DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JUN 28 2000

Melanie Bishop
Program Director
Drug Regulatory Affairs
Hoffmann-La Roche Inc.
Bldg. 1/2
340 Kingsland Street
Nutley, New Jersey 07110-1199

RE: NDA # 50-585
Rocephin (ceftriaxone sodium) IV/IM
MACMIS ID #8732

Dear Ms. Bishop:

As a part of the Division of Drug Marketing, Advertising, and Communications' (DDMAC) routine surveillance, we have reviewed promotional materials for Rocephin (ceftriaxone sodium) from your submissions of FDA form 2253 dated, December, 1999 and January, 2000. The submissions contained promotional sales aids for Rocephin (e.g. ID # 18-039-073-130-129, 18-039-073-126-129, 18-039-073-087-129). We find the sales aids to be in violation of the Federal Food, Drug, and Cosmetic Act and the applicable regulations. Specifically, the sales aids promote Rocephin for an unapproved use.

Unapproved Use:

- Rocephin is not approved to treat penicillin-resistant *streptococcus pneumoniae* (PRSP) infections. In your sales aids, you promote Rocephin for the treatment of PRSP in community-acquired pneumonia and non-meningeal infections. In addition, you make comparisons between Rocephin and the fluoroquinolones that imply superiority for Rocephin in the treatment of PRSP. These comparisons are not supported by substantial evidence. Therefore, we find the sales aids to be violative.

You should immediately cease distribution of the sales aids and other similar promotional materials for Rocephin that contain the same or similar claims or presentations. You should submit a written response on or before July 10, 2000 describing your intent and plans to comply with the above. Your letter should include a list of materials discontinued and the date on which these materials were discontinued.

You should direct your response to the undersigned by facsimile by at (301) 594-6759, or to the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #8732 in addition to the NDA number.

Sincerely,

/S/

James R. Rogers, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

THE TRUE WORKHORSE PARENTERAL

Compare Indications:

Infection	ROCEPHIN	QUINOLONES Ciprofloxacin[1]	QUINOLONES Levofloxacin[2]
Lower respiratory tract	✓	✓	
Community-acquired pneumonia	✓	✓	✓
Nosocomial pneumonia	✓	✓	
Skin & skin structure	✓	✓	✓ (uncomplicated only)
Urinary tract	✓	✓	✓
Septicemia	✓		
Bone & joint	✓	✓	
Intra-abdominal	✓	✓	
Surgical prophylaxis	✓		
Pelvic inflammatory disease	✓		
Gonorrhea	✓	✓*	
Acute otitis media†	✓		
Meningitis	✓		
Pediatric indications	✓		
Febrile neutropenia		✓	
Acute sinusitis		✓*	✓
Acute bacterial exacerbation of chronic bronchitis			✓

*Oral indication only.

†In one study, lower clinical cure rates were observed with a single dose of ROCEPHIN compared to 10 days of oral therapy. However, in a second study, comparable cure rates were observed between single-dose ROCEPHIN and the comparator. The potentially lower clinical cure rate of ROCEPHIN should be balanced against the potential advantages of one-dose injectable therapy.

Please see complete product information inside pocket.

Once-a-day

Rocephin® I.V. I.M.

ceftriaxone sodium

Usual adult daily dosage: 1 to 2 gm once a day

ROCEPHIN—OVER 15 YEARS OF STAYING POWER

Then and now, low MIC_{90}s for common pathogens

(derived from multiple sources)

	ROCEPHIN MIC_{90} (μg/mL)	
	1982-1983[3-6]	1996-1997[7-10]
Gram-positive		
Staphylococcus aureus (methicillin-susceptible)	4	4
Staphylococcus epidermidis	8	2
Streptococcus pneumoniae (penicillin-susceptible)*	0.06	0.064
(intermediately penicillin-resistant)†	0.5	0.5
(penicillin-resistant)‡	1	2
Streptococcus pyogenes	0.03	0.06
Viridans group streptococci	1	1
Gram-negative		
Escherichia coli	0.12	0.12
Haemophilus influenzae§	0.015	≤0.03
Klebsiella oxytoca	NA	0.5
Klebsiella pneumoniae	0.06	0.25
Moraxella catarrhalis§	NA	1
Morganella morganii	0.5	2
Neisseria gonorrhoeae	≤0.001	0.032
Neisseria meningitidis	≤0.001	≤0.12
Proteus mirabilis	0.008	≤0.03
Serratia marcescens	4	2

NA = not available.
*Penicillin-susceptible with penicillin MICs of ≤0.06 μg/mL.
†Penicillin-intermediate with penicillin MICs of 0.12 to 1.0 μg/mL.
‡Penicillin-resistant with penicillin MICs of ≥2.0 μg/mL.
§Including beta-lactamase–producing strains.

In vitro data do not necessarily correlate with clinical results but do provide a useful guide.

MIC_{90}s derived from published studies do not necessarily reflect local susceptibility data.

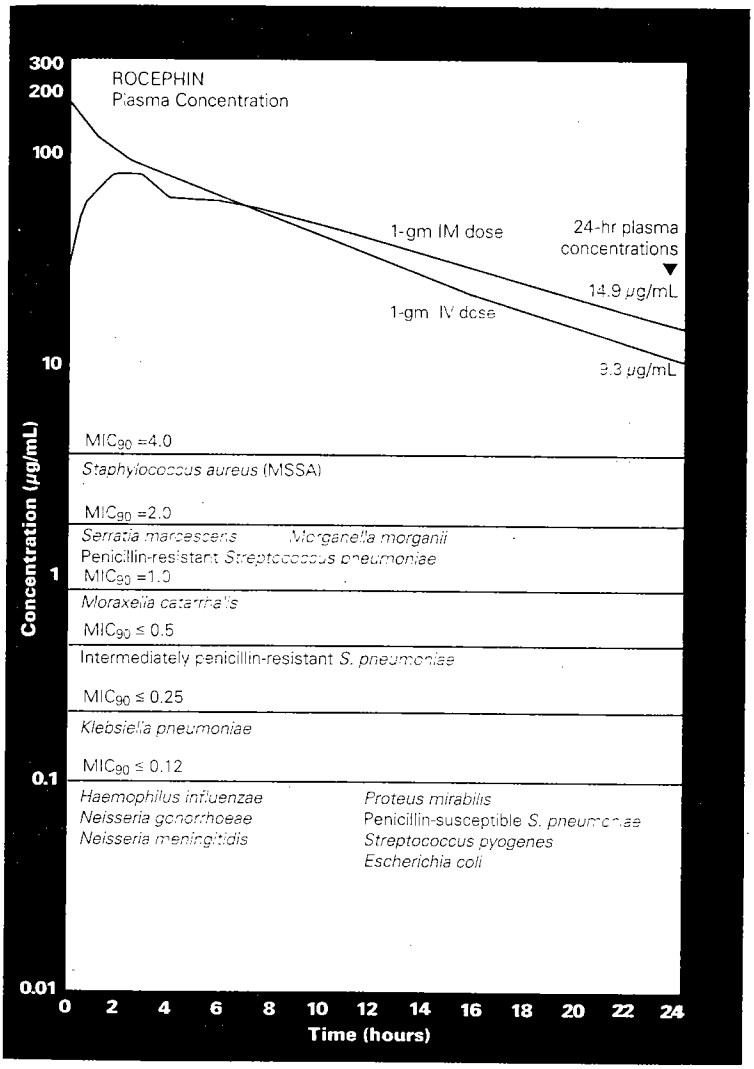
Please see complete product information inside pocket.

Once-a-day

Rocephin ceftriaxone sodium

Usual adult daily dosage: 1 to 2 gm once a day

24-hour IV[11] and IM[12] plasma levels remain above MIC_{90}s for common bacterial pathogens[7-10]



Concentration is regarded as important to therapeutic efficacy, but specific levels may not necessarily correlate with therapeutic results.

In vitro data do not necessarily correlate with clinical results but do provide a useful guide.

Please see complete product information inside pocket.

