DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Lifecycle Ventures
c/o
Mark J. Scheineson, Esq.
Reed Smith, L.L.P
1301 K Street, N.W.
Washington, DC 20005

RE: NDA # 50-605
Ceftin Tablets(cefuroxime axetil tablets)
MACMIS ID # 9811

Dear Mr. Scheineson:

As a part of the Division of Drug Marketing, Advertising, and Communications' (DDMAC) routine surveillance, we have reviewed promotional materials for Ceftin (cefuroxime axetil) from Lifecycle Venture's submission of FDA form 2253 dated January 01, 2001. The submission contained promotional sales aids for Ceftin (e.g. CEF-0006-A, CEF-0006-P, CEF-0008-P, and CEF-0008-A). We find the sales aids in violation of the Federal Food, Drug, and Cosmetic Act and its applicable regulations. Specifically, we object to the following:

Unapproved Use

- Ceftin is not approved to treat drug-resistant infections, such as resistant *streptococcus pneumonia* (PRSP) and resistant *haemophilus influenzae*. In your sales aids, you promote Ceftin for resistant bacteria with the taglines, "First-line in an era of bacterial resistance," and "In an era of drug-resistant *streptococcus pneumoniae*." These taglines are misleading because they are placed directly in conjunction with treatment and susceptibility information for Acute Otitis Media (AOM), sinusitis, and bronchitis and imply that Ceftin is approved for all listed pathogens, including resistant organisms. The efficacy of Ceftin for the treatment of PRSP and resistant *haemophilus influenzae* has not been demonstrated by substantial evidence. Therefore, we find the sales aids to be violative.

Misleading Economic Claims

- In your sales aids you present "cost-comparisons" between Ceftin and numerous antibiotic regimens for sinusitis, bronchitis, and AOM based on price differences taken from the 2000 Red Book Update (October 2000). You make claims such as, "cost-effective," "Ceftin savings," "manage the expense of treatment," and "cost of therapy." These claims are misleading because they are not supported by adequate evidence. These claims imply that all costs associated with therapy have been evaluated, not simply the acquisition price of the drug. In addition, your graph

entitled, "Ceftin savings: A better way to manage the expense of treatment in sinusitis," is misleading because it implies economic superiority based on the assumption that the outcomes of the different therapies are the same.

Requested Action

You should immediately cease distribution of the sales aids and other similar promotional materials for Ceftin that contain the same or similar claims or presentations. You should submit a written response on or before March 30, 2001 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) 594-6771, 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 # 9811 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

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

/s/

James Rogers
3/16/01 02:42:40 PM

IN AN ERA OF BACTERIAL RESISTANCE

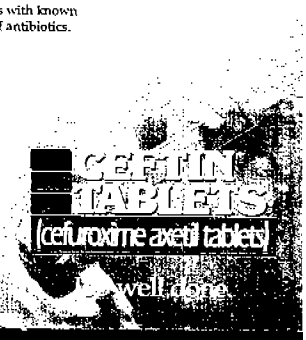
CEFTIN®: First-line in sinusitis.

- Bacterial resistance is on the rise in the US[1]
- Credible, third-party endorsements recommend the use of CEFTIN® as first-line therapy[1]
- CEFTIN® effectively covers *Streptococcus pneumoniae* and *Haemophilus influenzae*—the key pathogens responsible for sinusitis[2,3]
- Low incidence of adverse events

In US clinical trials with CEFTIN® Tablets, the most commonly reported adverse events were diarrhea/loose stools (3.7%) and nausea/vomiting (3%).

CEFTIN® Tablets is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

THE RIGHT TOOL FOR THE JOB MAY NOT BE THE NEWEST.



Please see enclosed full Prescribing Information.

LIFECYCLE

IN AN ERA OF DRUG-RESISTANT *S PNEUMONIA*

CEFTIN®: Effective therapy in AOM.

- Recommended by the CDC in AOM after amoxicillin failure[1]*
- CEFTIN® effectively covers *S pneumoniae*—the primary pathogen in AOM[2]
- The only antibiotic recommended* for AOM at the standard dose by the CDC[1]
- Low incidence of adverse events

In US clinical trials with CEFTIN® Oral Suspension, the most commonly reported adverse events were diarrhea/loose stools (8.6%), dislike of taste (5%), diaper rash (3.4%), and nausea/vomiting (2.6%).

