CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50675_S14

MICROBIOLOGY REVIEW

ENVIRONMENTAL ASSESSMENT
CLAIM FOR CATEGORICAL EXCLUSION

As cited at 21 CFR 25.15(d), an environmental assessment (EA) is not required if it is stated that the action requested qualifies for a categorical exclusion and, to the applicant's knowledge, no extraordinary circumstances exist.

An Environmental Assessment dated February 7, 1992 covering cefpodoxime proxetil as VANTIN Tablets (NDA 50-674) and VANTIN for Oral Suspension (NDA 50-675) was submitted to the Division of Anti-Infective Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration on February 12, 1992 and resubmitted on June 30, July 2, and July 14, 1992 to comply with FOI status.

These NDAs were approved on August 7, 1992, and the FDA wrote a finding of no significant impact (FONSI) on this EA dated August 12, 1992.

On June 18, 1996, the FDA provided clearance to market VANTIN for Oral Suspension and VANTIN Tablets under a new shortened dosing regime for tonsillitis and pharyngitis.

Under the new daily dosing regimen for pharyngitis and tonsillitis, doctors can prescribe 5 mg/kg of VANTIN for Oral Suspension twice daily for a treatment period of five to ten days. VANTIN for Oral Suspension's former dosing regimen for pharyngitis and tonsillitis was 5 mg/kg twice daily for ten days.

CATEGORICAL EXCLUSION

Pharmacia & Upjohn Company's supplement to NDA #50-675 qualifies for a categorical exclusion based on Sec. 25.31(a). Action on this supplemental NDA does not increase the use of the active moiety.

EXTRAORDINARY CIRCUMSTANCES

To P&U's knowledge, no extraordinary circumstances, as specified in 21 CFR 25.21, exist in connection with action on this NDA.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

SUBMISSION TYPE:	DOCUMENT DATE:	CDER DATE:	ASSIGNED DATE:
NDA 50-675	12/19/97	12/22/97	3/26/98
SUPPLEMENT			
SE1-014			1 of 30

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DRUG PRODUCT NAME:
Proprietary: Vantin® Oral Suspension
Nonproprietary: Cefpodoxime Proxetil
Code Name/#'s: N/A
Chemical Formula (empirical): See USP

INDICATIONS:
Treatment of: Acute Otitis Media

DOSAGE FORM: Oral
STRENGTH: 50mg/5mL and 100mg/5mL
ROUTE OF ADMINISTRATION: Oral
DOSAGE/DURATION: 5mg/kg Q 12 hours (10mg/kg daily) for five (5) days.

RELATED DOCUMENTS:
IND IND NDA 50-674, DMF

REMARKS/COMMENTS:

The issues of this submissions are the:

1. Duration of dosing for the treatment of "acute otitis media". Currently the applicant's label allows for the use of 10mg/kg Q 24 of an oral suspension of cefpodoxime for ten days for the treatment of "Acute Otitis Media". This submission is asking for labeling to

indicate that the oral suspension of cefpodoxime can be given Q 12 (5mg/kg/dose) for a period of 5 days for the treatment of "Acute Otitis Media".

2. The inclusion in the label of coverage for beta-lactamase producing strains of *Moraxella catarrhalis* suspected as being the cause of "Acute Otitis Media".

3. The addition of *Streptococcus pyogenes* to the "Acute Otitis Media" indication.

SUBMISSION TYPE:	DOCUMENT DATE:	CDER DATE:	ASSIGNED DATE:
NDA 50-675	12/19/97	12/22/97	3/26/98
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INTRODUCTION:

There is three (3) issues related to this particular submission.

1. The issue of this submissions is the duration of dosing for the treatment of "Acute Otitis Media". Currently the applicant's label allows for the use of 10mg/kg Q 24 of an oral suspension of cefpodoxime for ten days for the treatment of "Acute Otitis Media". This submission is asking for labeling to indicate that the oral suspension of cefpodoxime can be given Q 12 (5mg/kg/dose) for a period of 5 days for the treatment of "Acute Otitis Media". The organisms to be treated under this indication are: *Haemophilus influenzae* (including beta-lactamase producing strains), *Moraxella catarrhalis* (including beta-lactamase producing strains), *Streptococcus pneumoniae*, and *Streptococcus pyogenes*.

2. The inclusion in the label of coverage for beta-lactamase producing strains of *Moraxella catarrhalis* suspected as being the cause of "Acute Otitis Media".

3. The addition of *Streptococcus pyogenes* to the "Acute Otitis Media" indication.

INDICATIONS IN CURRENT LABEL:

Cefpodoxime proxetil is currently approved for the treatment of:

"Community Acquired Pneumonia" caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (including beta-lactamase producing strains).

"Acute Bacterial Exacerbation of Chronic Bronchitis" caused by *S. pneumoniae, H. influenzae* (non-beta lactamase-producing strains only) or *Moraxella catarrhalis* .

"Acute Otitis Media" caused by *S. pneumoniae, H. influenzae* (including beta-lactamase producing stains) or *M. catarrhalis* .

"Pharyngitis and/or Tonsillitis" caused by *Streptococcus pyogenes*

"Acute Uncomplicated Urethral and Cervical Gonorrhoeae" caused by *Neisseria gonorrhoeae* (including penicillinase-producing strains).

"Acute, Uncomplicated Ano-Rectal Infections in Women" due to *Neisseria gonorrhoeae* (including penicillinase-producing strains of *Neisseria gonorrhoeae*).

"Uncomplicated Skin and Skin Structure Infections" caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *S. pyogenes.*

"Uncomplicated Urinary Tract Infections (cystitis)" caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* or *Staphylococcus saprophyticus..*

PRE-CLINICAL EFFICACY (IN-VITRO)

SPECTRUM OF ACTIVITY:

A review of the spectrum of activity of cefopodoxime appears in the original NDA review. Cefpodoxime has been shown to have activity in-vitro against the organisms being requested to be included under "Acute Otitis Media" (1, 2, 3, 4, 5, 6). The exception being penicillin-resistant *Streptococcus pneumoniae* (3, 4, 5, 6). All of these organisms are currently included under indications that have been approved, however, the current label does not distinguish penicillin-susceptible from penicillin-resistant *S. pneumoniae.*

Recent reports in the literature have indicated that penicillin-resistant *S. pneumoniae* have decreased susceptibility to cefpodoxime with the MIC_{50s} (μg/mL) and MIC_{90s} (μg/mL) being 4 and 16 respectively (3), 2 and 8 respectively (4, 5), and 8 and 8 respectively (6). For *S. pneumoniae* that have intermediate-resistance to penicillin the MIC_{50s} and MIC_{90s} are 0.5 and 2.0 respectively (3), 0.25 and 1.0 respectively (4), and 0.50 and 2.0 respectively (5, 6).

The sponsor is asking that *Moraxella catarrhalis* (including beta-lactamase producing strains) be added to the label for the "Acute Otitis Media" indication.. The literature reports that over 95% of *M. catarrhalis* strains isolated from clinical infections produce beta-lactamase (1).