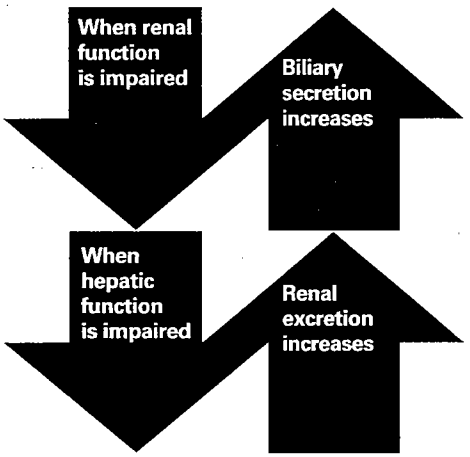
Roche Pharmaceuticals

ROCEPHIN® (ceftriaxone sodium) PROVIDES A DUAL MECHANISM OF ELIMINATION

- ROCEPHIN is excreted both renally and hepatically
- When one system is impaired, the other will compensate
- An important consideration in elderly patients, who are often renally and/or hepatically compromised
- No dosage adjustment is required in patients with impaired renal or hepatic function

Monitor ROCEPHIN blood levels in patients with severe renal impairment or with both renal and hepatic dysfunction.

Dual and compensatory elimination



EXCELLENT SAFETY PROFILE

Adverse clinical effects occur at levels similar to those of other cephalosporins — in adults: diarrhea (2.7%), rash (1.7%) and local reactions (≤1%); in pediatric patients treated for serious infections other than AOM: diarrhea (5.6%), rash (< 2%) and fever (1.1%). In pediatric patients treated for bacterial otitis media, except for injection-site reactions (1.6%), adverse clinical effects occurred at levels similar to other antimicrobials: diarrhea (14.1%), diaper rash (5.2%), rash (4.9%) and vomiting (1.4%).[13,14] Among adults in a small bioequivalence study (diluent reduction), the incidence of injection-site reaction was 17% (3/17). ROCEPHIN is contraindicated in patients with a known allergy to cephalosporins and should be used cautiously in penicillin-sensitive patients.

Roche Pharmaceuticals

AVOID DRUG INTERACTIONS

Drug Interaction or Warning	ROCEPHIN	QUINOLONES		
		Ciprofloxacin[1]	Levofloxacin[2]	Trovafloxacin[15]
Theophylline		X		
Caffeine		X		
Cyclosporine		X		
Phenytoin		X		
Antidiabetics		X	X	
Warfarin		X		
Probenecid		X		
NSAID			X	
Antacids			X	X
Sucralfate			X	X
Vitamins with minerals			X	X
IV morphine				X

Once-a-day

Rocephin® IV·IM

ceftriaxone sodium

Usual adult daily dosage: 1 to 2 gm once a day

Please see complete product information inside pocket.

Plandex 731221
18-039-073-130-129

Printed in USA

Roche **Pharmaceuticals**

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
www.rocheusa.com

References: 1. *Physicians' Desk Reference®*. 53rd ed. Montvale, NJ: Medical Economics Company, Inc.; 1999:641-651. **2.** *Physicians' Desk Reference®*. 53rd ed. Montvale, NJ: Medical Economics Company, Inc.; 1999:2192-2201. **3.** Jones RN, et al. Ceftriaxone: a summary of in vitro antibacterial qualities including recommendations for susceptibility tests with 30-μg disks. *Diagn Microbiol Infect Dis.* 1983;1:295-311. **4.** Neu HC. The new beta-lactamase-stable cephalosporins. *Ann Intern Med.* 1982;97:408-419. **5.** Tweardy DJ, et al. Susceptibility of penicillin-resistant pneumococci to eighteen antimicrobials: implications for treatment of meningitis. *J Antimicrob Chemother.* 1983;12:133-139. **6.** Fass RJ. Comparative in vitro activities of third-generation cephalosporins. *Arch Intern Med.* 1983;143:1743-1745. **7.** Fass RJ. In vitro activity of Bay 12-8039, a new 8-methoxyquinolone. *Antimicrob Agents Chemother.* 1997;41(8):1818-1824. **8.** Thornsberry C, et al. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* in the United States in 1996-1997 respiratory season. *Diagn Microbiol Infect Dis.* 1997;29:249-257. **9.** Biedenbach DJ, et al. Comparative assessment of Etest for testing susceptibilities of *Neisseria gonorrhoeae* to penicillin, tetracycline, ceftriaxone, cefotaxime, and ciprofloxacin: investigation using 510 (k) review criteria, recommended by the Food and Drug Administration. *J Clin Microbiol.* 1996;34(12):3214-3217. **10.** Fuchs PC, et al. Survey of antimicrobial activity of four commonly used third generation cephalosporins tested against recent bacterial isolates from ten American medical centers, and assessment of disk diffusion test performance. *Diagn Microbiol Infect Dis.* 1996;24:213-219. **11.** Patel IH, et al. Pharmacokinetics of ceftriaxone in humans. *Antimicrob Agents Chemother.* 1981;20(5):634-641. **12.** Scully BE, et al. Pharmacokinetics of ceftriaxone after intravenous infusion and intramuscular injection. *Am J Med.* 1984;77:112-116. **13.** Data on file (Ref. 073-045), Hoffmann-La Roche Inc., Nutley, NJ. **14.** Data on file (Ref. 073-046), Hoffmann-La Roche Inc., Nutley, NJ. **15.** *Physicians' Desk Reference®*. 53rd ed. Montvale, NJ: Medical Economics Company, Inc.; 1999:2414-2421.

Once-a-day

Rocephin® IV·IM

ceftriaxone sodium

Usual adult daily dosage: 1 to 2 gm once a day

Please see complete product information in this pocket.

Roche

EXPERT OPINIONS ON THE ROLE OF ROCEPHIN IN COMMUNITY-ACQUIRED PNEUMONIA (CAP)

Infectious Diseases Society of America Guidelines[1]:

- **ROCEPHIN**—a preferred agent for most patients on general wards
- **ROCEPHIN**—a preferred agent for intermediately penicillin-resistant *Streptococcus pneumoniae*
- **ROCEPHIN**—a preferred agent for combination therapy in ICU patients

The Medical Letter[2,3]

- **ROCEPHIN**—"recommended" and "a reasonable first choice" for hospitalized CAP patients
- **ROCEPHIN**—a "drug of first choice" for intermediately penicillin-resistant *S. pneumoniae*
- **ROCEPHIN**—a "drug of first choice" in combination therapy for highly penicillin-resistant *S. pneumoniae*

The Sanford Guide 1999[4]

- **ROCEPHIN**—a suggested primary regimen alone or in combination therapy for hospitalized patients with CAP

Please see complete product information in inside pocket.

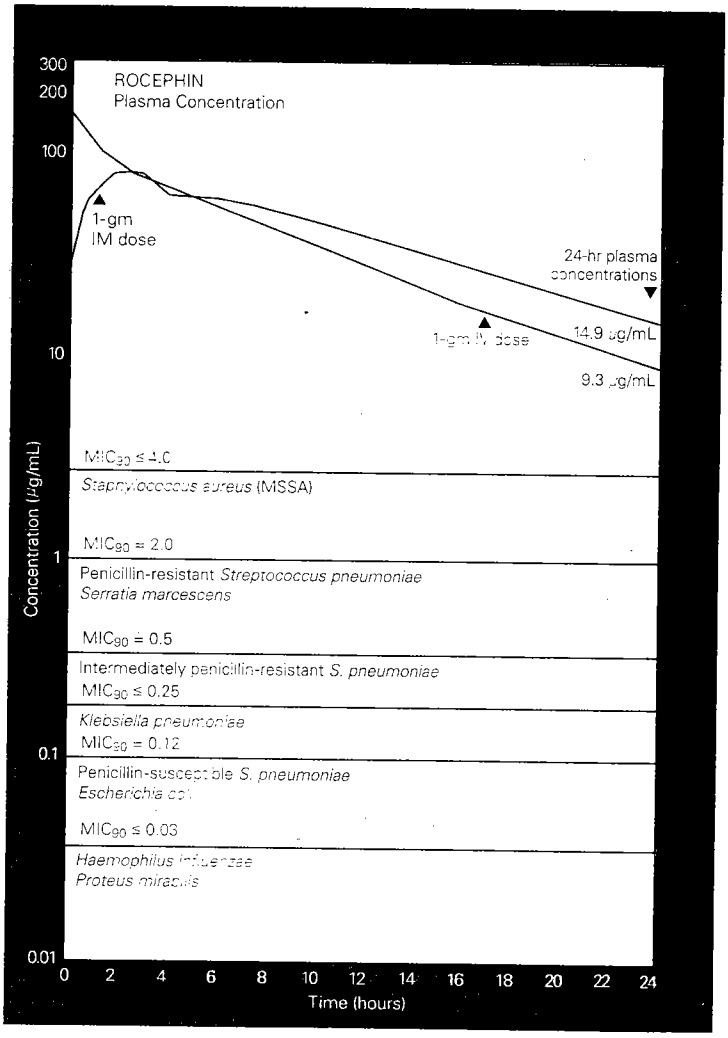
Once-a-day

Rocephin® IV·IM

ceftriaxone sodium

Usual adult daily dosage: 1 to 2 gm once a day

24-hour IV[5] and IM[6] plasma levels remain above MIC_{90}s for common CAP pathogens[7,8]



Concentration is regarded as important to therapeutic efficacy, but specific levels may not necessarily correlate with therapeutic results. In vitro data do not necessarily correlate with clinical results but do provide a useful guide.