CEFTIN® is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

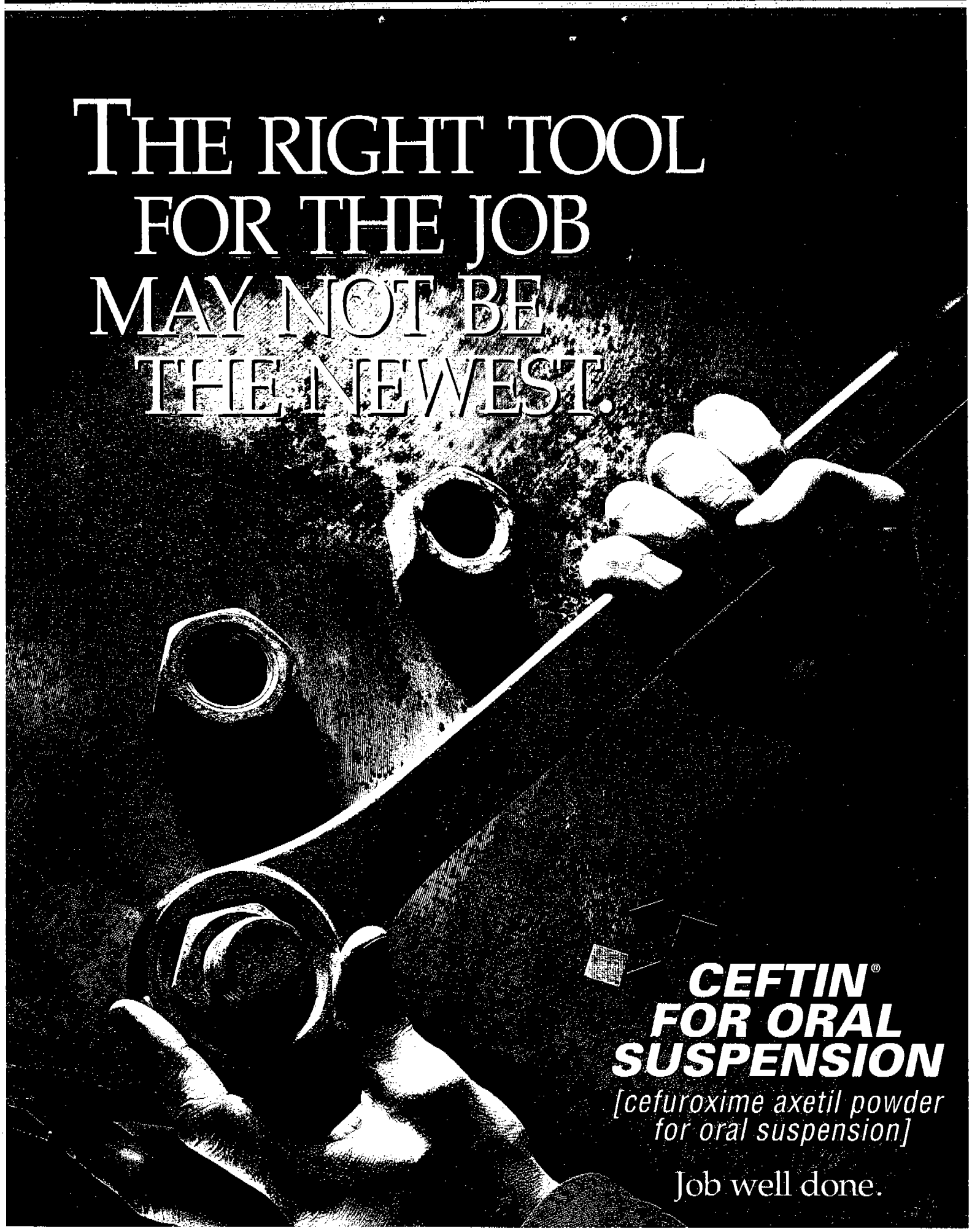
*After high-dose (80-90 mg/kg/d) amoxicillin failure, defined as lack of clinical improvement in symptoms such as ear pain, fever, and tympanic membrane findings of redness, bulging, or otorrhea.

Please see enclosed full Prescribing Information.

LIFECYCLE

IN AN ERA OF DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

THE RIGHT TOOL FOR THE JOB MAY NOT BE THE NEWEST.

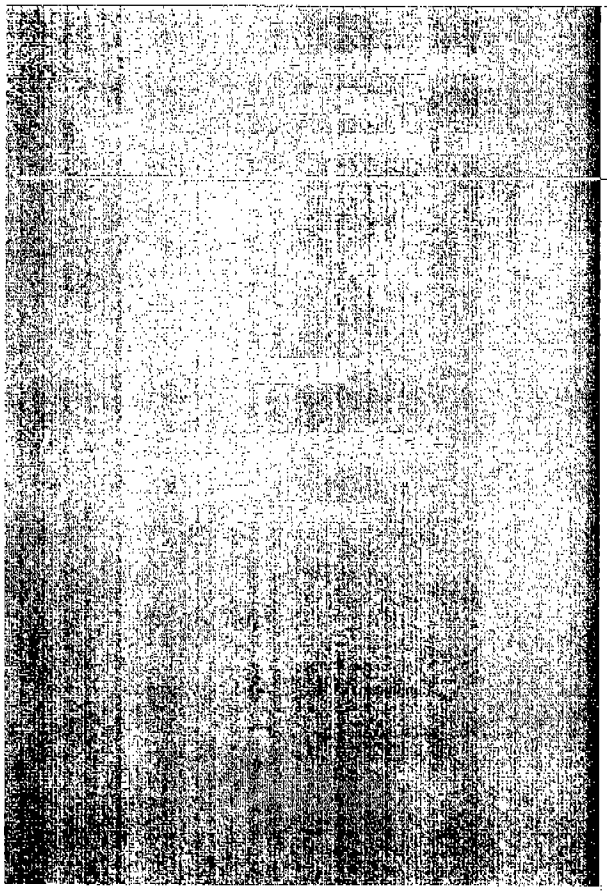


CEFTIN®
FOR ORAL SUSPENSION
[cefuroxime axetil powder for oral suspension]

Job well done.

THE EXPERTS AGREE. There's a right time and place for every antibiotic.

CEFTIN®: Recommended by the CDC for acute otitis media (AOM) after amoxicillin failure[1]†*



Antibiotics Not Recommended by the CDC After High-Dose (80-90 mg/kg/d) Amoxicillin Failure

cefaclor
ceftibuten
cefprozil
loracarbef
cefixime
cefpodoxime proxetil

azithromycin
clarithromycin
clindamycin
erythromycin

penicillin

trimethoprim/sulfamethoxazole

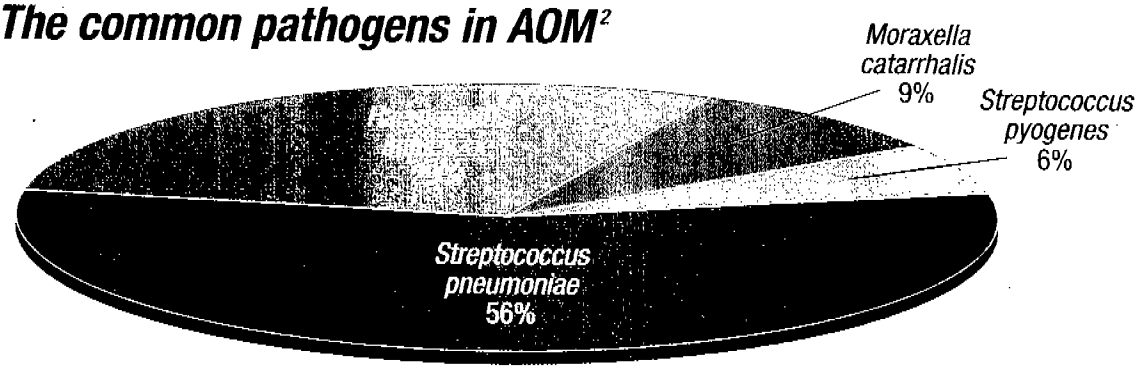
*Failure defined as lack of clinical improvement in symptoms such as ear pain, fever, and tympanic membrane findings of redness, bulging, or otorrhea.

