibitor clavulanate potassium (the potassium salt of
326 clavulanic acid) for intravenous administration. Ticarcillin is derived from the basic penicillin
327 nucleus, 6-amino-penicillanic acid.

328 Chemically, ticarcillin disodium is *N*-(2-Carboxy-3,3-dimethyl-7-oxo-4-thia-1-
329 azabicyclo[3.2.0]hept-6-yl)-3-thiophenemalonamic acid disodium salt and may be represented
330 as:



331
332 Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a
333 β -lactam structurally related to the penicillins and possesses the ability to inactivate a wide
334 variety of β -lactamases by blocking the active sites of these enzymes. Clavulanic acid is
335 particularly active against the clinically important plasmid-mediated β -lactamases frequently
336 responsible for transferred drug resistance to penicillins and cephalosporins.

337 Chemically, clavulanate potassium is potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-
338 oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate and may be represented structurally as:



339
340 TIMENTIN (ticarcillin disodium and clavulanate potassium) for Injection, the 3.1-gram
341 glass vial or the 31-gram Pharmacy Bulk Package, are white to pale yellow sterile powders to be
342 reconstituted and diluted for intravenous infusion. The reconstituted solution is clear, colorless or
343 pale yellow, with a pH of 5.5 to 7.5. The 3.1-gram glass vial of TIMENTIN for Injection
344 contains ticarcillin disodium equivalent to 3 grams ticarcillin and clavulanate potassium
345 equivalent to 0.1 gram clavulanic acid. The 31-gram TIMENTIN for Injection Pharmacy Bulk
346 Package contains ticarcillin disodium equivalent to 30 grams ticarcillin and clavulanate
347 potassium equivalent to 1 gram clavulanic acid.

348 TIMENTIN (ticarcillin disodium and clavulanate potassium) Injection in the GALAXY
349 Container (PL 2040 Plastic) is an iso-osmotic, sterile, nonpyrogenic, frozen solution containing
350 3.0 grams ticarcillin as ticarcillin disodium and 0.1 gram clavulanic acid as clavulanate
351 potassium. Approximately 0.3 gram sodium citrate hydrous, USP, is added as a buffer. Sodium
352 hydroxide is used to adjust pH and convert ticarcillin monosodium to ticarcillin disodium. The
353 pH may have been adjusted with hydrochloric acid. The solution is intended for intravenous use
354 after thawing to room temperature. The pH of thawed solution ranges from 5.5 to 7.5.

355 The GALAXY container is fabricated from a specially designed multilayer plastic, PL
356 2040. Solutions are in contact with the polyethylene layer of this container and can leach out
357 certain chemical components of the plastic in very small amounts within the expiration period.
358 The suitability of the plastic has been confirmed in tests in animals according to the USP
359 biological tests for plastic containers, as well as by tissue culture toxicity studies.

360 For the 3.1-gram dosage of TIMENTIN, the theoretical sodium content is 4.51 mEq
361 (103.6 mg) per gram of TIMENTIN. The theoretical potassium content is 0.15 mEq (6 mg) per
362 gram of TIMENTIN.

363 For the 3.1-gram dosage of TIMENTIN in the GALAXY Container, the theoretical total
364 sodium content of the 100-mL solution is 18.7 mEq (429 mg), of which 15.6 mEq (359 mg) is
365 contributed by the ticarcillin disodium component of TIMENTIN. The total theoretical
366 potassium content of the 100-mL solution is 0.50 mEq (19.63 mg).

367 12 CLINICAL PHARMACOLOGY

368 12.1 Mechanism of Action

369 TIMENTIN is an antibacterial drug [see *Clinical Pharmacology (12.4)*].

370 12.3 Pharmacokinetics

371 Absorption: After an intravenous infusion (30 minutes) of 3.1 grams of TIMENTIN,
372 peak serum concentrations of both ticarcillin and clavulanic acid were attained immediately after
373 completion of the infusion. Ticarcillin serum levels were similar to those produced by the
374 administration of equivalent amounts of ticarcillin alone with a mean peak serum level of
375 324 mcg/mL. The corresponding mean peak serum level for clavulanic acid was 8 mcg/mL. (See
376 Table 2.)
377

378 **Table 2. Mean Peak Serum Levels (mcg/mL) in Adults After a 30-Minute IV Infusion of**
379 **3.1 grams of TIMENTIN**