Once-a-day

Rocephin® IV·IM

ceftriaxone sodium

Usual adult daily dosage: 1 to 2 gm once a day

Roche Pharmaceuticals

ROCEPHIN—OVER 14 YEARS OF STAYING POWER

Then and now, low MIC_{90}s for common pathogens

(derived from multiple sources)

ROCEPHIN MIC_{90}s (μg/mL)	1982-1983[9-12]	1996-1997[7,8,13,14]
Gram-positive		
Staphylococcus aureus (methicillin-susceptible)	4	4
Staphylococcus epidermidis	8	2
Streptococcus pneumoniae		
(penicillin-susceptible)*	0.06	0.064
(intermediately penicillin-resistant)†	0.5	0.5
(penicillin-resistant)‡	1	2
Streptococcus pyogenes	0.03	0.06
Viridans group streptococci	1	1
Gram-negative		
Escherichia coli	0.12	0.12
Haemophilus influenzae§	0.015	≤0.03
Klebsiella oxytoca	NA	0.5
Klebsiella pneumoniae	0.06	0.25
Moraxella catarrhalis§	NA	1
Morganella morganii	0.5	2
Neisseria gonorrhoeae	≤0.001	0.032
Neisseria meningitidis	≤0.001	≤0.12
Proteus mirabilis	0.008	≤0.03
Serratia marcescens	4	2

NA = not available.

*Penicillin-susceptible with penicillin MICs of ≤0.06 μg/mL.

†Penicillin-intermediate with MICs of 0.12 to 1.0 μg/mL.

‡Penicillin-resistant with MICs of ≥2.0 μg/mL.

§Including beta-lactamase-producing strains.

In vitro data do not necessarily correlate with clinical results but do provide a useful guide.

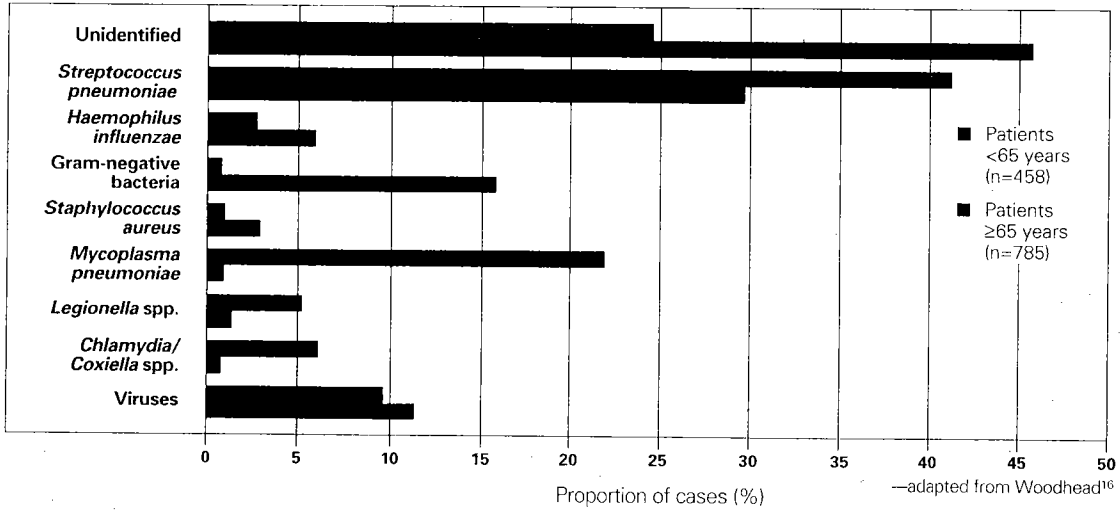
MIC_{90}s derived from published studies do not necessarily reflect local susceptibility data.

Most strains of enterococci are resistant to cephalosporins.

Adverse clinical effects in adults occur at levels similar to those of other cephalosporins: diarrhea (2.7%), rash (1.7%) and local reactions (≤1%). ROCEPHIN is contraindicated in patients with a known allergy to cephalosporins and should be used cautiously in penicillin-sensitive patients.

Please see complete product information in inside pocket.

Etiologic Agents of CAP[16]



—adapted from Woodhead[16]

Most common, highest mortality: *Streptococcus pneumoniae*

- The most commonly identified agent in severe CAP[17]
- Responsible for 66% of CAP with established etiology
- Accounts for about two thirds of pneumonia mortality[1]

Once-a-day
Rocephin® IV·IM
ceftriaxone sodium
Usual adult daily dosage: 1 to 2 gm once a day

Please see complete product information in inside pocket.

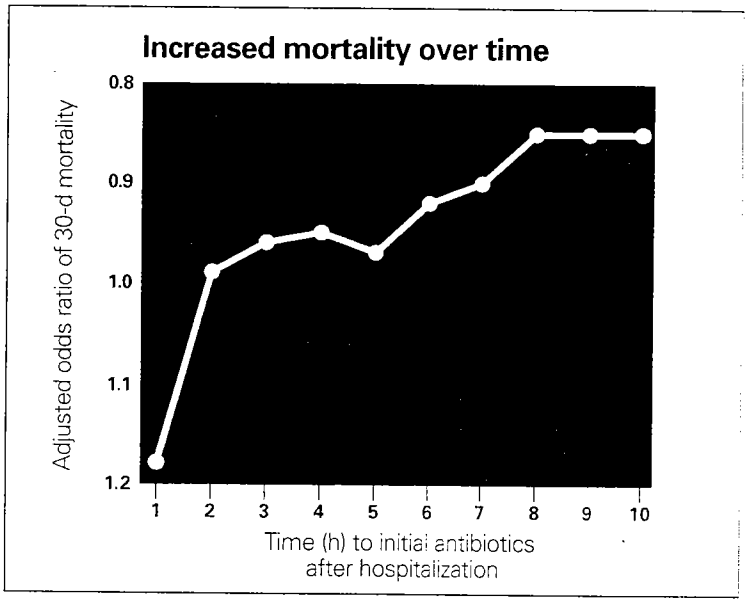
Plandex 731212
18 039 0/3-126 129

Printed in USA

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
www.rochecusa.com

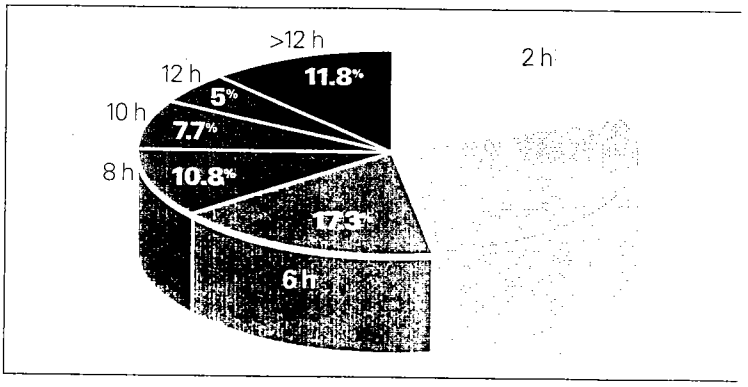
DELAY IN ANTIBIOTICS INCREASES RISK IN COMMUNITY-ACQUIRED PNEUMONIA (CAP)[15]



—adapted from Meehan[15]

MANY PATIENTS RECEIVE DELAYED ANTIBIOTICS IN HOSPITAL[15]

Percentage of patients receiving initial antibiotics within time frame after hospitalization (national average)