The MIC_{90s} of cefpodoxime for the organisms [*Haemophilus influenzae* (including beta-lactamase strains), *Moraxella catarrhalis, Streptococcus pneumoniae, Streptococcus pyogenes*] for which the sponsor is asking to be included under the indication of "Acute Otitis Media" have been reported in the recent literature to be:
Haemophilus influenzae (non-beta lactamase producers) 0.13μg/mL (2).
H. influenzae (beta-lactamase producers) <0.06μg/mL (2).
Moraxella catarrhalis (non-beta lactamase producers) 0.25μg/mL (1).

M. catarrhalis (beta lactamase producers) 2.0µg/mL (1).
M. catarrhalis (non-beta-lactamase and beta-lactamase producers) 1.0µg/mL (5).
Streptococcus pneumoniae (penicillin susceptible) 0.06µg/mL (3).
S. pneumoniae (penicillin intermediate) 2.0µg/mL (3).
S. pneumoniae (penicillin resistant) 16.0µg/mL (3).
Streptococcus pyogenes ≤0.06µg/mL (2).

MECHANISM OF ACTION:

A review of the mode of action of cefpodoxime, a prodrug, can be found in the original review of the NDA submission. Since that time no further significant knowledge concerning its mode of action has been elucidated.

MECHANISM OF RESISTANCE:

A review of the methods by which resistance to cefpodoxime can occur can be found in the original NDA review. A review of the recent literature found that cefpodoxime may be inactivated by certain classes of extended-spectrum beta-lactamases (7). Because these enzymes to date have been found only in members of the Enterobacteriaceae and not in the organisms that are commonly associated with acute maxillary sinusitis this review will not deal with subject.

EPIDEMIOLOGY:

A recent review of the literature in relation to the organisms which the sponsor wishes to include in the labeling for "Acute Otitis Media" revealed the following percentages in relation to these organisms producing enzymes which inactivate certain types of antimicrobials or showing intrinsic resistance to certain types of antimicrobials:

H. influenzae (beta-lactamase producers) - 35% with a range of 17% to 68% (8)
H. influenzae (beta-lactamase negative ampicillin resistant) - 4% (8)
S. pneumoniae (penicillin - intermediate) - 15% with a range of ~2% to 29% (3)
S. pneumoniae (penicillin - resistant) - 7.3% with a range of 5% to 30% (3)
M. catarrhalis (beta-lactamase producers) - 95% (1)
S. pyogenes - No evidence in the literature suggesting that there are strains of this organism resistant to penicillin.
S. pyogenes - Erythromycin resistant - 10% (1)

In relation to the prevalence of antimicrobial-resistant pathogens in the middle ear a recent study (9) has found the following for organisms isolated in the United States.

Haemophilus influenzae - 26% of patients had this organism isolated and 47% of these produced beta-lactamase. All of these *H. influenzae* isolates were untypeable.

Moraxella catarrhalis - 12% of the patients had this organism isolated and 100% of the isolates produced beta-lactamase.

Streptococcus pneumoniae - 26% of the patients had this organism isolated and 21% were intermediately or fully resistant to penicillin.

Streptococcus pyogenes - less than 10% of the patients had this organism isolated and there were no isolates found resistant to penicillin.

POSTANTIBIOTIC EFFECT:

No information presented in this NDA SUPPLEMENT.

INTRACELLULAR CONCENTRATIONS:

No information presented in this NDA supplement.

INTERACTION WITH OTHER ANTIBIOTICS:

No information presented in this NDA supplement.

PRE-CLINICAL (in-vitro) SUSCEPTIBILITY TEST METHODS:

The sponsor indicates that the in-vitro susceptibility methods to determine the susceptibility of isolates to cefpodoxime recovered from acute otitis media will continue to be the methods as described by the National Committee for Clinical Laboratory Standards (NCCLS) (10, 11). This is consistent with the laboratory practices at the time of this review. Whether the interpretive criteria for the organisms requested with the indication "Acute Otitis Media" are appropriate will be found in the "CLINICAL EFFICACY" section of this review.

The quality control criteria in the current labeling are listed below and are in agreement with the quality control criteria recommended by the NCCLS when providing information on the susceptibility of *Escherichia coli, Klebsiella pneumoniae, Proteus*

mirabilis, *Staphylococcus aureus* (including penicillinase producing strains), and *Staphylococcus saprophyticus* (12).

Minimal Inhibitory Concentration (MIC) Testing Quality Control Criteria

Organism	MIC range (µg/mL)
E. coli ATCC® 25922	0.25 - 1.0
S. aureus ATCC® 29213	1.0 - 8.0

Disc Diffusion Testing Quality Control Criteria

Organism	Zone Diameter Range (mm)
E. coli ATCC® 25922	23 - 28
S. aureus ATCC® 25923	19 - 25

The sponsor, however, needs to add to the package insert the quality control values for both MIC susceptibility testing and disk diffusion testing for the organisms listed below to reflect the latest NCCLS (12) criteria. These quality control criteria are necessary to assure that when reporting the results of susceptibility testing on *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus pneumoniae* the tests are performing correctly. These criteria are as follows:

Minimal Inhibitory Concentration (MIC) Testing Quality Control Criteria

Organism	MIC range (µg/mL)
Haemophilus influenzae ATTC® 49247	0.25 - 1.0*
Neisseria gonorrhoreae ATTC® 49226	0.03 - 0.12**
Streptococcus pneumoniae ATTC® 49619	0.03 - 0.12***

*These quality control ranges are applicable to tests conducted by a broth microdilution procedure using Haemophilus Test Medium (HTM).

**These quality control ranges are applicable to tests performed by agar dilution only using GC agar base and 1% defined growth supplement.

***These quality control ranges are applicable to tests performed by the broth microdilution method only using cation-adjusted Mueller-Hinton broth with 2 to 5 % lysed horse blood.

Disc Diffusion Testing Quality Control Criteria

Organism	Zone Diameter Range (mm)
Haemophilus influenzae ATTC® 49247	25 - 31*
Neisseria gonorrhoeae ATTC® 49226	35 - 43**
Streptococcus pneumoniae ATTC® 49619	28 - 34***

*These quality control limits only apply to tests conducted with *Haemophilus influenzae* using *Haemophilus* Test Medium (HTM).

**These quality control ranges are only applicable to tests performed by disk diffusion using GC agar base and 1% defined growth supplement.

***These quality control ranges are applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defribinated sheep blood, incubated in 5% CO_2.