†To meet CDC criteria after high-dose amoxicillin (80-90 mg/kg/d) failure, an agent must be effective against *S pneumoniae*, including most penicillin-resistant strains; and *Haemophilus influenzae* and *Moraxella catarrhalis*, including beta-lactamase–producing strains.

CEFTIN® Oral Suspension is indicated for the treatment of pediatric patients 3 months to 12 years of age with mild to moderate acute bacterial otitis media caused by susceptible strains of *S pneumoniae; H influenzae* and *M catarrhalis* (including beta-lactamase–producing strains); or *Streptococcus pyogenes*. CEFTIN® is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

CEFTIN®.
The right fit all around.

The common pathogens in AOM[2]

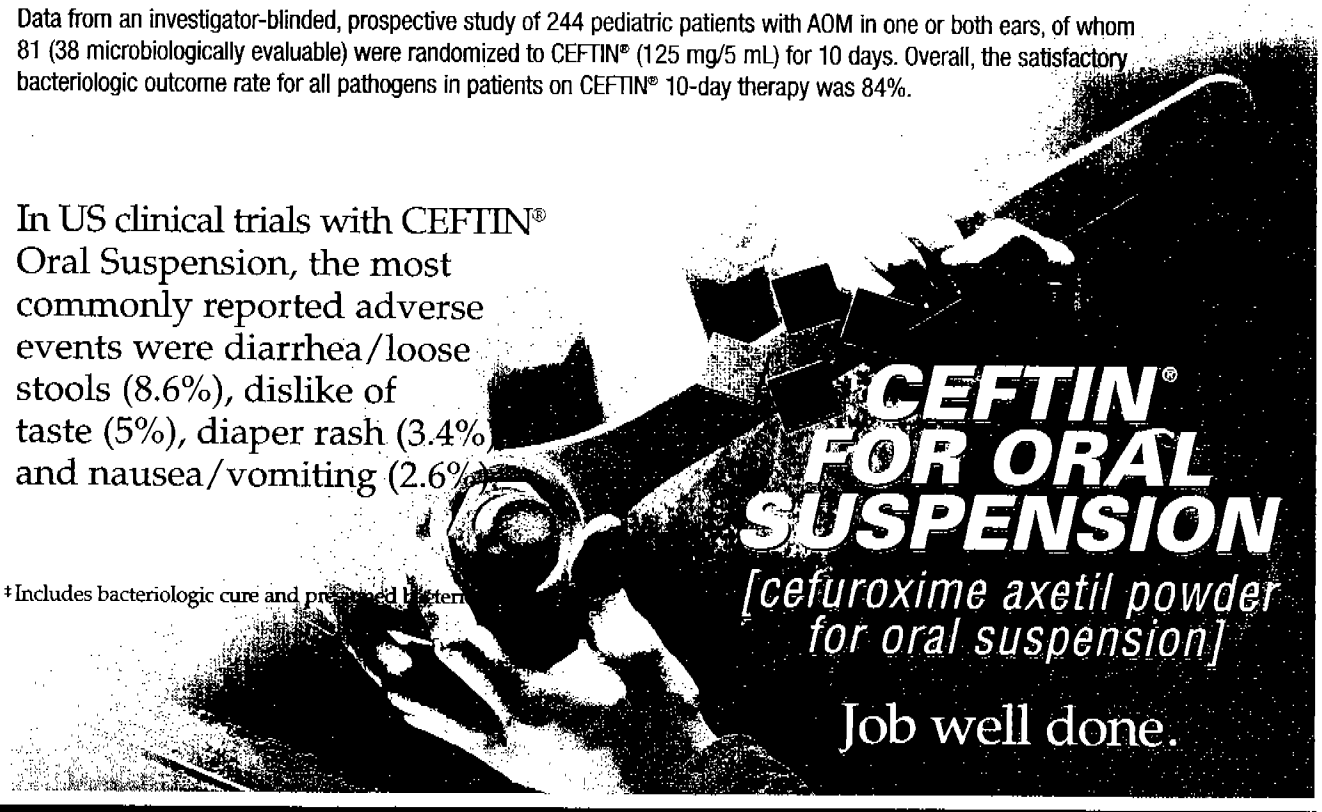


CEFTIN®: Effective coverage of S pneumoniae[3]

Data from an investigator-blinded, prospective study of 244 pediatric patients with AOM in one or both ears, of whom 81 (38 microbiologically evaluable) were randomized to CEFTIN® (125 mg/5 mL) for 10 days. Overall, the satisfactory bacteriologic outcome rate for all pathogens in patients on CEFTIN® 10-day therapy was 84%.

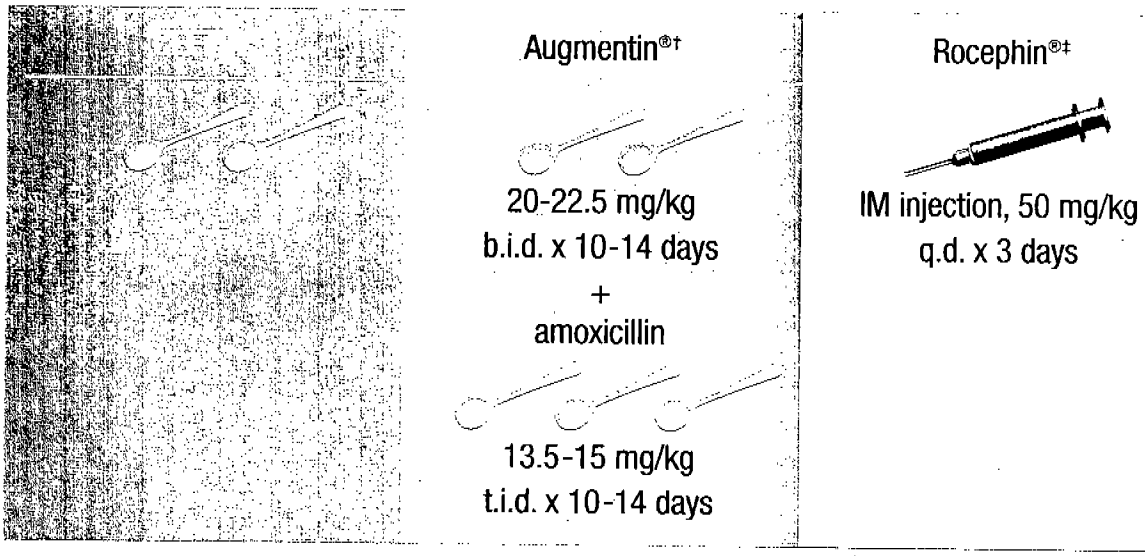
In US clinical trials with CEFTIN® Oral Suspension, the most commonly reported adverse events were diarrhea/loose stools (8.6%), dislike of taste (5%), diaper rash (3.4%) and nausea/vomiting (2.6%).