- 25% of elderly patients receive antibiotics ≥8 hours after hospitalization[15]

References: 1. Bartlett JG, et al. Guidelines from the Infectious Diseases Society of America. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis.* 1998;26:811-838. **2.** Sparfloxacin and levofloxacin. *The Medical Letter® on Drugs and Therapeutics.* New Rochelle, NY: The Medical Letter, Inc. 1997;39(999):41-43. **3.** The choice of antibacterial drugs. *The Medical Letter® on Drugs and Therapeutics.* New Rochelle, NY: The Medical Letter, Inc. 1998;40(1023):33-42. **4.** Gilbert DN, et al. *The Sanford Guide to Antimicrobial Therapy.* 29th ed. Hyde Park, VT: Antimicrobial Therapy, Inc; 1999. **5.** Pate IH, et al. Pharmacokinetics of ceftriaxone in humans. *Antimicrob Agents Chemother.* 1981; 20(5):634-641. **6.** Scully BE, et al. Pharmacokinetics of ceftriaxone after intravenous infusion and intramuscular injection. *Am J Med.* 1984;77:112-116. **7.** Fass RJ. In vitro activity of Bay 12-8039, a new 8-methoxyquinolone. *Antimicrob Agents Chemother.* 1997;41(8):1818-1824. **8.** Thornsberry C, et al. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* in the United States in 1996-1997 respiratory season. *Diagn Microbiol Infect Dis.* 1997;29:249-257. **9.** Jones RN, et al. Ceftriaxone: a summary of in vitro antibacterial qualities including recommendations for susceptibility tests with 30-µg disks. *Diagn Microbiol Infect Dis.* 1983;1:295-311. **10.** Neu HC. The new beta-lactamase-stable cephalosporins. *Ann Intern Med.* 1982;97:408-419. **11.** Tweardy DJ, et al. Susceptibility of penicillin-resistant pneumococci to eighteen antimicrobials: implications for treatment of meningitis. *J Antimicrob Chemother.* 1983;12:133-139. **12.** Fass RJ. Comparative in vitro activities of third-generation cephalosporins. *Arch Intern Med.* 1983;143:1743-1745. **13.** Biedenbach DJ, et al. Comparative assessment of Etest for testing susceptibilities of *Neisseria gonorrhoeae* to penicillin, tetracycline, ceftriaxone, cefotaxime, and ciprofloxacin: investigation using 510(k) review criteria, recommended by the Food and Drug Administration. *J Clin Microbiol.* 1996;34(12):3214-3217. **14.** Fuchs PC, et al. Survey of antimicrobial activity of four commonly used third generation cephalosporins tested against recent bacterial isolates from ten American medical centers, and assessment of disk diffusion test performance. *Diagn Microbiol Infect Dis.* 1996;24:213-219. **15.** Meehan TP, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA.* 1997; 278(23):2080-2084. **16.** Woodhead M. Pneumonia in the elderly. *J Antimicrob Chemother.* 1994;34(suppl A):85-92. **17.** Bartlett JG. Assessment of response to antimicrobial therapy and time to discharge in patients hospitalized with community-acquired pneumonia. *Infect Dis Clin Pract.* 1996;9(suppl 4):S148-S153.

Once-a-day

Rocephin® IV·IM

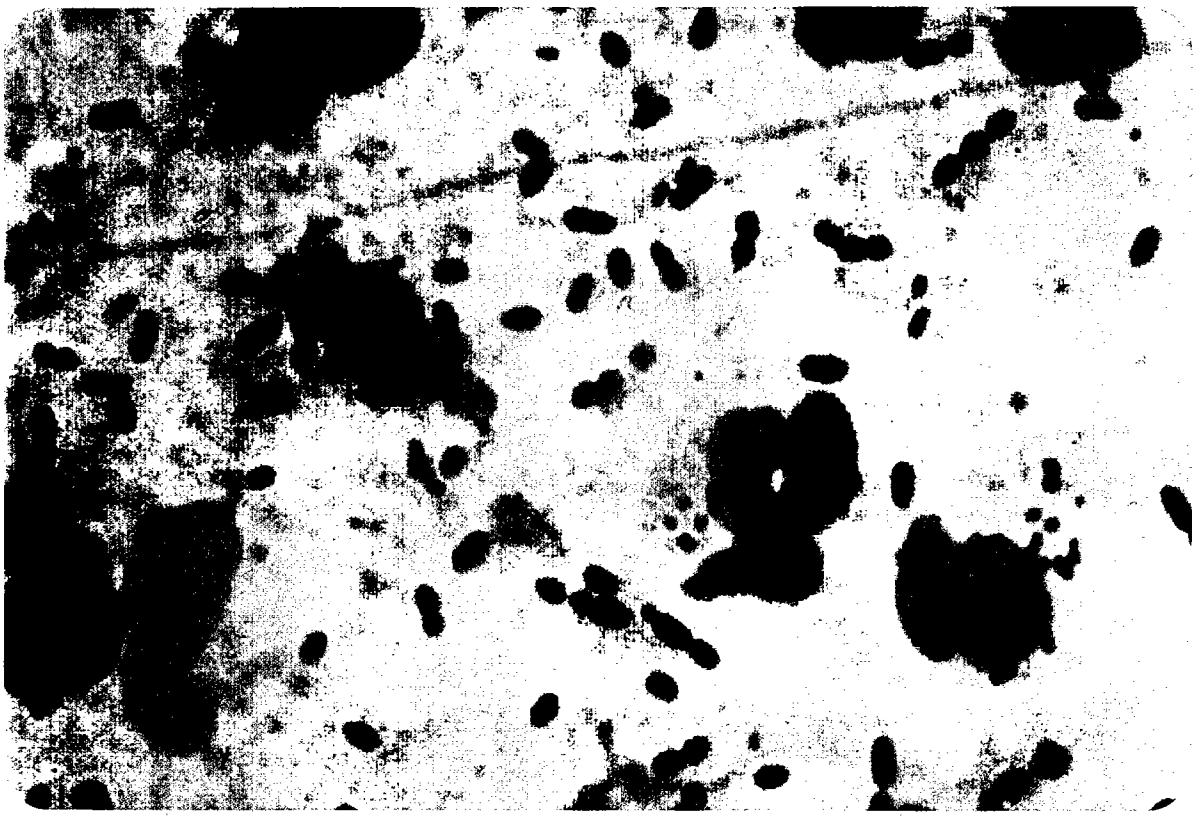
ceftriaxone sodium

Usual adult daily dosage: 1 to 2 gm once a day

Please see complete product information in this pocket.

Roche

Penicillin-resistant pneumococci:



An evolving challenge in antibiotic therapy

Penicillin-resistant pneumococci:

A global perspective

Worldwide incidence of penicillin-resistant pneumococci varies considerably—with regional "hot spots" reported[1,2]

An overview of these studies reveals the following trends:

- Among western European countries, Spain and France have been the focus of penicillin-resistant pneumococci[3]
  —The incidence of resistance in Spain was reported at 50%[4]
  —In France, resistance was reported at 25%[3]
- In eastern Europe, the incidence of penicillin-resistant pneumococci has been reported to be as high as 58% of strains from Hungary and 25% from Romania[1]
- African data show the highest incidence of resistance occurring in South Africa[1]
  —A pediatric study revealed that 45% of pneumococcal isolates from blood and CSF were penicillin resistant[5]
- Published reports from Israel and Saudi Arabia cite prevalence of penicillin-resistant pneumococci approximately 20% to 25%[4]