Time	Ticarcillin Peak (Range)	Clavulanic Acid Peak (Range)
0	324 (293 - 388)	8.0 (5.3 - 10.3)
15 minutes	223 (184 - 293)	4.6 (3.0 - 7.6)
30 minutes	176 (135 - 235)	2.6 (1.8 - 3.4)
1 hour	131 (102 - 195)	1.8 (1.6 - 2.2)
1.5 hours	90 (65 - 119)	1.2 (0.8 - 1.6)
3.5 hours	27 (19 - 37)	0.3 (0.2 - 0.3)
5.5 hours	6 (5 - 7)	0

380
381 The mean area under the serum concentration curve was 485 mcg•hr/mL for ticarcillin
382 and 8.2 mcg•hr/mL for clavulanic acid.

383 Distribution: Ticarcillin has been found to be approximately 45% bound to human serum
384 protein and clavulanic acid approximately 25% bound. Ticarcillin can be detected in tissues and
385 interstitial fluid following parenteral administration.

386 Distribution of ticarcillin into bile and pleural fluid has been demonstrated. The results of
387 experiments involving the administration of clavulanic acid to animals suggest that this
388 compound, like ticarcillin, is well distributed in body tissues.

389 **Elimination:** Approximately 60% to 70% of ticarcillin and approximately 35% to 45% of
390 clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a
391 single dose of TIMENTIN to normal volunteers with normal renal function. Two hours after an
392 intravenous injection of 3.1 grams of TIMENTIN, concentrations of ticarcillin in urine generally
393 exceed 1,500 mcg/mL. The corresponding concentrations of clavulanic acid in urine generally
394 exceed 40 mcg/mL. By 4 to 6 hours after injection, the urine concentrations of ticarcillin and
395 clavulanic acid usually decline to approximately 190 mcg/mL and 2 mcg/mL, respectively.

396 The mean serum half-life of both ticarcillin and clavulanic acid in healthy volunteers was
397 1.1 hours.

398 **Pediatrics:** In pediatric patients receiving approximately 50 mg/kg of TIMENTIN (30:1
399 ratio ticarcillin to clavulanate), mean ticarcillin serum half-lives were 4.4 hours in neonates
400 (n = 18) and 1.0 hour in infants and children (n = 41). The corresponding clavulanate serum
401 half-lives averaged 1.9 hours in neonates (n = 14) and 0.9 hour in infants and children (n = 40).
402 Area under the serum concentration time curves averaged 339 mcg•hr/mL in infants and children
403 (n = 41), whereas the corresponding mean clavulanate area under the serum concentration time
404 curves was approximately 7 mcg•hr/mL in the same population (n = 40).

405 **Renal Impairment:** An inverse relationship exists between the serum half-life of
406 ticarcillin and creatinine clearance. The half-life of ticarcillin in patients with renal failure is
407 approximately 13 hours. The dosage of TIMENTIN need only be adjusted in cases of severe
408 renal impairment [*see Dosage and Administration (2.3)*].

409 Ticarcillin may be removed from patients undergoing dialysis; the actual amount
410 removed depends on the duration and type of dialysis.

411 **12.4 Microbiology**

412 **Mechanism of Action:** Ticarcillin disrupts bacterial cell wall development by inhibiting
413 peptidoglycan synthesis and/or by interacting with penicillin-binding proteins.

414 Ticarcillin is susceptible to degradation by β -lactamases, so the spectrum of activity does
415 not normally include organisms which produce these enzymes.

416 Clavulanic acid is a β -lactam, structurally related to the penicillins, which inactivates
417 some β -lactamase enzymes that are commonly found in bacteria resistant to penicillins and
418 cephalosporins. In particular, it has good activity against the clinically important
419 plasmid-mediated β -lactamases frequently responsible for transferred drug resistance.

420 The formulation of ticarcillin with clavulanic acid in TIMENTIN protects ticarcillin from
421 degradation by β -lactamase enzymes, effectively extending the antibacterial spectrum of
422 ticarcillin to include many bacteria normally resistant to ticarcillin and other β -lactam
423 antibacterials.

424 Interaction With Other Antimicrobials: In vitro synergism between TIMENTIN and
425 gentamicin, tobramycin, or amikacin against multi-resistant isolates of *Pseudomonas aeruginosa*
426 has been demonstrated.