INTERPRETIVE CRITERIA FOR SUSCEPTIBILITY TESTING USED DURING THE CLINICAL TRIALS FOR THIS NDA SUPPLEMENT:

In studies (M/1140/0098-A and M/1140/0098-B) where aspiration samples were cultured prior to treatment to isolate the infecting organism and determine its susceptibility to study drug susceptibility testing was done by disc diffusion. The criteria for interpreting the zone size are indicated below. The sponsor in their submission does not indicate that dilution testing was done on isolates. The interpretive criteria used during the clinical trials for support of the sponsors application of the addition of "Acute Otitis Media" to their label were originally determined from data submitted in support of their original label claims. These disc diffusion interpretive criteria were:

Disc Diffusion (10ug) Zone Diameters (mm)	Interpretation
≥21	Susceptible (S)
18 - 20	Intermediate (I)
≤17	Resistant (R)

This review of the data submitted to support the request for inclusion of "Acute Otitis Media" in the sponsors label for cefpodoxime proxetil tablets will evaluate if these interpretive criteria were appropriate for interpreting the susceptibility results for the organisms associated with "Acute Otitis Media".

The sponsor's current label has dilution testing interpretive criteria of:

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
8	Resistant (R)

These interpretive criteria are not what is indicated as interpretive criteria in the current NCCLS document (12) for *Haemophilus* spp., *Streptococcus* spp. and *Streptococcus pneumoniae*. The NCCLS criteria for these organisms are:

Haemophilus spp. * Isolates with the following susceptibility profile: MIC ≤2.0µg, or Zone diameter ≥21mm can be considered susceptible for approved indications. Intermediate and resistant criteria have not been determined .

Streptococcus pneumoniae * *- Isolates of pneumococci with a penicillin MIC of ≤0.06µg/mL or an oxacillin zone size of ≥20mm can be considered susceptible to cefpodoxime for approved indications (12).

Streptococcus spp. (other than *S. pneumoniae*) ** - A streptococcal isolate that is susceptible to penicillin (MIC ≤0.12µg/mL = susceptible, or Zone diameter ≥28mm = susceptible) can be considered susceptible to cefpodoxime for approved indications (12).

* Susceptibility testing interpretive criteria are based on testing being done with Haemophilus test media.
** Susceptibility testing criteria are based on testing being done with Mueller Hinton broth with lysed horse blood (2-5%v/v) for MIC determination and Mueller Hinton agar with 5% sheep blood for disc diffusion testing. Agar plates are incubated in 5% CO_2.

PRE-CLINICAL -IN-VIVO

PHARMACOKINETICS:

The sponsor conducted a study (protocol M1140/0016) to determine the concentration of cefpodoxime proxetil in the middle ear of humans ages 6 months to 10 years with acute otitis media for dosage regimens of 5mg/kg (200mg max) twice a day (BID) and 10mg/kg (400mg max) once a day. Twenty-five (25) patients were in each study group with 17 in each group being evaluable.. This protocol was a randomized, open-label study.

After at least one complete day of treatment with either regimen, tympanocentesis was performed at either 2, 4, 6 or 8 hours after the morning dose. A blood sample was collected at the same time as the tympanocentesis. The data from this study are shown below.

Median (range) of cefpodoxime concentration in middle ear effusion of pediatric patients with otitis media

	5mg/kg BID (n=17)		10mg/kg QD (n=17)	
Collection time (hr.)	No. of samples	Concentration (µg/mL)	No. of samples	Concentration (µg/mL)
2	5	2.28 (0.90 - 3.27)	5	1.72 (0.65 - 1.92)
4	6	0.98 (0.36 - 1.55)	6	3.24 (2.11 - 12.1)
6	6	0.88 (0.33 - 1.41)	3	0.55 (0.20 - 3.12)
8	5	0.97 (0.53 - 1.28)	5	1.55 (0.92 - 4.03)

The levels of cefpodoxime achieved over the 8 hour period for the 5mg/kg BID regimen of cefpodoxime seem appropriate for eradication of *H. influenzae* both non-beta-lactamase and beta-lactamase producers (2) were the reported MIC_{90} is $\leq$0.13µg/ mL, for *M. catarrhalis* non-beta-lactamase producers were the reported MIC_{90} is 0.25µg/mL (1), for penicillin-susceptible *S. pneumoniae* the reported MIC_{90} is 0.06µg/mL (3) and *S. pyogenes* were the reported MIC_{90} to Cefpodoxime is $\leq$0.06µg/mL. However, these levels of cefpodoxime for treatment of infections due to beta-lactamase-producing *M. catarrhalis* were the reported MIC_{90} ranges between 1.0 to 2.0µg/mL (1, 2) and for penicillin-intermediate *S. pneumoniae* were the reported MIC_{90s} are reported to be 2.0µg/mL (3) would not appear to be efficacious for the treatment of these infections. These levels do not appear to be sufficient for the treatment of infections due to penicillin-resistant strains of *S. pneumoniae* were the reported MIC_{90s} for cefpodoxime is 16.0µg/mL (3).

The levels of cefpodoxime achieved over the 8 hour period for the 10mg/kg QD regimen also appear to be sufficient to treat infections due to *H. influenzae* both non-beta-lactamase and beta lactamase producers, for *M catarrhalis* non-beta-lactamase producers for penicillin-susceptible *S. pneumoniae* and for *S. pyogenes*. These levels also seem to be more appropriate for the treatment of infections due to beta-lactamase producing strains of *M. catarrhalis* and penicillin-intermediate strains of *S. pneumoniae* then the levels achieved with the 5mg/kg BID regimen. The levels achieved with the 10mg/kg QD

regimen would appear not to be sufficient to treat infections due to penicillin-resistant *S. pneumoniae.*

CLINICAL EFFICACY

CLINICAL MICROBIOLOGY:

Isolates - Relevance to Proposed Indications

Acute Otitis Media:
Haempohilus influenzae (including beta-lactamase producing strains)
Streptococcus pneumoniae
Moraxella catarrhalis (including beta-lactamase producing strains)
Streptococcus pyogenes

These organisms have been shown to be associated with acute otitis media and are thus appropriate for this indication (10).

Overall Correlation of Therapeutic Data with Susceptibility Test Results

Data for the efficacy of the 5mg/kg BID regimen was provided through two Phase III, prospective, randomized, evaluator-blind studies (M/1140/0098-A and M/1140/0098-B) that were identical with respect to design, study conduct, methods, and analyses. The comparator for these studies was cefixime at a dose of 8mg/kg every 24 hours for ten days. These studies were conducted at 12 and 19 sites respectively.

In addition, the efficacy of the 5-day regimen as determined from integrated data from protocols 0098-A and 0098-B was retrospectively compared with that of a 10-day cefpodoxime regimen. The 10-day data was from the three studies (M/1140/0013, M/1140/0014, and M/1140/0060) in which pediatric patients with otitis media were treated with either cefpodoxime at a dose of 5mg/kg BID for 10 days or amoxicillin/clavulanate potassium at a dose of 13.3mg/kg TID for 10 days.

Four primary efficacy measures were selected for protocols 0098-A and 0098-B: percentage of patients with clinical success at an end of therapy and at a "Test of Cure" visit and percentage of patients with bacteriologic cure at End of Therapy and "Test of Cure" evaluations.

The secondary efficacy measures were (1) percentages of clinical success or bacteriologic cure at Visit 2, Visit 3 and Final Visit and (2) change in temperature from post treatment values.