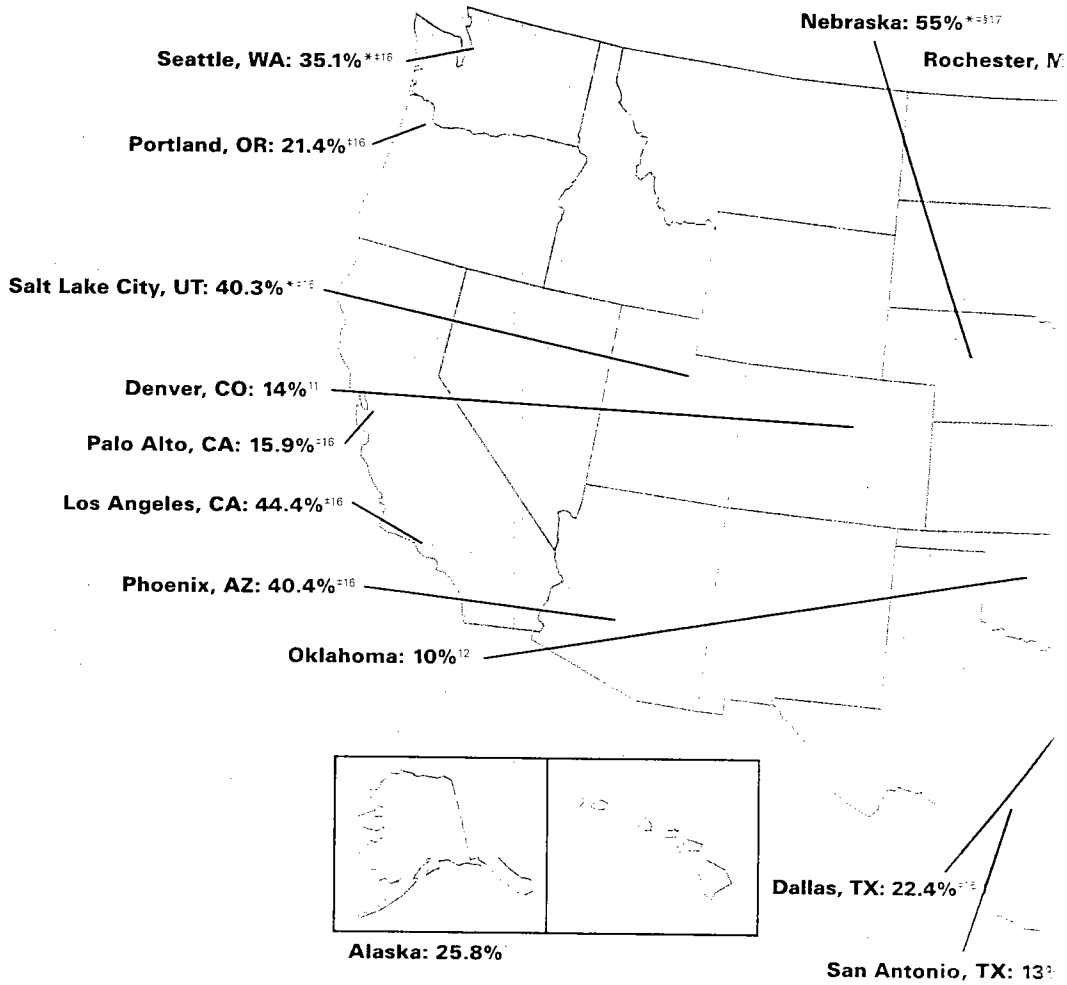
- In Asia, incidence of penicillin-resistant pneumococci has also increased dramatically
  - —In Japan, resistance rose from ≤1.0% during 1974-1982 to between 5.9% and 27.8% during 1984-1991[1]
  - —In Hong Kong, between 1993 and 1995, overall incidence was 30%[4]; in one hospital, resistance rose from 7% in 1993 to 56% in 1995[6]
  - —In 1996, Korea was the site of the highest reported rate of penicillin-resistant *S. pneumoniae* isolates worldwide with 70% of isolates having either intermediate or high-level resistance[4]; a study published in 1998 revealed a similar incidence of resistant isolates (71%) in a pediatric population in Kaohsiung,Taiwan[7]

Transmission of resistant strains may be highly localized or international[8]

- Prior exposure to antibiotics contributes to carriage of, and infection with, resistant strains[8]
  - — In addition, transmission of resistant strains is facilitated in institutional settings such as day care centers and hospitals[8]
- International travel provides another potential route for the spread of resistant strains[8]

In the United States, resistance rates among *Streptococcus pneumoniae* strains also exhibit regional variations[1]

- While penicillin resistance nationwide was reported to be 2% in 1979, it increased to 24% in 1995[4]
  - —By 1993, some parts of the country had reported rates of up to 25% to 29%[9,10]; by 1996, some sites reported rates up to 55%‡[16,17]



*Pediatric population.

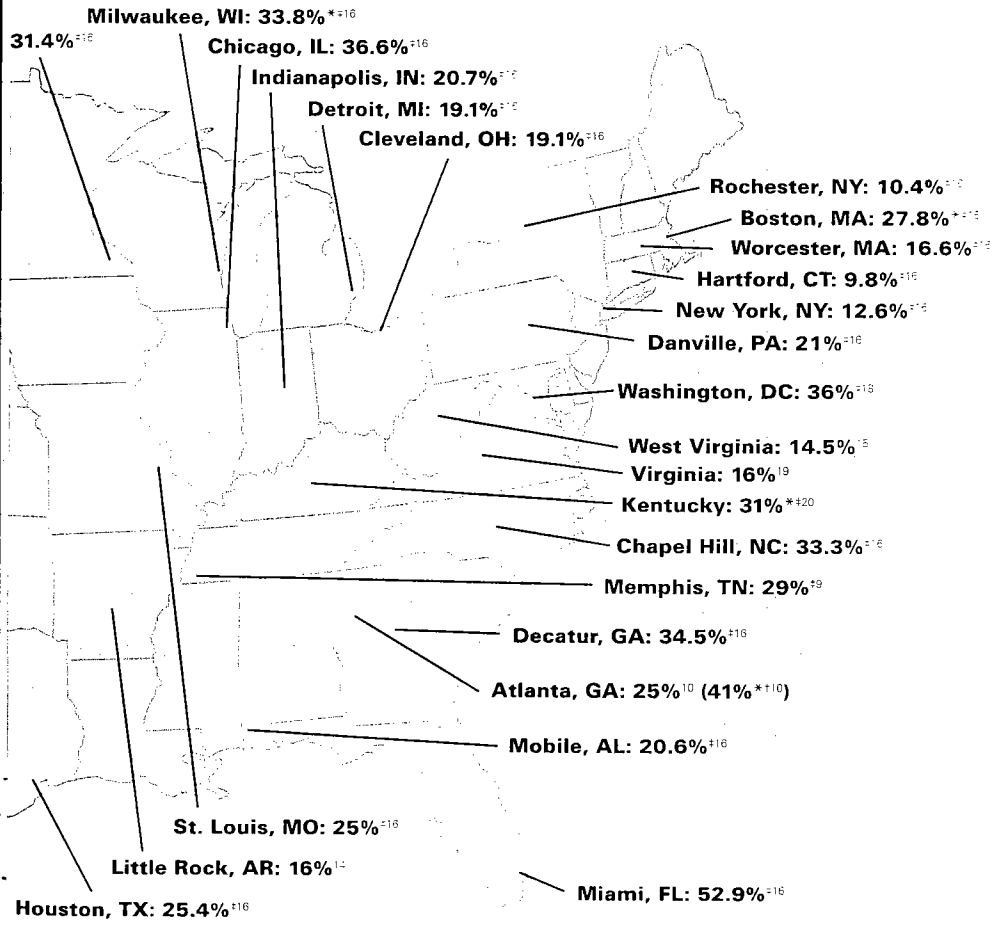
†In white children under the age of 6 years.

‡Intermediately penicillin-resistant and resistant strains.

§Omaha, Freemont, Lincoln, Hastings, NE.

A sampling of surveys of penicillin resistance among isolates of *S. pneumoniae* (multiple sources cited)

These studies were conducted at various times between 1980 and the present. Findings may represent incidence in a single institution, community, city or state.