‡Includes bacteriologic cure and pr[illegible]d b[illegible]teri[illegible]



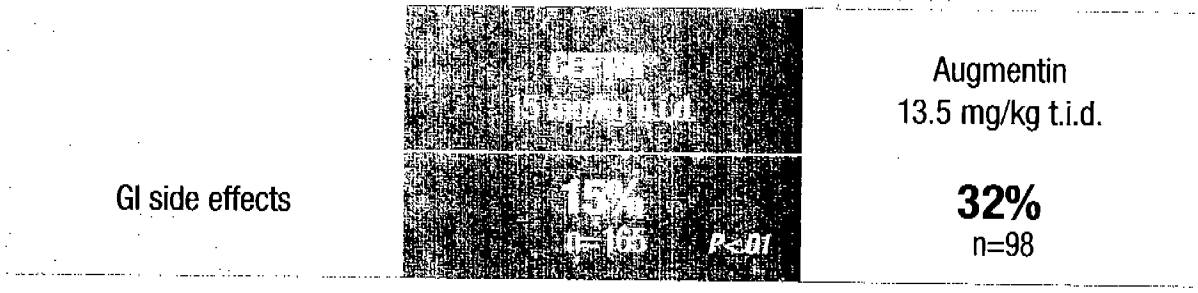
CEFTIN®. Measures up right where it should.

Only CEFTIN® is recommended at the standard dose by the CDC[1]*



- An increase in the dose of the amoxicillin component of Augmentin therapy (up to a total of 80-90 mg/kg/d) is recommended[1]
- Two additional daily Rocephin IM injections are recommended, for a total of 3 q.d. doses[1]

Significantly lower incidence of GI side effects vs Augmentin[4]



Data from an investigator-blinded study in which 263 pediatric patients (aged 3 months to 11 years) were treated for 10 days. Overall clinical cure/improvement rates were: CEFTIN® 77%, Augmentin 74%.

*After high-dose (80-90 mg/kg/d) amoxicillin failure, defined as lack of clinical improvement in symptoms such as ear pain, fever, and tympanic membrane findings of redness, bulging, or otorrhea.

†Amoxicillin/clavulanate.

‡Ceftriaxone.

A convenient and cost-effective way to manage the expense of treatment in AOM

Cost of 10 Days of Therapy for AOM§

$29.26

CEFTIN® Oral Suspension
50-mL bottle
1/2 tsp (250 mg/5 mL) b.i.d.

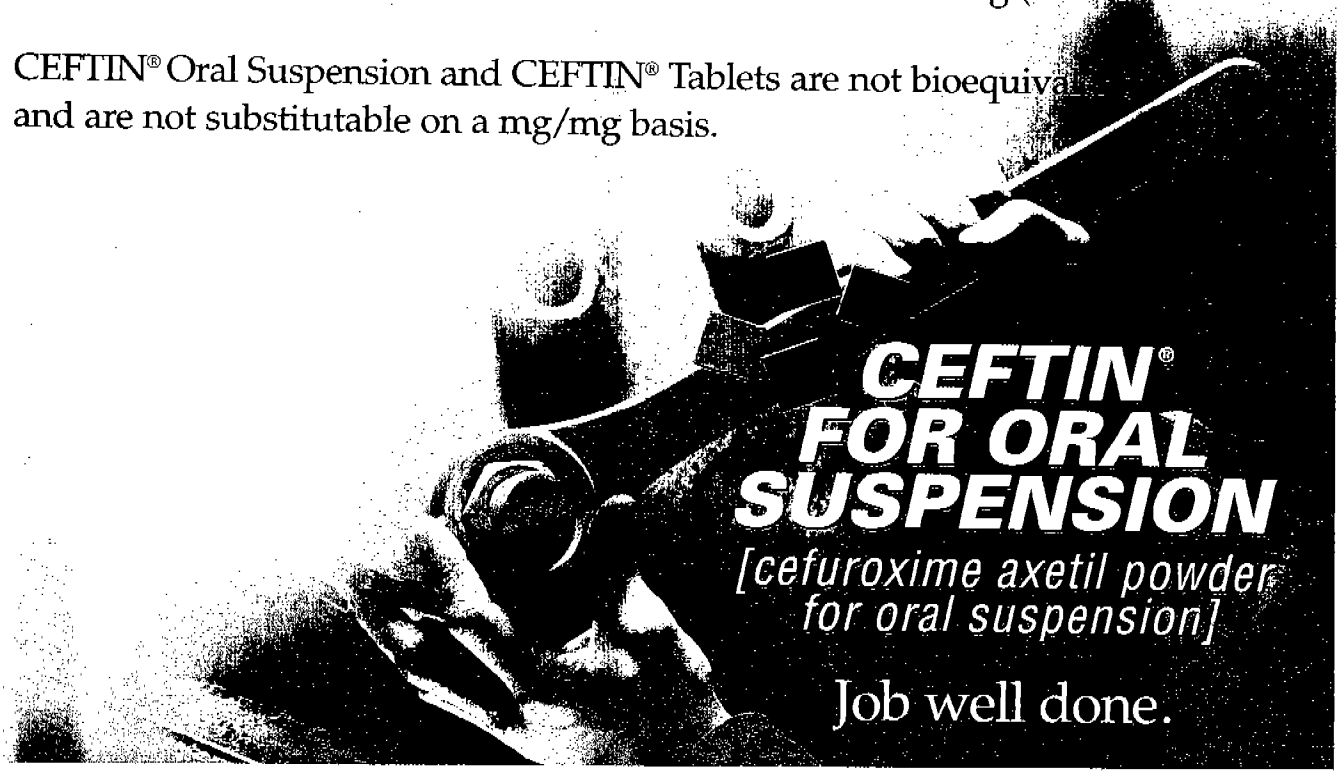
$37.10

Augmentin Suspension
50-mL bottle
1/2 tsp (400 mg/5mL) b.i.d.
+
amoxicillin suspension
75-mL bottle
1/2 tsp (250 mg/5 mL) t.i.d.