The overall clinical evaluation was independent of any bacteriologic evaluation. An overall bacteriologic evaluation was obtained for each patient at each post-pretereatment visit. Tympanocentesis was not necessarily done at all visits.

The following data are excerpted from the sponsors report. These data are presented for review purposes. All data are derived from protocols 0098-A and 0098-B.

Overall Clinical Evaluation

Summary of End of Therapy* Overall Clinical Evaluation

Evaluation	Results	Cefpodoxime N=260	Cefixime N=272
Success	Cured	83 (32%)	145 (53%)
	Improved	143 (55%)	69 (25%)
	Total Clinical Success	226 (87%)	214 (79%)
Failure	Failure	28 (11%)	37 (14%)
	Side Effect Failure	5 (2%)	7 (3%)
	Antibiotic Non-investigational	1 (<1%)	14 (5%)
	Total Failures	34 (13%)	58 (21%)

*End of therapy = visit 2 (days 7-10) for cefpodoxime and visit 3 (days 12-15) for cefixime

Overall Bacteriologic Evaluation
The overall bacteriologic cure rate, which comprised both bacteriologic cures (i.e., patients with culture-proven eradication) and presumptive bacteriologic cures (i.e., patients judged clinically cured or improved) was driven by the success rate since few repeat cultures were done.

Summary of End of Therapy * Overall Bacteriologic Evaluation

Cure	Evaluation	Cefpodoxime N=260	Cefixime N=272
Cure	Bacteriologic	—	1 (1%)
	Presumptive	226 (87%)	214 (79%)
	Total cures	226 (87%)	215 (80%)
Failure	Bacteriologic	1 (1%)	7 (3%)
	Presumptive	25 (10%)	25 (9%)
	Side effect	5 (2%)	7 (3%)
	Antibiotic noninvestigational	1 (<1%)	14 (5%)
	Total failures	34 (13%)	57 (21%)

* End of therapy = Visit 2 (days 7-10) for cefpodoxime) and visit 3 (days 12-15) for cefixime

End of Therapy by Pathogen Bacteriologic Evaluation

The following table lists eradication rates of all pathogens isolated at pretreatment.

Summary of End of Therapy* Eradication Rates by Pathogen

Pathogen	Cefpodoxime n/N ** (%)	Cefixime n/N (%)
Haempohilus influenzae	1/1 (100)	7/9 (78)
H. influenzae (β-lactamase negative)	37/41 (90)	33/38 (87)
H. influenzae (β-lactamase positive)	34/37 (92)	32/38 (84)
Moraxella catarrhalis	2/4 (50)	5/8 (63)
M. catarrhalis (β-lactamase negative)	3/4 (75)	3/3 (100)
M. catarrhalis (β-lactamase positive)	23/32 (72)	25/33 (76)
Streptococcus pneumoniae	119/127 (94)	101/132 (77)
Streptococcus pyogenes	22/25 (88)	17/24 (71)

* End of therapy = visit 2 (days 7-10 for cefpodoxime and visit 3 (days 12-15) for cefixime.

** n/N = No. patients with pathogen eradicated/ No. of patients with assessable response at pretreatment.

"Test of Cure"

Summary of "Test of Cure" Overall Clinical Evaluation at 4-21 Days Post Therapy

Evaluation	Results	Cefpodoxime N=245*	Cefixime N=258*
Success	Cured	111 (44%)	125 (48%)
	Improved	60 (24%)	40 (16%)
	Total clinical successes	171 (67%)	165 (64%)
Failure	Failure	76 (30%)	76 (29%)
	Side effect failure	5 (2%)	6 (2%)
	Antibiotic noninvestigational	2 (1%)	11 (4%)
	Total clinical failures	83 (33%)	93 (36%)

* N=245 and 258 in the cefpodoxime and cefixime treatment groups, respectively, because 6 patients in the cefpodoxime and 14 patients in the cefixime group had no data available in the 4-21 day window.

"Test of Cure" Overall Bacteriologic Evaluation

Summary of "Test of Cure" Overall Bacteriologic Evaluation * at 4-21 Days Post Therapy

Evaluation	Results	Cefpodoxime N=245*	Cefixime N=258*
Cure	Bacteriologic	–	–
	Presumptive	171 (67%)	165 (64%)
	Total cures	171 (67%)	165 (64%)
Failure	Bacteriologic	3 (1%)	11 (4%)
	Presumptive	67 (26%)	59 (23%)
	Superinfection	6 (2%)	5 (2%)
	Side effect	5 (2%)	6 (2%)
	Antibiotic noninvestigational	2 (1%)	11 (4%)

* N=245 and 258 in the cefpodoxime and cefixime treatment groups, respectively, because 6 patients in the cefpodoxime and 14 patients in the cefixime group had no data available in the 4-21 day window.

"Test of Cure" by Pathogen Bacteriologic Evaluation

Summary of "Test of Cure" Eradication Rates by Pathogen at 4-21 Days Post Therapy

Pathogen	Cefpodoxime n/N (%)*	Cefixime n/N (%)*
H. influenzae	1/1 (100)	6/9 (67)
H. influenzae (β-lactamase negative)	27/41 (66)	30/37 (81)
H. influenzae (β-lactamase positive)	22/34 (65)	25/35 (71)
M. catarrhalis	2/5 (50)	4/7 (57)
M. catarrhalis (β-lactamase negative)	3/4 (75)	2/3 (67)
M. catarrhalis (β-lactamase positive)	17/31 (55)	17/31 (55)
Streptococcus pneumoniae	88/122 (72)	72/124 (58)
Streptococcus pyogenes	20/25 (80)	13/23 (57)

* n/N = No. patients with pathogen eradicated/ No. of patients with assessable response at pretreatment.

Final Visit Overall Clinical Evaluation

Summary of Final Visit* Overall Clinical Evaluation

Evaluation	Results	Cefpodoxime N=249**	Cefixime N=262**
Success	Cured	149 (60%)	150 (57%)
	Improved	12 (5%)	20 (8%)
	Total clinical success	161 (65%)	170 (65%)
Failure	Recurrence/reinfection	35 (14%)	39 (15%)
	Side effect	6 (2%)	7 (3%)
	Antibiotic noninvestigational	47 (19%)	46 (18%)
	Total clinical failures	88 (35%)	92 (35%)

* Final visit = days 25-38
** N = 249 or 262 because 11 patients in the cefpodoxime group and 10 patients in the cefixime group had not data available at Final Visit.

Final Visit Overall Bacteriologic Evaluation

Summary of Final Visit* Overall Bacteriologic Evaluation

Evaluation	Results	Cefpodoxime N=249**	Cefixime N=262**
Cure	Bacteriologic	–	–
	Presumptive	161 (65%)	170 (65%)
	Total cures	161 (65%)	170 (65%)
Failure	Bacteriologic	32 (13%)	33 (13%)
	Side effect	6 (2%)	7 (3%)
	Superinfection	3 (1%)	1 (<1%)
	Antibiotic noninvestigational	47 (19%)	46 (18%)
	Total failures	88 (35%)	92 (53%)

* Final visit = Days 25-38
** N = 249 or 262 because 11 patients in the cefpodoxime group and 10 patients in the cefixime group had not data available at Final Visit.