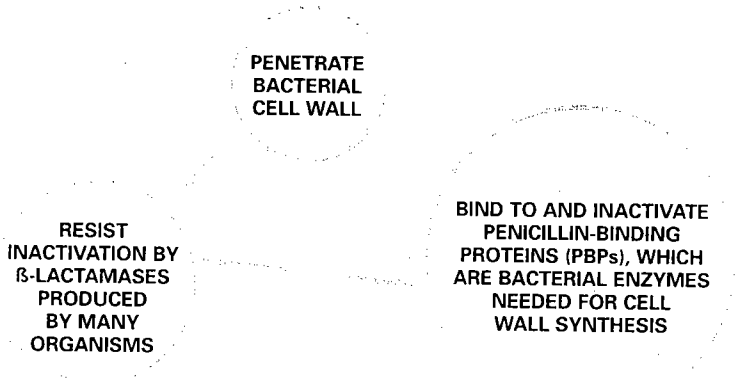


Health departments in 13 states and one city have made reporting of drug-resistant *S. pneumoniae* mandatory. In addition, the CDC has formed a multidisciplinary working group to survey, investigate, prevent and control drug-resistant *S. pneumoniae*.[2]

Roche

Requirements for ß-lactam antimicrobial activity[22]

Antibacterial activity is dependent on the drug's ability to:



- Depending on the organism, resistance mechanisms may interfere with drug activity at any of these steps[22]

Bacterial resistance to ß-lactam antibiotics

Two mechanisms are frequently responsible for development of resistance to ß-lactam drugs like penicillin[23]:

- ß-lactamase production
  - — Commonly associated with *Haemophilus influenzae, Escherichia coli, Klebsiella* spp. and staphylococci[23]
  - — The organism produces an enzyme that splits the amide bond of the ß-lactam ring in the antibiotic, thereby rendering it inactive[23]
- Alterations in bacterial enzymes called penicillin-binding proteins (PBPs)
  - — Commonly associated with pneumococci and methicillin-resistant staphylococci[23]
  - — A change in the microbe's PBPs results in decreased affinity of the drug for those PBP targets[23,24]

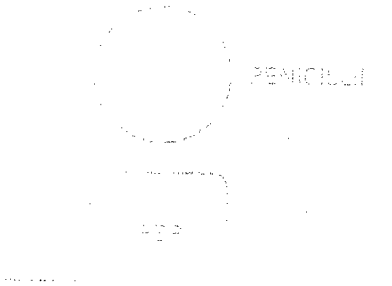
Penicillin-resistant *Streptococcus pneumoniae:*

A case of altered penicillin-binding proteins

- Penicillin, like all ß-lactams, exerts antimicrobial activity by binding to PBPs and disrupting cell wall synthesis[22,23]

Pneumococci can become resistant to penicillin as a result of:

- Changes in their PBP genes (mutations), which occur randomly and spontaneously during cell division[25,26]
- Acquisition of altered PBP genes from other streptococci[26]



Both mechanisms result in alterations in the shape or conformation of the microbe's PBPs. These alterations lead to less effective binding of the penicillin and decreased antibacterial activity of the drug.[23,24]

Penicillin-resistant *Streptococcus pneumoniae:*

The dynamics of susceptibility

- If an organism displays elevated penicillin MICs, its MICs for other ß-lactam agents will also increase[2]
  - — However, the magnitude of this increase varies, depending on the agent in question[2]

Activity of ß-lactam antibiotics against penicillin-resistant *S. pneumoniae*[2,27]

Antibiotic	MIC_{90} (µg/mL) for indicated group of strains		
	Penicillin-susceptible*	Intermediately penicillin-resistant†	Penicillin-resistant‡
Penicillin G	0.015-0.03	0.5-1	4-16
Ampicillin	0.015-0.03	0.5-1	8
Injectable cephalosporins			
1st Generation			
Cephalothin	0.12-0.25	1-8	8-32
2nd Generation			
Cefuroxime	0.06	2	16
3rd Generation			
Cefixime	0.5	16	32
Cefoperazone	0.12	1-2	2-8
Cefotaxime	0.01-0.03	0.25-0.5	1-4
Ceftazidime	0.25	32	64
Ceftizoxime	0.5	16	32
Ceftriaxone	0.064	0.5	2
Oral cephalosporin			
Cefaclor	0.5	32	64

*Pneumococci with penicillin MICs ≤0.06 µg/mL.[5]
†Pneumococci with penicillin MICs ranging from 0.12 to 1.0 µg/mL.[5]
‡Pneumococci with penicillin MICs >1.0 µg/mL.[5]

In vitro data do not necessarily correlate with clinical results, but do provide a useful guide. MIC_{90}s derived from published studies do not necessarily reflect local susceptibility data.

Making a therapeutic choice against penicillin-resistant pneumococci

- ß-lactam agents that maintain some affinity for the altered PBPs (penicillin-binding proteins) found in resistant pneumococci will continue to exert an antimicrobial effect
- Since pneumococcal resistance is mediated by altered PBPs rather than ß-lactamase production, agents that combine a ß-lactamase inhibitor with a ß-lactam agent (eg, Timentin®, Unasyn®, Zosyn®) do not offer a therapeutic advantage against penicillin-resistant *S. pneumoniae*[26]

Timentin® (ticarcillin disodium/clavulanate potassium) is a registered trademark of SmithKline Beecham Pharmaceuticals.
Unasyn® (ampicillin sodium/sulbactam sodium) is a registered trademark of Pfizer Inc.
Zosyn® (piperacillin sodium/tazobactam sodium) is a registered trademark of Lederle Laboratories/Wyeth-Ayerst Laboratories.

Roche

Once-a-day

Rocephin® IV·IM

ceftriaxone sodium

A viable choice for treatment of infections due to penicillin-resistant *Streptococcus pneumoniae*

ROCEPHIN delivers a high degree of antimicrobial activity with low MIC_{90}s

Pneumococci	ROCEPHIN MIC_{90} (μg/mL)[27]
Susceptible* to penicillin	0.064
Intermediate resistance† to penicillin	0.5
Resistant‡ to penicillin	2

*Pneumococci with penicillin MICs ≤0.06 μg/mL.[27]
†Pneumococci with penicillin MICs ranging from 0.12 to 1.0 μg/mL.[27]
‡Pneumococci with penicillin MICs >1.0 μg/mL.[27]

In vitro data do not necessarily correlate with clinical results, but do provide a useful guide.

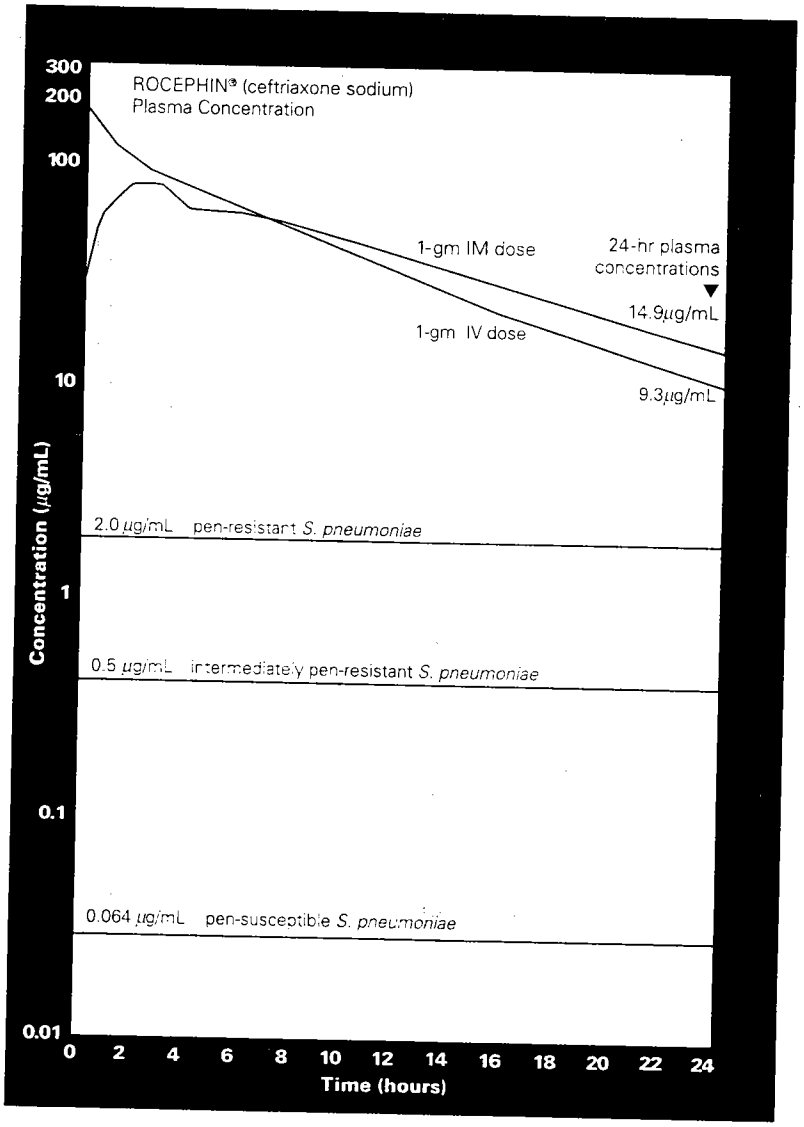
NCCLS§ guidelines define breakpoints (MIC_{90}s) for pneumococcal susceptibility to ceftriaxone as follows[28]:

- Susceptible: ≤0.5 μg/mL
- Intermediately resistant: 1 μg/mL
- Resistant: ≥2 μg/mL

§National Committee for Clinical Laboratory Standards.