427 Ticarcillin/clavulanic acid has been shown to be active against most isolates of the
428 following bacteria, both in vitro and in clinical infections [see *Indications and Usage (1)*].

429 Susceptibility to ticarcillin/clavulanic acid will vary with geography and time; local
430 susceptibility data should be consulted, if available.

431 **Gram-positive bacteria**

432 *Staphylococcus aureus* (methicillin-susceptible isolates only)

433 *Staphylococcus epidermidis* (methicillin-susceptible isolates only)

434

435 **Gram-negative bacteria**

436 *Citrobacter* spp.^a

437 *Enterobacter* spp.^a

438 *E. cloacae*^a

439 *Escherichia coli*^a

440 *Haemophilus influenzae*^b

441 *Klebsiella* spp.^a

442 *K. pneumoniae*^a

443 *Pseudomonas* spp.^a

444 *P. aeruginosa*^a

445 *Serratia marcescens*^a

446

447 **Anaerobic bacteria**

448 *Bacteroides fragilis* group

449 *Prevotella melaninogenicus*

450

451 ^a Some extended spectrum β -lactamase (ESBL)-producing isolates are resistant to
452 ticarcillin/clavulanic acid. Most carbapenemase-producing isolates are resistant to
453 ticarcillin/clavulanic acid.

454 ^b β -lactamase-negative, ampicillin-resistant (BLNAR) isolates of *H. influenzae* must be
455 considered resistant to ticarcillin/clavulanic acid.

456

457 The following in vitro data are available, but their clinical significance is unknown.

458 At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory
459 concentration (MIC) less than or equal to the susceptible breakpoint for ticarcillin/clavulanic
460 acid. However, the efficacy of ticarcillin/clavulanic acid in treating clinical infections due to
461 these bacteria have not been established in adequate and well-controlled clinical trials.

462

463 **Gram-positive bacteria**

- 464 *Staphylococcus saprophyticus* (methicillin-susceptible isolates only)
- 465 *Streptococcus agalactiae* (Group B)
- 466 *Streptococcus bovis*
- 467 *Streptococcus pneumoniae* (penicillin-susceptible isolates only)
- 468 *Streptococcus pyogenes*
- 469 *Streptococcus* spp. viridans group (penicillin-susceptible isolates only)

470

471 **Gram-negative bacteria**

- 472 *Moraxella catarrhalis*
- 473 *Pasteurella multocida*

474

475 **Anaerobic bacteria**

- 476 *Clostridium* spp.
- 477 *C. perfringens*
- 478 *C. difficile*
- 479 *C. sporogenes*
- 480 *C. ramosum*
- 481 *C. bifermentans*
- 482 *Eubacterium* spp.
- 483 *Fusobacterium* spp.
- 484 *F. nucleatum*
- 485 *F. necrophorum*
- 486 *Peptostreptococcus* spp.
- 487 *Veillonella* spp.

488

489 **Susceptibility Testing:** When available, the clinical microbiology laboratory should
490 provide the results of in vitro susceptibility test results for antimicrobial drug products used in
491 local hospitals and practice areas to the physician as periodic reports that describe the
492 susceptibility profile of nosocomial and community-acquired pathogens. These reports should
493 aid the physician in selecting an antibacterial drug product for treatment.

494 ***Dilution Techniques:*** Quantitative methods are used to determine antimicrobial
495 minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility
496 of bacteria to antimicrobial compounds. The MICs should be determined using a standardized
497 test method^{2,4} (broth and/or agar). The MIC values should be interpreted according to criteria
498 provided in Table 3.

499 ***Diffusion Techniques:*** Quantitative methods that require measurement of zone
500 diameters can also provide reproducible estimates of the susceptibility of bacteria to
501 antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to
502 antimicrobial compounds. The zone size should be determined using a standardized test
503 method.^{3,4} These procedures use paper disks impregnated with 85 mcg of ticarcillin/clavulanate

504 potassium (75 mcg ticarcillin plus 10 mcg clavulanate potassium) to test the susceptibility of
505 bacteria to ticarcillin/clavulanic acid. The disc diffusion interpretive criteria are provided in
506 Table 3.

507 *Anaerobic Techniques:* For anaerobic bacteria, susceptibility to ticarcillin/clavulanic
508 acid can be determined by standardized test methods.^{4,5} The MIC values obtained should be
509 interpreted according to the criteria in Table 3.