Final Visit By Pathogen Bacteriologic Evaluation

Summary of Final Visit* Eradication Rates by Pathogen

Pathogen	Cefpodoxime n/N (%)	Cefixime n/N (%)
H. influenzae	1/1 (100)	6/9 (67)
H. influenzae (β-lactamase negative)	24/38 (63)	25/33 (76)
H. influenzae (β-lactamase positive)	18/36 (50)	27/36 (75)
M. catarrhalis	2/4 (50)	5/8 (63)
M. catarrhalis (β-lactamase negative)	3/4 (75)	3/3 (100)
M. catarrhalis (β-lactamase positive)	20/29 (69)	19/32 (59)
S. pneumoniae	86/125 (69)	76/130 (58)
S. pyogenes	16/23 (70)	14/23 (61)

Summary of Pivotal Studies

Summary of Clinical Success and Bacteriologic Cure Rates (%) in Pivotal Studies of Cefpodoxime Proxetil 5-Day Twice Daily Regimen in Pediatric Patients with Acute Suppurative Otitis Media
Protocols 0098-A and 0098-B

Treatment	Primary Efficacy Endpoints				Secondary Efficacy Endpoints					
					Visits					
Group	End of Therapy		"Test of Cure"		1		3		Final	
	Clin	Bact	Clin	Bact	Clin	Bact	Clin	Bact	Clin	Bact
Cefpodoxime	87	87	67	67	87	87	74	74	65	65
Cefixime	79	79	64	64	87	87	79	79	65	65

"Test of Cure" = 4-21 days post therapy, End of therapy = Days 7-10 for cefpodoxime and days 12-15 for cefixime
Visit 2 = days 7-10, visit 3 = days 12-15, and final visit = days 25-38

SUMMARY

The percentages of *M. catarrhalis* and *H. influenzae* isolated in these studies that were beta-lactamase producing strains is consistent with the percentages of such strains one would expect to encounter. However, the data from the sponsor does not indicate for the *S. pneumoniae* how many isolates were either somewhat resistant (intermediate) or fully resistant to penicillin. Because of the documented decrease noted in the literature (3, 4, 5, 6) of fully penicillin resistant *S. pneumoniae* to cefpodoxime the labeling for this organism involved in all indications previously allowed and for this indication needs to read *S. pneumoniae* (excluding penicillin-resistant isolates).

For the 5mg/kg BID the level of cefpodoxime achieved in the middle ear over eight hours and the fact that the level is above the MIC_{90s} of *H. influenzae* [non-beta-lactamase and beta-lactamase producers whose MIC_{90s} for cefpodoxime are $\leq$0.13µg/mL (2)], for *M. catarrhalis* (non-beta-lactamase producers) whose MIC_{90} is 0.25µg/mL (1) for penicillin-susceptible *S. pneumoniae* whose MIC_{90} is $\leq$0.06µg/mL (3) and *S. pyogenes* whose reported MIC_{90} to cefpodoxime is $\leq$0.06µg/mL (2) for greater than 40% (13) of the time the proposed dosage regimen for cefpodoxime seems appropriate for eradication of these organisms. In addition, bacteriologic eradication data at "The End of Therapy" for these organisms were greater than 88%. However, the levels of cefpodoxime over eight hours are below or just on the border of the MIC_{90s} for beta-lactamase producing *M. catarrhalis*

[1 to 2μg/mL (1, 2)] and for *S. pneumoniae* moderately resistant to penicillin whose MIC_{90} for cefpodoxime is 2.0μg/mL and these levels are not above the MIC of these organisms for >40% of the time. In fact, this may be one explanation for the fact that the bacteriologic cure rates are below 85% (13). Thus the success that cefpodoxime would have in eradicating these organisms at this site of infection is questionable. Because the level of cefpodoxime achieved in the middle ear is considerably less than the MIC_{90} of penicillin-resistant *S. pneumoniae* to cefpodoxime [16μg/mL (3)] over the eight hours the use of cefpodoxime to treat acute otitis media caused by this type of *S. pneumoniae* is inappropriate.

Because the literature shows that as much as one-third of acute otitis media infections often resolve without the use of antibiotics (2) it becomes difficult to determine the efficacy of most antibiotics in treating "acute otitis media". Thus the efficacy of the antimicrobial may have to be based not only on the pharmacokinetics/pharmacodynamics of the antimicrobial but also on the clinical outcomes of these trials. In this case treatment of acute otitis media caused *M. catarrhalis* (both non-beta-lactamase and beta-lactamase producing strains) may be appropriate but it should be noted in the label that the success rate of treating acute otitis media due to *M. catarrhalis* was 72% based on end of therapy results.

The sponsor did not provide data on the number of infections caused by *S. pneumoniae* that were moderately (intermediate) susceptible to penicillin or the number of infections caused by penicillin-resistant *S. pneumoniae* that were treated either with cefpodoxime or cefixime. Because of this fact and the fact that the MIC_{90s} for these two types of organism are just at or considerably above the levels and the levels do not stay above the organisms MICs for >40% of the time of cefpodoxime achieved in the middle ear labeling should state "*Streptococcus pneumoniae* (penicillin-susceptible strains only)".

The disc diffusion interpretive criteria used for this study appears appropriate since there were good correlation's with the bacteriologic and clinical outcomes seen in this study. However, the label for this product does not include the susceptibility testing interpretive criteria for *Haemophilus spp.*, *Streptococcus pneumoniae*, and *Streptococcus* spp. as noted in the current NCCLS document (12). Currently there are no NCCLS interpretive criteria for *M. catarrhalis*. Revising the label to the current NCCLS interpretive criteria should not impact the correlation between susceptibility test results and clinical outcome since as indicated below the NCCLS interpretive criteria are more stringent then what is indicated in the current labeling which was used as the interpretive criteria for this study.

SUBMISSION TYPE:	DOCUMENT DATE:	CDER DATE:	ASSIGNED DATE:
NDA 50-675	12/19/97	12/22/97	3/26/98
SUPPLEMENT			
SE1-014			20 of 30

INTERPRETIVE CRITERIA

ORGANISM	METHOD	CURRENT LABEL	STUDY	NCCLS (12)
Haemophilus spp.	Dilution	None [a]	None	<2.0µg/mL = S
	Disc	>21mm = S 18-20mm = I ≤17mm = R	Same as Label	>21mm = S No I or R criteria
S. pneumoniae	Dilution	None	None	Susceptible to penicillin (≤0.06 µg/mL) then susceptible to cefpodoxime.
	Disc	Same as above	Same as above	"Oxacillin" zone size of ≥20mm then susceptible to cefpodoxime.
Streptococcus spp.	Dilution	None	None	Susceptible to penicillin (≤0.12µg/mL) then susceptible to cefpodoxime.
	Disc	Same as above	Same as above	Penicillin zones: ≥28mm = S Susceptible to penicillin then susceptible to cefpodoxime.

a. The current package labeling indicates for dilution interpretive criteria: ≤2µg/mL = S; 4µg/mL = I; ≥8µg/mL = R.