Maintains activity for a full 24 hours

IV[29] or IM[30] plasma levels remain above MIC_{90}s[27] for penicillin-resistant pneumococci 24 hours after a single 1-gm dose



Concentration is regarded as important to therapeutic efficacy, but specific levels may not necessarily correlate with therapeutic results.

In vitro data do not necessarily correlate with clinical results, but do provide a useful guide.

Usual adult daily dosage: 1 to 2 gm once a day
Please see inside back cover pocket for complete product information.

Roche

Once-a-day

Rocephin® IV·IM

ceftriaxone sodium

ROCEPHIN offers key benefits to treat important infections caused by pneumococci

In the United States, *all* strains of *Streptococcus pneumoniae* are responsible for[21]:

—An estimated 3000 cases of meningitis per year

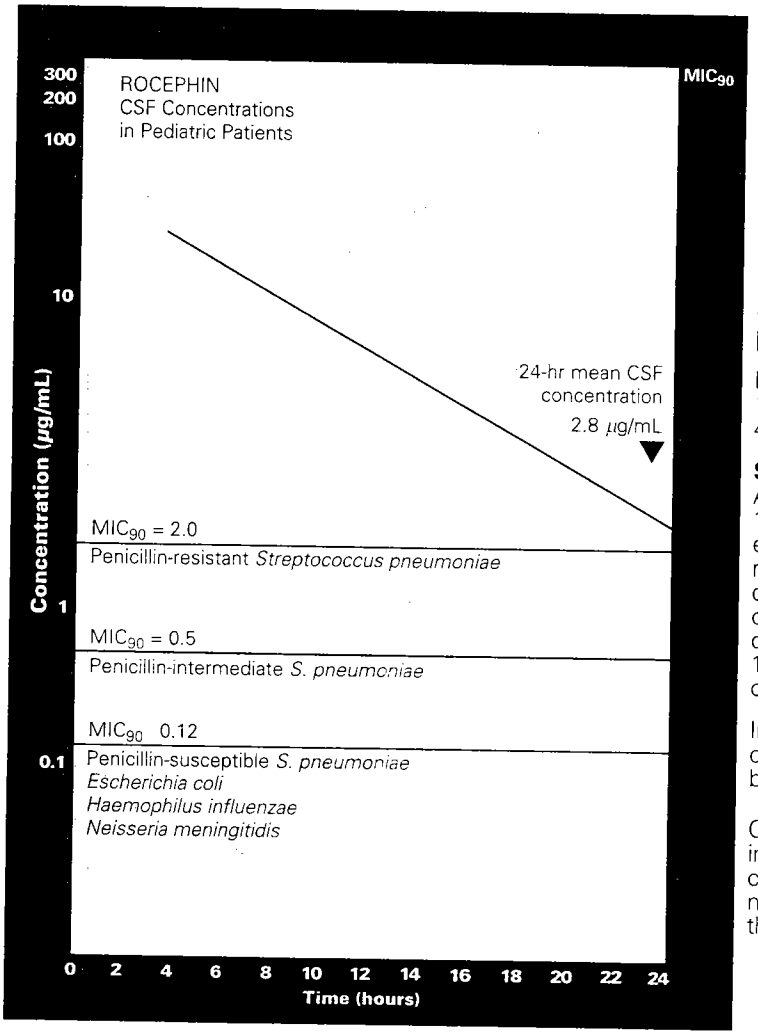
—An estimated 500,000 cases of pneumonia per year

—An estimated 50,000 cases of bacteremia per year

In meningitis... Excellent CSF penetration

- With one dose daily, penetration into the cerebrospinal fluid (CSF) results in concentrations for 24 hours exceeding the MIC_{90}s of commonly isolated meningitis pathogens,[27,31,32] as well as penicillin-resistant pneumococci[27]
- For penicillin-nonsusceptible pneumococci, the American Academy of Pediatrics[33] recommends ROCEPHIN as a drug of choice (combined with vancomycin pending culture results)

CSF concentrations of ROCEPHIN® (ceftriaxone sodium) in neonates (n=5) and infants (n=4) with bacterial meningitis who received from 50 mg/kg to 144 mg/kg of ROCEPHIN IV[27,31,32,34]



Dosing in pediatric meningitis

Initial therapeutic dose: 100 mg/kg (not to exceed 4 grams).

Subsequent therapy: A total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

In vitro data do not necessarily correlate with clinical results, but do provide a useful guide.

Concentration is regarded as important to therapeutic efficacy, but specific levels may not necessarily correlate with therapeutic results.

Usual adult daily dosage: 1 to 2 gm once a day

Please see inside back cover pocket for complete product information.

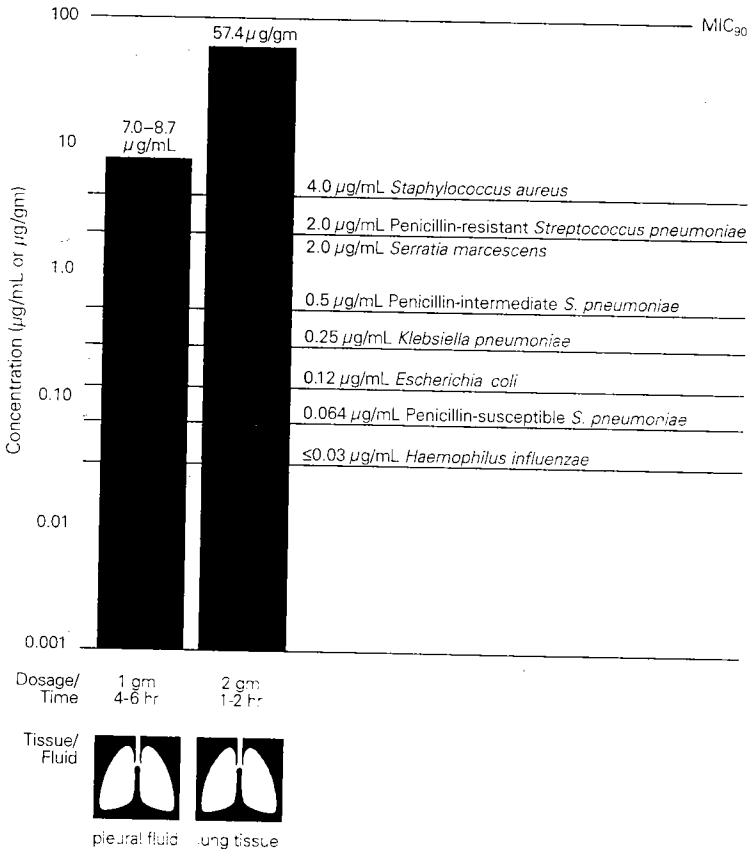
Roche

INFORMATION

Once-a-day Rocephin® IV·IM ceftriaxone sodium

In pneumonia... Gets to the site of infection

Concentrations of ROCEPHIN in lungs[35,36] and pleura surpass MICs for commonly isolated organisms and penicillin-resistant *Streptococcus pneumoniae*[27,31]



- Half-life of ceftriaxone in pleural fluid is two to four times longer than that in serum[35]

In vitro data do not necessarily correlate with clinical results, but do provide a useful guide.

Concentration is regarded as important for therapeutic efficacy, but specific levels may not necessarily correlate with therapeutic results.

Recommended in the treatment of pneumonia in these authoritative sources

American Thoracic Society: ROCEPHIN recommended as monotherapy for treatment of community-acquired pneumonia[§37]	✓
Principles and Practice of Infectious Diseases: ROCEPHIN—drug class (third-generation cephalosporins) recommended for treatment of community-acquired pneumonia[38]	✓
The Sanford Guide to Antimicrobial Therapy: ROCEPHIN—effective against penicillin-resistant *S. pneumoniae* in nonmeningeal infections[39]	✓
Infectious Diseases Society of America CAP guidelines: ROCEPHIN—a preferred agent for intermediately penicillin-resistant *S. pneumoniae* in CAP[40]	✓
The Medical Letter: ROCEPHIN—a "drug of first choice" for penicillin-intermediate *S. pneumoniae*, and in combination therapy for penicillin-resistant *S. pneumoniae*[41]	✓

§In hospitalized patients.