§Dose calculated for a 20-lb (9-kg) child. Average wholesale price for 10 days of therapy. Prices shown are taken from *2000 Red Book® Update* (October 2000), and may not represent actual prices paid by pharmacies or consumers. In the absence of comparative data, the comparable efficacy of these products has not been shown.

In US clinical trials with CEFTIN® Oral Suspension, the most commonly reported adverse events were diarrhea/loose stools (8.6%), dislike of taste (5%), diaper rash (3.4%), and nausea/vomiting (2.6%).

CEFTIN® Oral Suspension and CEFTIN® Tablets are not bioequiva[illegible] and are not substitutable on a mg/mg basis.



CEFTIN®: Effective therapy in AOM.

- Recommended by the CDC in AOM after amoxicillin failure*
- CEFTIN® 15 mg/kg b.i.d. x 10 days effectively covers *S pneumoniae* —the primary pathogen in AOM
- The only antibiotic recommended* for AOM at the standard dose by the CDC
- Significantly fewer GI side effects than Augmentin

In US clinical trials with CEFTIN® Oral Suspension, the most commonly reported adverse events were diarrhea/loose stools (8.6%), dislike of taste (5%), diaper rash (3.4%), and nausea/vomiting (2.6%).

THE RIGHT TOOL FOR THE JOB MAY NOT BE THE NEWEST.

*After high-dose (80-90 mg/kg/d) amoxicillin failure, defined as lack of clinical improvement in symptoms such as ear pain, fever, and tympanic membrane findings of redness, bulging, or otorrhea.

References:
1. Dowell SF, Butler JC, Giebink GS, et al. Acute otitis media: management and su... in an era of pneumococcal resistance—a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Pediatr Infect Dis J.* 1999;18:1-9. 2. Ja... MR. Increasing importance of antibiotic-resistant *Streptococcus pneumoniae* in acute otitis me... *Pediatr Infect Dis J.* 1996;15:940-943. 3. Gooch WM III; Blair E, Puopolo A, et al. Effe... of five days of therapy with cefuroxime axetil suspension for the treatment of ... media. *Pediatr Infect Dis J.* 1996;15:157-164. 4. McLinn SE, Moskal M, Gold... Comparison of cefuroxime axetil and amoxicillin-clavulanate suspension in ... of acute otitis media with effusion in children. *Antimicrob Agents Chemother.* 19...

FIRST-LINE IN AN ERA OF BACTERIAL RESISTANCE

THE RIGHT TOOL FOR THE JOB MAY NOT BE THE NEWEST.

CEFTIN®
TABLETS
(cefuroxime axetil tablets)

Job well done.

THE EXPERTS AGREE. There's a right time and place for every antibiotic.

CEFTIN®: Recommended first-line in sinusitis

by representatives of the CDC in consultation with other public health medical experts and the Sinus and Allergy Health Partnership[1]

Product	Mild Sinusitis	Mild or Moderate Sinusitis
amoxicillin	YES	YES
[illegible]	[illegible]	[illegible]
amoxicillin/clavulanate	YES	YES
cefpodoxime proxetil	YES	YES
azithromycin	NOT INDICATED FOR SINUSITIS	
clarithromycin	NO	NO

No macrolides or quinolones appear as first-line recommendations for mild to moderate sinusitis

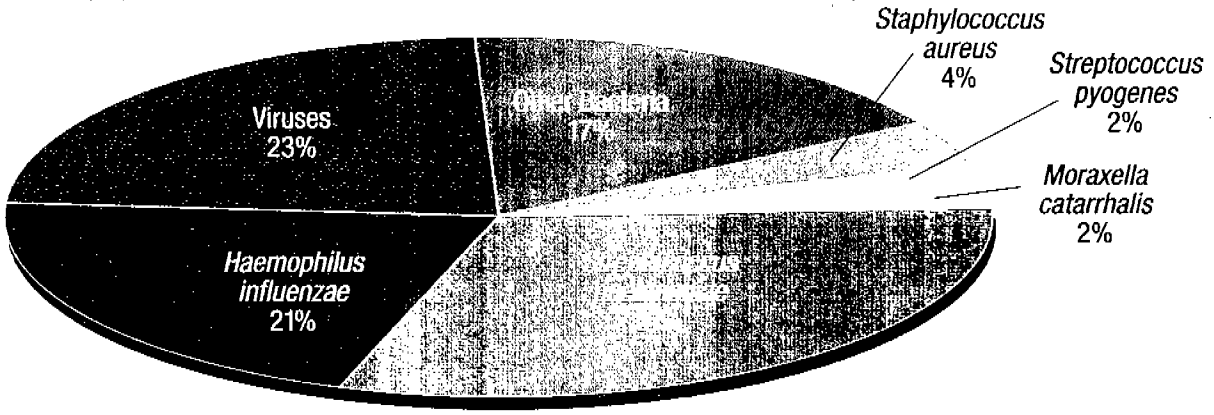
In US clinical trials with CEFTIN® Tablets, the most commonly reported adverse events were diarrhea/loose stools (3.7%) and nausea/vomiting (3%).

CEFTIN® Tablets is indicated for the treatment of mild to moderate infections of acute bacterial maxillary sinusitis caused by susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-beta-lactamase–producing strains only). CEFTIN® Tablets is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

CEFTIN®. The right fit all around.