In addition to updating the label's interpretive criteria the label also needs to include the quality control interpretive ranges for dilution and disc susceptibility testing for

Haemophilus spp., *S. pneumoniae* and *Streptococcus* spp. This information is included in the labeling portion of this review.

At this time there are no specific susceptibility interpretive criteria for *M. catarrhalis*. The interpretive criteria in the current label as judged by this current study seem appropriate for this organism. In addition, there are no specific quality control criteria for *M. catarrhalis* thus the quality control for this organism will need to depend on that done with quality control organisms currently in the label.

The current label also does not reflect the current interpretive and quality control information for *Neisseria gonorrhoeae*. This information needs to be updated to what is in the current NCCLS document (12). Here as with the organisms noted above the NCCLS interpretive criteria are more stringent then what is in the current label thus there most likely would not be any impact on success of clinical outcome when cefpodoxime is used.

INTERPRETIVE CRITERIA

ORGANISM	METHOD	CURRENT LABEL	NCCLS (12)
N. gonorrhoeae	Dilution	≤2µg/mL = S 4µg/mL = I ≥8µg/mL = R	≤0.5µg/mL = S No I or R
	Disc	≥21mm = S 18 - 20 = I ≤17 = R	≥29mm = S No I or R

The quality control interpretive criteria for dilution and disc susceptibility testing as indicated in the current NCCLS document (12) is included in the labeling portion of this review.

CONCLUSION AND RECOMMENDATIONS

The microbiology data and information provided by the sponsor is sufficient from the microbiology perspective to allow "Acute Otitis Media" caused by the following organisms to be included in the label: *Haemophilus influenzae* (including beta-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella (Branhamella) catarrhalis* (including beta-lactamase producing strains).

It is suggested, however, that the label state the fact the there was a clinical cure rate of 72% for otitis media caused by *Moraxella catarrhalis*. This cure rate is consistent with the finding that if the concentration of a beta-lactam is not above the MIC_{90} of the of the infecting organism for >40% of the time (13) cure rates decline. Data provided in this submission showed that the concentration of cefpodoxime in the middle ear was not above the MIC_{90} of beta-lactamase producing stains of *M. catarrhalis* for >40% of the time. In addition, since the literature indicates that the 95 to 100% of *M. catarrhalis* isolates are beta-lactamase producers (1, 9) there is a reduced probability that a non-beta-lactamase producing strain of *M. catarrhalis* will be the cause of an acute otitis media event and if the infecting *M. catarrhalis* were a non-beta-lactamase producer the data provided in this submission showed a cure rate with cefpodoxime of 75% for these organisms.

It is necessary, to add to all *Streptococcus pneumoniae* claims "penicillin-susceptible strains only" since the activity of cefpodoxime against penicillin-resistant and penicillin-intermediate strains of *S. pneumoniae* has been shown to reduced in relation to its activity against penicillin-susceptible strains (3, 4, 5, 6).

The label is approved with the indicated microbiology modifications noted in this review.

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12. NCCLS. Performance standards for antimicrobial susceptibility testing; Eighth informational supplement. NCCLS document M100-S8 [ISBN 1-56238-337-x]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1989.
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PROPOSED CEFPODOXIME PROXETIL ORAL SUSPENSION PACKAGE INSERT

Cefpodoxime is active against a wide- spectrum of Gram-positive and Gram-negative bacteria. Cefpodoxime is stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and cephalosporins, due to their production of beta lactamase, may be susceptible to cefpodoxime. Cefpodoxime is inactivated by certain extended spectrum beta-lactamases.

The bactericidal activity of cefpodoxime results from its inhibition of cell wall synthesis.

Cefpodoxime has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic Gram-positive microorganisms
Staphylococcus aureus (including penicillinase-producing strains)
NOTE: Cefpodoxime is inactive against methicillin-resistant staphylococci.
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic Gram-negative microorganisms
Escherichia coli
Haemophilus influenzae (including beta-lactamase producing strains)
Klebsiella, pneumoniae
Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae (including penicillinase-producing strains)
Proteus mirabilis

The following in vitro data are available, **but their clinical significance is unknown.** Cefpodoxime exhibits in vitro minimum inhibitory concentrations (MICs) of $\leq$2.0µg/mL against most ($\geq$90%) of isolates of the following microorganisms. However, the safety and efficacy of cefpodoxime in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus agalactiae
Streptococcus spp. (Groups C, F, G)
NOTE: Cefpodoxime is inactive against enterococci.

Aerobic Gram-negative microorganisms
Citrobacter diversus
Haemophilus parainfluenzae
Klebsiella oxytoca
Proteus vulgaris
Providencia rettgeri

NOTE: Cefpodoxime is inactive against most strains of *Pseudomonas* and *Enterobacter*

Anaerobic Gram-positive microorganisms
Peptostreptococcus magnus

SUSCEPTIBILITY TESTING:

Dilution techniques

Quantitative methods are used to determine antimicrobial inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of microorganisms to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution method [1,2] (broth or agar) or equivalent using standardized inoculum concentrations, and standardized concentrations of cefpodoxime from a powder of known potency. The MIC values should be interpreted according to the following criteria:

FOR SUSCEPTIBILITY TESTING OF *ENTEROBACTERIACEAE*, AND *STAPHYLOCOCCUS* SPP.

MIC (µg/mL)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

FOR SUSCEPTIBILITY TESTING OF *HAEMOPHILUS* SPP. [a]

MIC (µg/mL)	Interpretation [b]
≤2.0	Susceptible (S)

a. The interpretive criteria for *Haemophilus* spp. is applicable only to broth microdilution susceptibility testing done with Haemophilus Test Medium (HTM) broth (2).
b. "Intermediate" and "Resistant" categories have not been determined.

FOR SUSCEPTIBILITY TESTING OF *NEISSERIA GONORRHOEAE.* [c]

MIC (µg/mL)	Interpretation [d]
≤0.5	Susceptible (S)

c. The interpretive value for *N. gonorroheae* is applicable only to agar dilution susceptibility testing done with *Neisseria gonorrhoeae* susceptibility test medium (2).
d. "Intermediate" and "Resistant" categories have not been determined.

FOR SUSCEPTIBLITY TESTING OF *STREPTOCOCCUS PNEUMONIAE* [e]

A pneumococcal isolate that is susceptible to **penicillin (MIC ≤0.06µg/mL)** can be considered susceptible to cefpodoxime. Testing of cefpodoxime against penicillin-intermediate or penicillin-resistant isolates is not recommended because reliable interpretive criteria for this agent with *S. pnuemoniae* is not available Clinical response rates with cefpodoxime may be lower in strains that are not susceptible to penicillin.

e. The interpretive value for *S. pneumoniae* is applicable only to broth microdilution susceptibility testing done with cation-adjusted Mueller Hinton broth with lysed horse blood (LHB) (2-5% v/v) (2).