In bacterial septicemia...

ROCEPHIN plasma levels exceed MIC_{90}s for many commonly isolated organisms, as well as penicillin-resistant *S. pneumoniae* for 24 hours after a 1-gm IV or IM dose.[27,29,30]

A well-established safety profile

Adverse clinical effects in adults occur at levels similar to those of other cephalosporins: diarrhea (2.7%), rash (1.7%) and local reactions (≤1%). ROCEPHIN is contraindicated in patients with a known allergy to cephalosporins and should be used cautiously in penicillin-sensitive patients.

Usual adult daily dosage: 1 to 2 gm once a day
Please see inside this pocket for complete product information.

Roche

PRODUCT INFORMATION

Once-a-day Rocephin® IV·IM ceftriaxone sodium

A therapeutic choice in infections due to penicillin-resistant *Streptococcus pneumoniae*

- Exhibits a high degree of antimicrobial activity with low MIC_{90}s[2,27]
- Delivers drug to hard-to-reach infection sites
- Effective therapy in the infections commonly associated with *S. pneumoniae*[9]
  - —Pneumonia
  - —Acute meningitis
  - —Sepsis

References: **1.** Appelbaum PC. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clin Infect Dis.* 1992;15:77-83. **2.** Jacobs MR. Treatment and diagnosis of infections caused by drug-resistant *Streptococcus pneumoniae*. *Clin Infect Dis.* 1992;15:119-127. **3.** Pradier C, et al. Pneumococcal resistance patterns in Europe. *Eur J Clin Microbiol Infect Dis.* 1997;16:644-647. **4.** Appelbaum PC. Epidemiology and in vitro susceptibility of drug-resistant *Streptococcus pneumoniae*. *Pediatr Infect Dis J.* 1996;15(10):932-939. **5.** Leggiadro RJ. Penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*: an emerging microbial threat. *Pediatrics.* 1994;93:500-503. Commentaries. **6.** Lyon DJ, et al. Rapid emergence of penicillin-resistant pneumococci in Hong Kong. *Scand J Infect Dis.* 1996;28:375-376. **7.** Chiou C-CC,et al. Extremely high prevalence of nasopharyngeal carriage of penicillin-resistant *Streptococcus pneumoniae* among children in Kaohsiung, Taiwan. *J Clin Microbiol.* 1996;36(7):1933-1937. **8.** Klugman KP. Pneumococcal resistance to antibiotics. *Clin Microbiol Rev.* 1990;3:171-196. **9.** Centers for Disease Control. Drug-resistant *Streptococcus pneumoniae*—Kentucky and Tennessee, 1993. *MMWR.* 1994;43:23-25,31. **10.** Hofmann J, et al. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. *N Engl J Med.* 1995;333:481-486. **11.** Kronenberger CB, et al. Invasive penicillin-resistant pneumococcal infections: a prevalence and historical cohort study. *Emerging Infectious Diseases.* 1996;2:121-124. **12.** Haglund LA, et al. Invasive pneumococcal disease in central Oklahoma: emergence of high-level penicillin resistance and multiple antibiotic resistance. *J Infect Dis.* 1996;169:1532-1536. **13.** Moreno F, et al. The clinical and molecular epidemiology of bacteremias at a university hospital caused by pneumococci not susceptible to penicillin. *J Infect Dis.* 1995;172:427-432. **14.** Thompson JW, et al. Antibiotic-resistant pneumococcal disease at Arkansas Children's Hospital, 1990 to 1993. *Pediatr Infect Dis J.* 1994;13:408-409. **15.** Stanek RJ, Mufson MA. Emergence of penicillin-resistant invasive pneumococci in a single American community. *Am J Med Sci.* 1995;310:150-155. **16.** Doern GV, et al. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994-95: results of a 30-center national surveillance study. *Antimicrob Agents Chemother.* 1996;40:1208-1213. **17.** Boken DJ, et al. Colonization with penicillin nonsusceptible *Streptococcus pneumoniae* in urban and rural child-care centers. *Pediatr Infect Dis J.* 1996;15:667-672. **18.** Fairchok MP, et al. Carriage of penicillin-resistant pneumococci in a military population in Washington, DC: risk factors and correlation with clinical isolates. *Clin Infect Dis.* 1996;22:966-972. **19.** Evans TG, et al. Pneumococcal resistance in southwest Virginia. *Antimicrob Agents Chemother.* 1995;39(4):985-986. **20.** Block SL, et al. Penicillin-resistant *Streptococcus pneumoniae* in acute otitis media: risk factors, susceptibility patterns and antimicrobial management. *Pediatr Infect Dis J.* 1995;14(9):751-759. **21.** Centers for Disease Control. Defining the public health impact of drug-resistant *Streptococcus pneumoniae*: report of a working group. *MMWR.* 1996;45(suppl):1-20. **22.** Eliopoulos GM. Mechanisms of bacterial resistance to antimicrobial drugs. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases.* Philadelphia: W.B Saunders Co. 1992:280-289. **23.** Mayer KH, et al. Mechanisms of antibiotic resistance. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases.* 4th ed. New York: Churchill Livingstone. 1995:212-225. **24.** Malouin F, Bryan LE. Modification of penicillin-binding proteins as mechanisms of ß-lactam resistance. *Antimicrob Agents Chemother.* 1986;30:1-5. **25.** McGowan JE Jr. Multiple drug resistance: a major problem for contemporary medicine. *Challenges in Infectious Diseases.* 1994;1(4):1-6. **26.** Chesney PJ. The escalating problem of anti-microbial resistance in *Streptococcus pneumoniae*. *AJDC.* 1992;146:912-916. Editorial. **27.** Thornsberry C, et al. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* in the United States in 1996-1997 respiratory season. *Diagn Microbiol Infect Dis.* 1997;29:249-257. **28.** National Committee for Clinical Laboratory Standards 1997. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically—fourth edition; approved standard. NCCLS document M7-A4. **29.** Patel IH, et al. Pharmacokinetics of ceftriaxone in humans. *Antimicrob Agents Chemother.* 1981;20:634-641. **30.** Scully BE, et al. Pharmacokinetics of ceftriaxone after intravenous infusion and intramuscular injection. *Am J Med.* 1984;77:112-115. **31.** Fass RJ. In vitro activity of Bay 12-8039, a new 8-methoxyquinolone. *Antimicrob Agents Chemother.* 1997;41(8):1815-1824. **32.** Fuchs PC, et al. Survey of antimicrobial activity of four commonly used third generation cephalosporins tested against recent bacterial isolates from ten American medical centers, and assessment of disk diffusion test performance. *Diagn Microbiol Infect Dis.* 1996;24:213-219. **33.** American Academy of Pediatrics. Therapy for children with invasive pneumococcal infections. *Pediatrics.* 1997;99(2):289-299. **34.** Martin E, et al. Pharmacokinetics of ceftriaxone in neonates and infants with meningitis. *J Pediatr.* 1984;105(3):475-481. **35.** Benon G, et al. Penetration of ceftriaxone into human pleural fluid. *Antimicrob Agents Chemother.* 1986;29:906-908. **36.** Just H-M, et al. Concentrations of ceftriaxone in serum and lung tissue. *Chemotherapy.* 1984;30:81-83. **37.** Niederman MS, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis.* 1993;148:1418-1426. **38.** Donowitz GR, Mandell GL. Acute pneumonia. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases.* 4th ed. New York: Churchill Livingstone. 1995:619-637. **39.** *The Sanford Guide to Antimicrobial Therapy.* 29th ed. Hyde Park,VT: Antimicrobial Therapy Inc. 1999:29,50. Gilbert DN, et al, eds. **40.** Bartlett JG, et al. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis.* 1998;26:811-838. **41.** *Med Lett Drugs Ther.* The choice of antibacterial drugs. 1998;40:1023:33-42.

Usual adult daily dosage: 1 to 2 gm once a day
Please see inside back cover pocket for complete product information.

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
www.rocheusa.com

Printed in USA

Plandex 73858
18-039-073-087-129