The common pathogens in sinusitis[2]

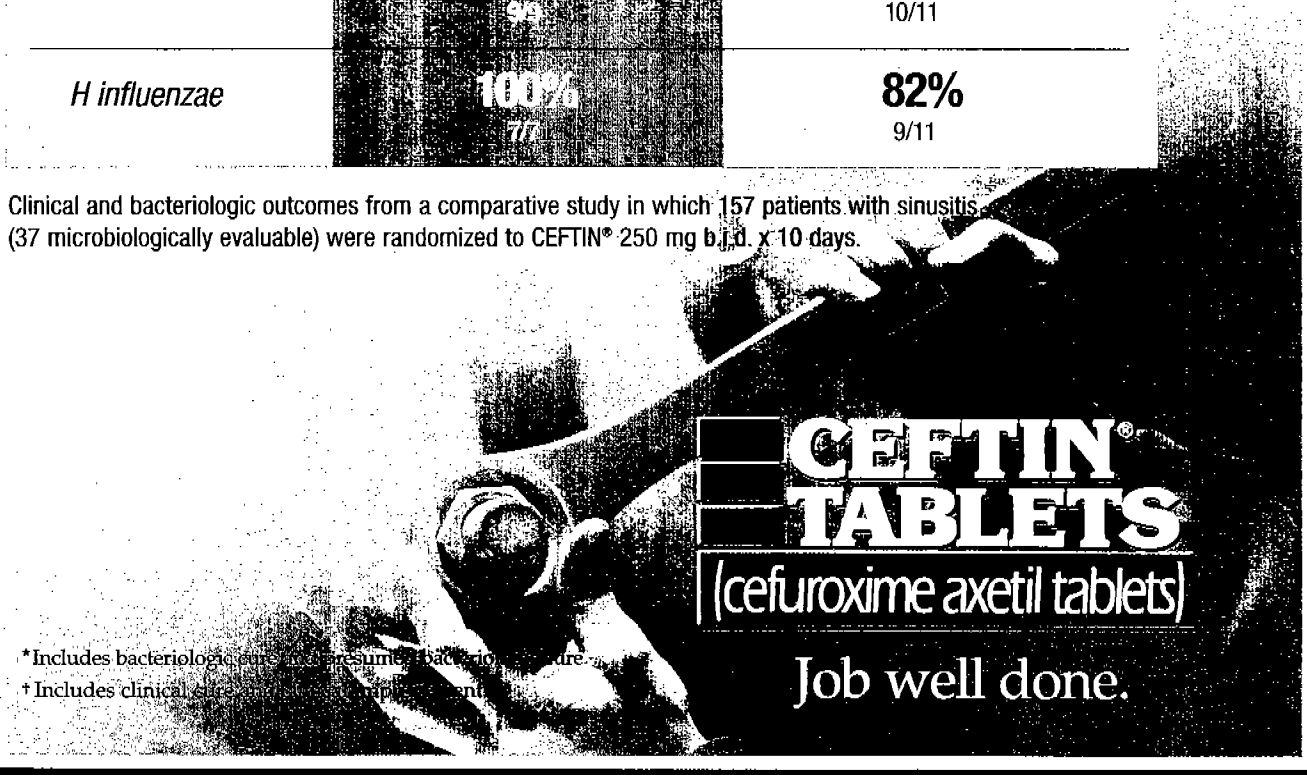
There is no evidence to suggest that atypical pathogens play a significant role in sinusitis[3]



CEFTIN®: Effective coverage of the key pathogens in sinusitis[4]

		Satisfactory Clinical Outcome†
S pneumoniae	100% 9/9	**91%** 10/11
H influenzae	100% 7/7	**82%** 9/11

Clinical and bacteriologic outcomes from a comparative study in which 157 patients with sinusitis (37 microbiologically evaluable) were randomized to CEFTIN® 250 mg b.i.d. x 10 days.



*Includes bacteriologic cure [illegible] presumed bacterial [illegible]

†Includes clinical cure [illegible]

CEFTIN®. Measures up right where it should.

*CEFTIN® efficacy: Proven comparable to Augmentin®4**

	Satisfactory Bacteriologic Outcome†		Satisfactory Clinical Outcome‡	
	CEFTIN®	Augmentin	CEFTIN®	Augmentin
S pneumoniae	94% 15/16	94% 15/16	91% 10/11	86% 18/21
H influenzae	67% 2/3	60% 3/5	82% 9/11	50% 3/6

Clinical and bacteriologic efficacy comparable to Augmentin, from a comparative study of 317 patients with sinusitis in which 157 patients were assigned to CEFTIN® (250 mg b.i.d. x 10 days) and 160 patients were assigned to Augmentin (500 mg t.i.d. x 10 days); 37 and 39 patients, respectively, were microbiologically evaluable.

Total microbiologic eradication rates were CEFTIN® 84%, Augmentin 87% (*P*=NS).