FOR SUSCEPTIBILITY TESTING OF *STREPTOCOCCUS* SPP. OTHER THAN *STREPTOCOCCUS PNEUMONIAE* [f]

A streptococcal isolate that is susceptible to **penicillin (MIC≤0.12µ/mL)** can be considered susceptible to cefpodoxime for approved indications, and need not be tested against cefpodoxime.

f. The interpretive value for *Streptococcus* spp. is applicable only to broth microdilution susceptibility testing done with cation-adjusted Mueller-Hinton broth with lysed horse blood (LHB) (2-5% v/v) (2).

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the concentration of the antimicrobial compound in the blood reaches usually achievable levels. A report of "Intermediate" indicates that the results should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality control

A standardized susceptibility test procedure requires the use of laboratory control organisms to control the technical aspects of the laboratory procedures. Standard cefpodoxime powder should provide the following MIC values with the indicated quality control strains:

Microorganism (ATCC®#)	MIC Range (µg/mL)
Escherichia coli (25922)	0.25 - 1.0
Haemophilus influenzae (49247)	0.25 - 1.0 [g]
Neisseria gonorrhoeae (49226)	0.03 - 0.12 [h]
Staphylococcus aureus (29213)	1.0 - 8.0
Streptococcus pneumoniae (49619) [i]	0.03 - 0.12 [i]

g. These quality control ranges are applicable to tests conducted by a broth microdilution procedure using Haemophilus Test Medium (HTM).

h. These quality control ranges are applicable to tests performed by agar dilution only using GC agar base and 1% defined growth supplement.

i. These quality control ranges are applicable to tests performed by the broth microdilution method only using cation-adjusted Mueller-Hinton broth with 2 to 5 % lysed horse blood.

j. When susceptibility testing *Streptococcus pneumoniae* or *Streptococcus* spp. this quality control stain should be tested.

Diffusion techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10µg disks to test the susceptibility of microorganisms to cefpodoxime. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10µg cefpodoxime disk should be interpreted according to the following criteria.

FOR SUSCEPTIBILITY TESTING OF *ENTEROBACTERIACEAE*, AND *STAPHYLOCOCCUS* SPP.

Zone Diameter (mm)	Interpretation
≥21	Susceptible (S)
18 -20	Intermediate (I)
≤17	Resistant (R)

FOR SUSCEPTIBILITY TESTING OF *HAEMOPHILUS* SPP. [k]

Zone Diameter (mm)	Interpretation [l]
≥21	Susceptible (S)

k. The zone diameter for Haemophilus spp. is applicable only to tests performed on Haemophilus Test Medium (HTM) agar incubated under 5% CO_2 (2).
l. Intermediate and Resistant criteria have not been determined.

FOR SUSCEPTIBILITY TESTING OF *NEISSERIA GONORRHOEAE.* [m]

Zone Diameter (mm)	Interpretation [n]
≥29	Susceptible (S)

m. The zone diameter for *N. gonorrhoeae* is applicable only to tests performed on GC agar base and 1% defined growth supplement incubated under 5% CO_2 (2).
n. "Intermediate" and "Resistant" categories have not been determined.

FOR SUSCEPTIBLITY TESTING OF *STREPTOCOCCUS PNEUMONIAE* [o]

Isolates of pneumococci with oxacillin zone sizes of ≥20 mm are susceptible (MIC ≤0.06µg/mL) to penicillin and can be considered susceptible to cefpodoxime for approved indications and cefpodoxime need not be tested.

o. The zone diameter for *S. pneumoniae* is applicable only to tests performed on Mueller Hinton agar with 5% sheep blood incubated in 5% CO_2 (2).

FOR SUSCEPTIBILITY TESTING OF *STREPTOCOCCUS* SPP. OTHER THAN *STREPTOCOCCUS PNEUMONIAE* [p]

A streptococcal isolate that is susceptible to penicillin (**zone diameter ≥28mm**) can be considered susceptible to cefpodoxime for approved indications, and cefpodoxime need not be tested.

p. The zone diameter for *Streptococcus* spp. is applicable only to tests performed on Mueller Hinton agar with 5% sheep blood incubated in 5% CO_2 (2).

Quality Control

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique the 10µg cefpodoxime disk should provide the following zone diameters with the quality control strains listed below.

Microorganism (ATCC ® #)	Zone Diameter Range (mm)
Escherichia coli (25922)	23-38
Haemophilus influenzae (49247)	25 - 31 [q]
Neisseria gonorrhoeae (49226)	35 - 43 [r]
Staphylocccus aureus (25923)	19-25
Streptococcus pneumoniae (49619) [t]	28 - 34 [s]

q. This zone diameter range is only applicable to tests performed on *Haemophilus* Test Medium (HTM) agar incubated in 5% CO_2.

r. This zone diameter range is only applicable to tests performed on GC agar base and 1% defined growth supplement incubated in 5% CO_2.

s. This zone diameter range is only applicable to tests performed on Mueller-Hinton agar supplemented with 5% defribinated sheep blood, incubated in 5% CO_2.

t. This organism is to be used for quality control testing for both *S. pneumoniae* and *Streptococcus* spp.

ATCC® is a registered trademark of the American Type Culture Collection

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2. NCCLS. Performance standards for antimicrobial susceptibility testing; Eighth informational supplement. NCCLS document M100-S8 [ISBN 1-56238-337-x]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1989.

3. NCCLS. Performance standards for antimicrobial disk susceptibility tests - sixth edition; approved standard. NCCLS document M2-A6 (ISBN 1-56238-306-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087 - 1898, 1997.

/S/ 10/27/98
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Review Microbiologist

cc: Original 50-675
HFD-520 Divisional File
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BD#1 and Final Initialed 10/27/98 ATS
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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
ADDENDUM TO REVIEW ASSIGNED 3/26/98, DATED 10/27/98

SUBMISSION TYPE:	DOCUMENT DATE:	CDER DATE:	ASSIGNED DATE:
NDA 50-675	12/19/97	12/22/97	11/12/98
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SE2-014			

NAME AND ADDRESS OF APPLICANT:
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DRUG PRODUCT NAME:
Proprietary: Vantin® Oral Suspension
Nonproprietary: Cefpodoxime Proxetil
Code Name/#'s: N/A
Chemical Formula (empirical): See USP

INDICATIONS:
Treatment of: Acute Otitis Media

DOSAGE FORM: Oral
STRENGTH: 50mg/5mL and 100mg/5mL
ROUTE OF ADMINISTRATION: Oral
DOSAGE/DURATION: 5mg/kg Q 12 hours (10mg/kg daily) for five (5) days.

RELATED DOCUMENTS:
IND IND NDA 50-674, DMF

REMARKS/COMMENTS:

This addendum was written to provide the information to support the labeling change to indicate that cefpodoxime should not be used for the treatment of acute otiitis media caused by penicillin-resistant *Streptococcus pneumoniae*.