510

511 **Table 3. Susceptibility Test Interpretive Criteria for Ticarcillin/Clavulanic Acid**

Microorganism	Minimum Inhibitory Concentration (mcg/mL)			Disc Diffusion (Zone Diameter mm)		
	S	I	R	S	I	R
Anaerobes	≤32/2	64/2	≥128/2	-	-	-
<i>Enterobacteriaceae</i>	≤16/2	32/2 - 64/2	≥128/2	≥20	15 - 19	≤14
<i>Pseudomonas aeruginosa</i>	≤16/2	32/2 - 64/2	≥128/2	≥24	16 - 23	≤15

512

513 Susceptibility of staphylococci to ticarcillin/clavulanate may be deduced by testing penicillin and
514 either oxacillin or ceftioxin.⁴

515

516 A report of “Susceptible” indicates the antimicrobial is likely to inhibit growth of the
517 pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary
518 to inhibit growth of the pathogen. A report of “Intermediate” indicates that the result should be
519 considered equivocal, and, if the bacterium is not fully susceptible to alternative, clinically
520 feasible drugs, the test should be repeated. This category implies possible clinical applicability in
521 body sites where the drug product is physiologically concentrated or in situations where a high
522 dosage of the drug product can be used. This category also provides a buffer zone that prevents
523 small uncontrolled technical factors from causing major discrepancies in interpretation. A report
524 of “Resistant” indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the
525 antimicrobial compound reaches the concentrations usually achievable at the infection site; other
526 therapy should be selected.

527 *Quality Control:* Standardized susceptibility test procedures require the use of
528 laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents
529 used in the assay, and the techniques of the individual performing the tests.^{2,3,4,5} Standard
530 ticarcillin/clavulanic acid powder should provide the following range of MIC values noted in
531 Table 4. For the diffusion technique using the 85 mcg of ticarcillin/clavulanate potassium
532 (75 mcg ticarcillin plus 10 mcg clavulanate potassium), the criteria in Table 4 should be
533 achieved.

534

535 **Table 4. Acceptable Quality Control Ranges for Ticarcillin/Clavulanic Acid**

QC Strain	Broth MIC (mcg/mL)	Zone Diameter (mm)	Agar Dilution MIC (mcg/mL)
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	0.5/2 - 2/2	-	0.5/2 - 2/2
<i>Clostridium difficile</i> ATCC 700057	-	-	16/2 - 64/2
<i>Enterococcus faecalis</i> ATCC 29212	16/2 - 64/2	-	-
<i>Escherichia coli</i> ATCC 25922	4/2 - 16/2	24 - 30	-
<i>Escherichia coli</i> ATCC 35218	8/2 - 32/2	21 - 25	-
<i>Eubacterium lentum</i> ATCC 43055	8/2 - 32/2	-	16/2 - 64/2
<i>Pseudomonas aeruginosa</i> ATCC 27853	8/2 - 32/2	20 - 28	-
<i>Staphylococcus aureus</i> ATCC 29213	0.5/2 - 2/2	-	-
<i>Staphylococcus aureus</i> ATCC 25923	-	29 - 37	-

536 ATCC = American Type Culture Collection

537 MIC = Minimum Inhibitory Concentration

538

539 **13 NONCLINICAL TOXICOLOGY**

540 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

541 Long-term studies in animals have not been performed to evaluate carcinogenic potential.
542 Results from in vitro assays in bacteria (Ames tests), yeast, and human lymphocytes, and in vivo
543 in mouse bone marrow (micronucleus test) indicate TIMENTIN is without genotoxic potential.

544 Reproduction studies have been performed in rats given doses up to 1,050 mg/kg/day
545 (approximately half of the recommended human dose based on body surface area) and have
546 revealed no evidence of impaired fertility due to TIMENTIN.

547 **14 CLINICAL STUDIES**

548 TIMENTIN has been studied in 296 pediatric patients (excluding neonates and infants
549 less than 3 months) in 6 controlled clinical trials. The majority of patients studied had
550 intra-abdominal infections, and the primary comparator was clindamycin and gentamicin with or
551 without ampicillin. At the end-of-therapy visit, comparable efficacy was reported in the trial
552 arms using TIMENTIN and an appropriate comparator.