CEFTIN® safety: Significantly lower incidence of GI side effects4

	CEFTIN® (n=157)	Augmentin (n=160)
GI side effects	1.9% *P*=.001	11.9%

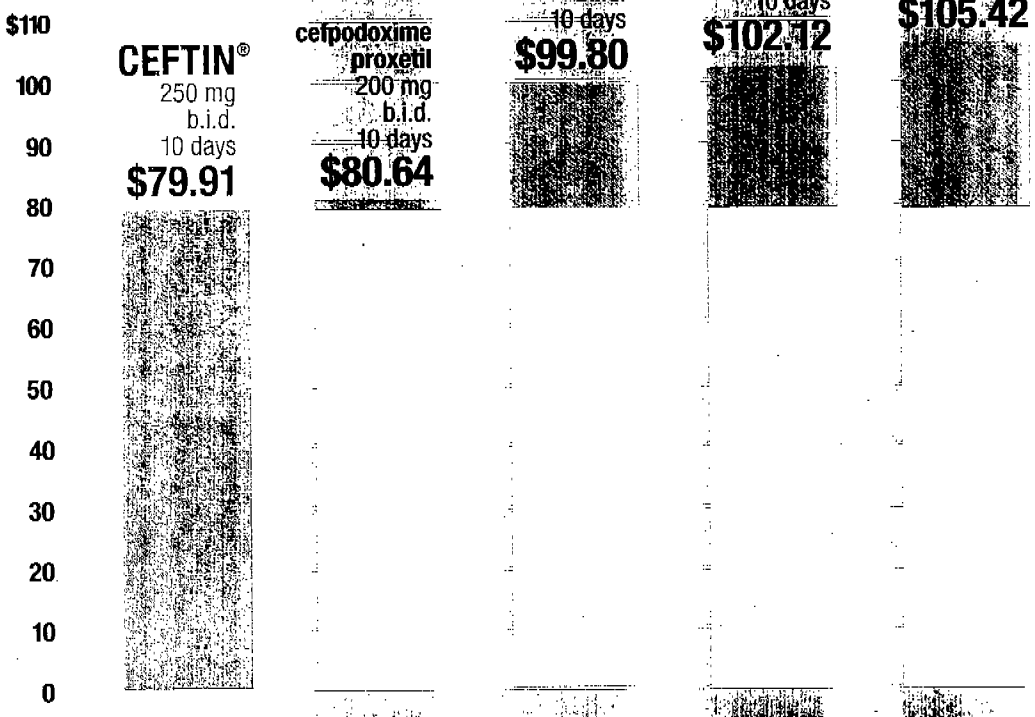
- Significantly lower incidence of drug-related adverse events in patients treated with CEFTIN® (*P*=.001) — particularly diarrhea (0.6% with CEFTIN® vs 8.1% with Augmentin, *P*=.001)[4]

*Amoxicillin/clavulanate.

†Includes bacteriologic cure and presumed bacteriologic cure.

‡Includes clinical cure and clinical improvement in microbiologically evaluable patients.

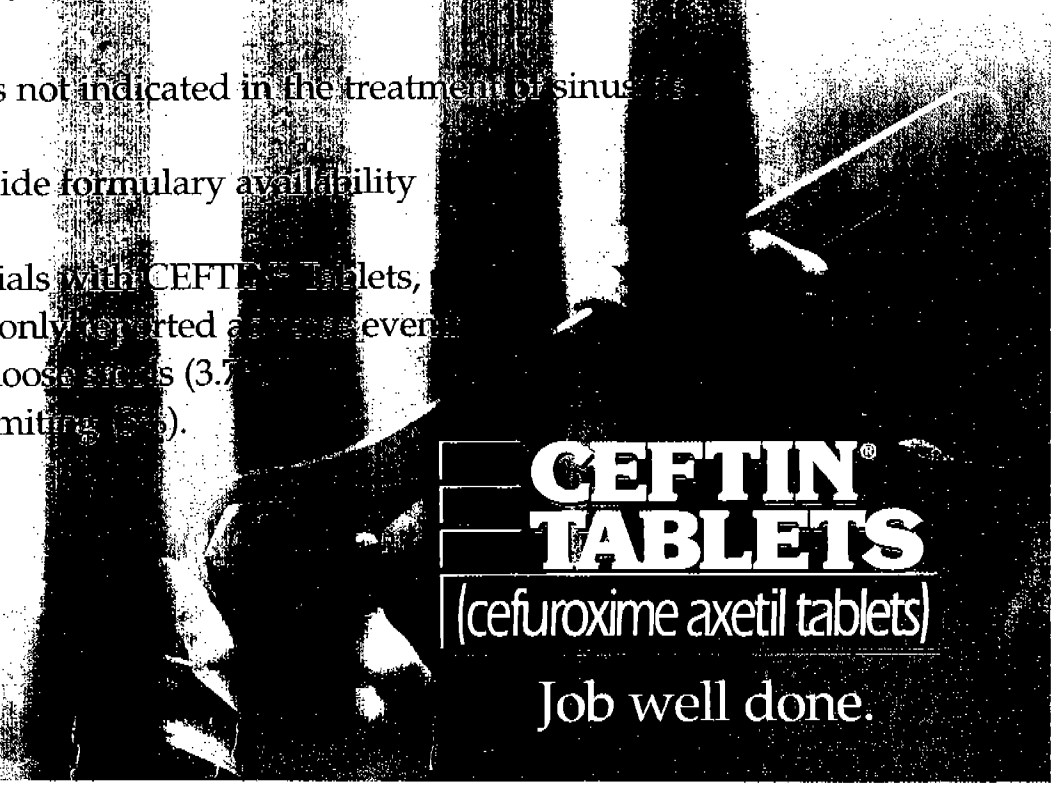
CEFTIN® savings: A better way to manage the expense of treatment§ in sinusitis



§ Average wholesale prices taken from *2000 Drug Topics® Red Book®* (October 2000) for full course of therapy for sinusitis taken from prescribing information for each product. Prices shown may not represent actual prices paid by pharmacies or consumers.

- Azithromycin is not indicated in the treatment of sinus
- CEFTIN® has wide formulary availability

In US clinical trials with CEFTIN® Tablets, the most commonly reported adverse events were diarrhea/loose stools (3.7%) and nausea/vomiting (3%).



IN AN ERA OF BACTERIAL RESISTANCE

CEFTIN®: First-line in sinusitis.

- Bacterial resistance is on the rise in the US[1]
- Credible, third-party endorsements recommend the use of CEFTIN® as first-line therapy
- CEFTIN® 250 mg b.i.d. x 10 days effectively covers *S pneumoniae* and *H influenzae*—the key pathogens responsible for sinusitis
- Clinical and bacteriologic efficacy comparable to Augmentin, with fewer side effects

In US clinical trials with CEFTIN® Tablets, the most commonly reported adverse events were diarrhea/loose stools (3.7%) and nausea/vomiting (3%).

THE RIGHT TOOL FOR THE JOB MAY NOT BE THE NEWEST.

References:

1. Sinus and Allergy Health Partnership. Antimicrobial Treatment Guidelines for Acute Bacterial Rhinosinusitis. *Otolaryngology – Head and Neck Surgery.* 2000;123:S1-S32. 2. Gwaltney JM Jr. Sinusitis. In: Mandell GL, Bennett JG, Dolin R, eds. *Principles and Practice of Infectious Diseases.* 4th ed. New York, NY: Churchill Livingstone Inc; 1999:585-590. 3. Poole MD. Antimicrobial therapy for sinusitis. *Otolaryngologic Clinics of North America.* 1997;30:331-339. 4. Camacho AE, Cobo R, Otte J, et al. Clinical comparison of cefuroxime axetil and amoxicillin/clavulanate in the treatment of patients with acute bacterial maxillary sinusitis. *Am J Med.* 1992;93:271-276.