This addendum provides information from the published literature on the in-vitro activity, as determined by susceptibility testing, of cefpodoxime proxetil against *Streptococcus*

pneumoniae that are intermediate and fully resistant to penicillin. This information will be correlated with the information provided by the applicant as to the concentration of cefpodoxime achieved in the middle ear fluid of patients with acute otitis media.

ETIOLOGY OF ACUTE OTITIS MEDIA

The three main causes of acute otitis media are in the order of there prevalence: *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The highest incidence of acute otitis media occurs on the age range of 1 month to 6 years (1). In a recent report on the pathogens isolated from otitis treatment failures *S. pneumoniae* with reduced susceptibility to penicillin (minimal inhibitory concentration $\geq$ 0.125µg/mL) were the organisms most commonly isolated (2).

MININAL INHIBITORY CONCENTRATION BREAKPOINTS FOR PENICILLIN AGAINST *STREPTOCOCCUS PNEUMONIAE* (3)

The breakpoints below will be used in this document as the definitions of susceptible, intermediate, and resistant strains of *S. pneumoniae* to penicillin. The articles referenced in this report will only be those that use these same criteria.

Susceptible	$\leq$0.06µg/mL
Intermediate (Moderately Susceptible)	0.12 - 1.0µg/mL
Resistant	$\geq$2.0µg/mL

INCIDENCE AND EPIDEMIOLOGY OF PENICILLIN RESISTANT *STREPTOCOCCUS PNEUMONIAE*

The incidence of *S. pneumoniae* with decreased susceptibility to penicillin in the United States has increased over the past years as indicated in the table below (4).

Susceptibility Profile of *Streptococcus pneumoniae* to Penicillin over Several Years

	Percent that are:		
Year	Susceptible	Intermediate resistance	Resistant
1979	95	5	0
1988 - 89	95	4	1
1990 - 91	80	18	2
1994 - 95	75	15	10

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The highest rates of penicillin resistance is noted in the pneumococci isolated from pediatric patients; in particular, those with infections such as otitis media and sinusitis (4). In a recent study it was shown that the highest percentage of *S. pneumoniae* resistant to penicillin occurred in the <12 month old age group (5).

ACTIVITY OF CEFPODOXIME AGAINST *STREPTOCOCCUS PNEUMONIAE* ISOLATES

The in-vitro activity of cefpodoxime against *S. pneumoniae* isolates as reported from various studies is indicated below. These articles are those which had data on the activity of cefpodoxime against isolates of *S. pneumoniae* that were intermediate as well as fully resistant to penicillin. The activity of cefpodoxime against penicillin-susceptible strains of *S. pneumoniae* is not indicated because these studies show that cefpodoxime is highly active against these strains.

In vitro activity of cefpodoxime against *S. pneumoniae* isolates* based on penicillin susceptibility

Antibiotic (reference)	Penicillin intermediate Number tested	Penicillin intermediate µg/mL MIC_{50}	Penicillin intermediate µg/mL MIC_{90}	Penicillin resistant Number tested	Penicillin resistant µg/mL MIC_{50}	Penicillin resistant µg/mL MIC_{90}
Cefpodoxime (6)		0.5	2.0		4.0	8.0
Cefpodoxime (7)	216	0.5	2.0	145	4.0	16.0
Cefpodoxime (8)	487	0.5	2.0	267	2.0	8.0
Cefpodoxime (9)	122	0.25	1.0	84	2.0	8.0
Cefpodoxime (10)		—	—	32	2.0	2.0

* All studies cited had isolates from the middle ear.

PHARMACOKINETICS:

The sponsor conducted a study (protocol M1140/0016) to determine the concentration of cefpodoxime proxetil in the middle ear of humans ages 6 months to 10 years with acute otitis media for dosage regimens of 5mg/kg (200mg max) twice a day (BID) and 10mg/kg

(400mg max) once a day. Twenty-five (25) patients were in each study group with 17 in each group being evaluable.. This protocol was a randomized, open-label study.

After at least one complete day of treatment with either regimen, tympanocentesis was performed at either 2, 4, 6 or 8 hours after the morning dose. A blood sample was collected at the same time as the tympanocentesis. The data from this study are shown below.

Median (range) of cefpodoxime concentration in middle ear effusion of pediatric patients with otitis media

	5mg/kg BID (n=17)		10mg/kg QD (n=17)	
Collection time (hr.)	No. of samples	Concentration (µg/mL)	No. of samples	Concentration (µg/mL)
2	5	2.28 (0.90 - 3.27)	5	1.72 (0.65 - 1.92)
4	6	0.98 (0.36 - 1.55)	6	3.24 (2.11 - 12.1)
6	6	0.88 (0.33 - 1.41)	3	0.55 (0.20 - 3.12)
8	5	0.97 (0.53 - 1.28)	5	1.55 (0.92 - 4.03)

The level of cefpodoxime in both the 5mg/kg BID and 10mg/kg QD regimens never reaches the MIC_{90} for penicillin-resistant *S. pneumoniae* during the entire eight hour period. Thus it is most probable that cefpodoxime would not successfully treat acute otitis media caused by penicillin-resistant *S. pneumoniae*. This conclusion is in agreement with the results of a study done recently by van Dyke (11) where he showed that patients given a single oral dose of 4mg/kg of cefpodoxime did not achieve concentrations of cefpodoxime in the middle ear fluid that were high enough to eradicate penicillin-resistant *S. pneumoniae*.

In the case of *S. pneumoniae* with intermediate resistance to penicillin the level of cefpodoxime at the two hour collection period for the 5mg/kg BID dose just achieves the MIC_{90} of these strains and for the remainder of the time is well below the MIC_{90}. For the 10mg/kg QD regimen the MIC_{90} of intermediately resistant strains is exceeded at the 6 hour collection time but the concentration of cefpodoxime is well below the MIC_{90} for the other collection times indicated. Craig in his paper (12) suggests that in order for an antibiotic to achieve a success rate of 85% to 100% the concentration of an antimicrobial most be above the MIC of the organism for better than 40% of the time. Thus according to his postulation cefpodoxime would have a success rate of less than 85% in treating acute otitis media infections caused by *S. pneumoniae* with intermediate susceptibility to

penicillin. In fact, the data provided by the applicant shows a success rate of 72% at the "Test of Cure". Whether this is due to the presence of *S. pneumoniae* with intermediate resistance to penicillin or penicillin-resistant strains is not known since the applicant was not able to provide penicillin susceptibility testing results for any of *S. pneumoniae* isolates.

CONCLUSION

The concentration of cefpodoxime achieved in the middle ear fluid is below the MIC_{90} of cefpodoxime against penicillin-resistant *S. pneumoniae*. The sponsor, in addition, is not able to provide data on the penicillin susceptibility of any of the *S. pneumoniae* isolated during the clinical trails submitted to support their requests in this application. Due to these facts the labeling for cefpodoxime proxetil (Vantin ®) should indicate for the treatment of acute otitis media caused by *Streptococcus pneumoniae* excluding penicillin-resistant strains.

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