553 TIMENTIN was also evaluated in an additional 408 pediatric patients (excluding
554 neonates and infants less than 3 months) in 3 uncontrolled US clinical trials. Patients had a broad
555 range of presenting diagnoses including: Infections in bone and joint, skin and skin structure,
556 lower respiratory tract, urinary tract, as well as intra-abdominal and gynecologic infections.
557 Patients received TIMENTIN, either 300 mg/kg/day (based on the ticarcillin component) divided
558 every 4 hours for severe infection or 200 mg/kg/day (based on the ticarcillin component) divided
559 every 6 hours for mild to moderate infections. Efficacy rates were comparable to those obtained
560 in controlled trials.

561 The adverse event profile in these 704 pediatric patients treated with TIMENTIN was
562 comparable to that seen in adult patients.

563 **15 REFERENCES**

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582 **16 HOW SUPPLIED/STORAGE AND HANDLING**

583 Each 3.1-gram vial of TIMENTIN for Injection contains sterile ticarcillin disodium
584 equivalent to 3 grams ticarcillin and sterile clavulanate potassium equivalent to 0.1 gram
585 clavulanic acid.

NDC 0029-6571-26 3.1-gram Vial

586 Each 31-gram Pharmacy Bulk Package of TIMENTIN for Injection contains sterile
587 ticarcillin disodium equivalent to 30 grams ticarcillin and sterile clavulanate potassium
588 equivalent to 1 gram clavulanic acid.

NDC 0029-6579-21 31-gram Pharmacy Bulk Package

589 Each 100-mL single-dose GALAXY Container (PL 2040 Plastic) of TIMENTIN
590 Injection contains ticarcillin disodium equivalent to 3.0 grams ticarcillin and clavulanate
591 potassium equivalent to 0.1 gram clavulanic acid.

NDC 0029-6575-31 100 mL GALAXY Container (PL 2040 Plastic)

592 3.1-gram Vials and 31-gram Pharmacy Bulk Packages of TIMENTIN for Injection
593 should be stored at or below 25°C (77°F).

594 GALAXY Containers (PL 2040 Plastic) of TIMENTIN Injection should be stored at or
595 below -20°C (-4°F). Avoid unnecessary handling of containers.

596 **Thawing of Plastic Containers:** Thaw frozen container at room temperature 22°C
597 (72°F) or in a refrigerator 4°C (39°F). [Do not force thaw by immersion in water baths or by
598 microwave irradiation.] Check for minute leaks by squeezing container firmly. If leaks are
599 detected discard solution as sterility may be impaired. Do not add supplementary medication.

600 The container should be visually inspected. Thawed solutions should not be used unless
601 clear; solutions will be light to dark yellow in color. Components of the solution may precipitate
602 in the frozen state and will dissolve upon reaching room temperature with little or no agitation.
603 If, after visual inspection, the solution remains cloudy or if an insoluble precipitate is noted or if
604 any seals or outlet ports are not intact, the container should be discarded.

605 The thawed solution is stable for 24 hours at room temperature 22°C (72°F) or for 7 days
606 under refrigeration 4°C (39°F).

607 Do not refreeze.

608 **17 PATIENT COUNSELING INFORMATION**

609 Drug Resistance: Inform patients that antibacterial drugs, including TIMENTIN,
610 should only be used to treat bacterial infections. They do not treat viral infections (e.g., the
611 common cold). When TIMENTIN is prescribed to treat a bacterial infection, inform patients that
612 although it is common to feel better early in the course of therapy, the medication should be
613 taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1)
614 decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that
615 bacteria will develop resistance and will not be treatable by TIMENTIN or other antibacterial
616 drugs in the future.

617 Clostridium difficile Associated Diarrhea: Inform patients that diarrhea is a common
618 problem caused by antibacterials, and it usually ends when the antibacterial is discontinued.
619 Sometimes after starting treatment with antibacterials, patients can develop watery and bloody
620 stools (with or without stomach cramps and fever) even as late as 2 or more months after having
621 taken their last dose of the antibacterial. If this occurs, advise patients to contact their physician
622 as soon as possible.

623 Allergic Reactions: Inform patients that TIMENTIN contains a penicillin that can cause
624 allergic reactions in some individuals [*see Warnings and Precautions (5.1)*].

625

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627 GALAXY is a registered trademark of Baxter International Inc.

628



629

630

631 GlaxoSmithKline

632 Research Triangle Park, NC 27709

633

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