For demonstration purposes only.
Not to be left with physician.

THE RIGHT TOOL FOR BRONCHITIS MAY NOT BE THE NEWEST.

*CEFTIN® efficacy: 5 days proven comparable to 10 days[1]**

	Microbiologic Eradication	
Dosing	*H influenzae*	*H parainfluenzae*
CEFTIN® 250 mg b.i.d. x 5 days	**86%** 19/22	**88%** 14/16
CEFTIN® 250 mg b.i.d. x 10 days	**100%** 14/14	**82%** 14/17

Microbiologic eradication includes presumed eradication and cure with colonization. Overall bacteriologic efficacy for CEFTIN® 5-day or 10-day therapy was 87% (52/60) and 91% (53/58).

Five-day indication is for secondary bacterial infections of acute bronchitis.

Save with CEFTIN®

Agent/Dosing	Cost of Therapy ($)†
CEFTIN® 250 mg b.i.d. x 5 days	**39.95**
azithromycin 500 mg q.d. x 1 day, 250 mg q.d. x 4 days	40.53

In US clinical trials with CEFTIN® Tablets, the most commonly reported adverse events were diarrhea/loose stools (3.7%) and nausea/vomiting (3%).

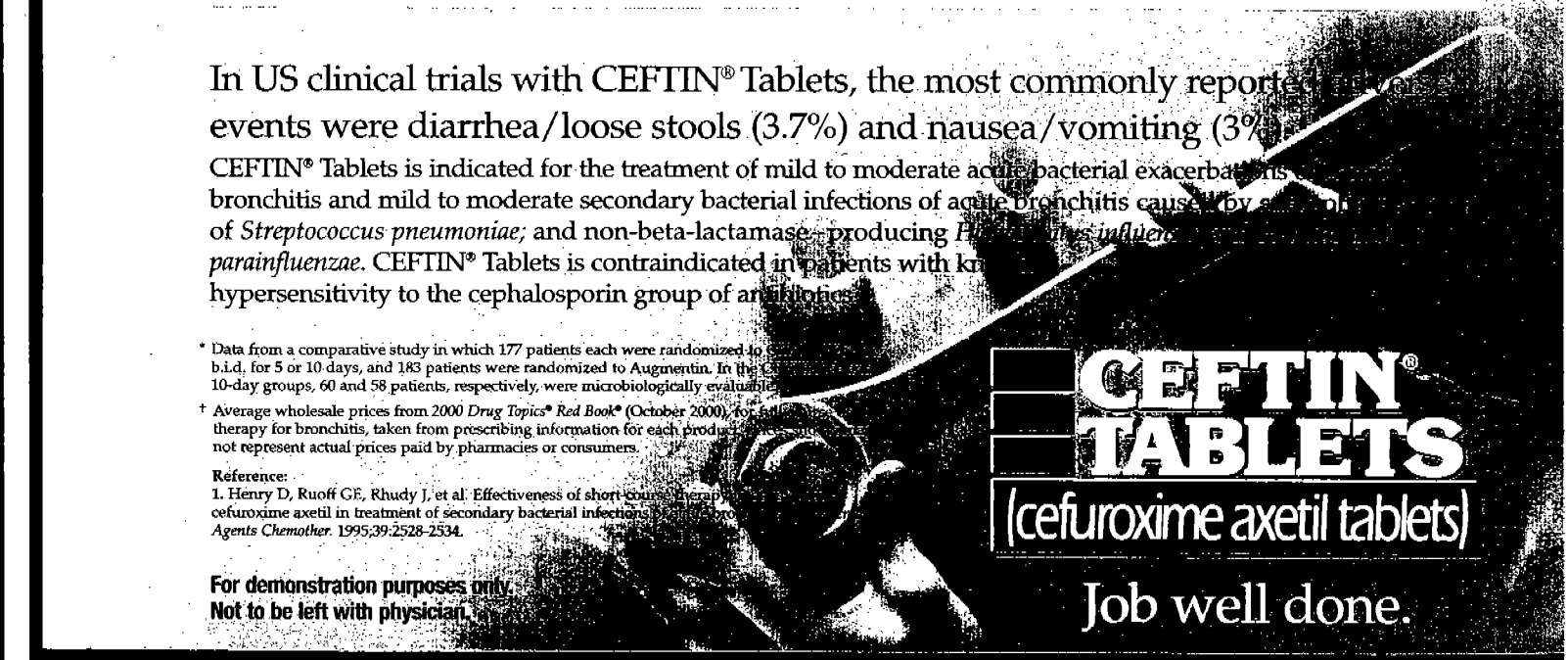
CEFTIN® Tablets is indicated for the treatment of mild to moderate acute bacterial exacerbations of chronic bronchitis and mild to moderate secondary bacterial infections of acute bronchitis caused by susceptible isolates of *Streptococcus pneumoniae;* and non-beta-lactamase–producing *Haemophilus influenzae* and *parainfluenzae*. CEFTIN® Tablets is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

* Data from a comparative study in which 177 patients each were randomized to CEFTIN® 250 mg b.i.d. for 5 or 10 days, and 183 patients were randomized to Augmentin. In the CEFTIN® 5- and 10-day groups, 60 and 58 patients, respectively, were microbiologically evaluable.

† Average wholesale prices from *2000 Drug Topics® Red Book®* (October 2000), for selected therapy for bronchitis, taken from prescribing information for each product. Prices do not represent actual prices paid by pharmacies or consumers.

Reference:
1. Henry D, Ruoff GE, Rhudy J, et al. Effectiveness of short-course therapy with cefuroxime axetil in treatment of secondary bacterial infections of acute bronchitis. *Antimicrob Agents Chemother.* 1995;39:2528-2534.

For demonstration purposes only. Not to be left with physician.



CEFTIN® TABLETS
(cefuroxime axetil tablets)

Job well done.