CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-674/S-012 & NDA 50-675/S-015

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

SUBMISSION TYPE:	**DOCUMENT DATE:**	**CDER DATE:**	**ASSIGNED DATE:**
NDA 50-674	**2/23/98**	**2/24/98**	**3/26/98**
SUPPLEMENT			
SE1-012			1 of 26

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

INDICATIONS:
Treatment of "Acute Maxillary Sinusitis".

DOSAGE FORM: Tablet
STRENGTH: 100mg and 200mg
ROUTE OF ADMINISTRATION: Oral
DOSAGE/DURATION: Adults and adolescents (≥13 years old) - 200mg Q 12 hours (400mg daily)

RELATED DOCUMENTS:
IND , IND , NDA 50-675, DMF

REMARKS/COMMENTS:

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

1. The issue, as requested by the sponsor, to add the indication "Acute Maxillary Sinusitis" for both adults and adolescents (≥13 years old) to the label.
2. The issue, as raised by this Reviewer, of adding to the label the exclusion of coverage by cefpodoxime of penicillin-resistant *Streptococcus pneumoniae*

3. The issue, as raised by this Reviewer, of updating the label.

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INTRODUCTION:

This application is for a proposal to add "Acute Maxillary Sinusitis" in adults, and adolescents, caused by the following pathogens [*Haemophilus influenzae* (including beta-lactamase producing strains), *Streptococcus pneumoniae*, *Moraxella (Branhamella) catarrhalis* (including beta-lactamase producing strains), *Staphylococcus aureus*, and *Streptococcus pyogenes*] to the labeling for this product.

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

1. The issue, as requested by the sponsor, to add the indication "Acute Maxillary Sinusitis" for both adults and adolescents (≥13 years old) to the label.
2. The issue, as raised by this Reviewer, of adding to the label the exclusion of coverage by cefpodoxime of penicillin-resistant *Streptococcus pneumoniae*.
3. The issue, as raised by this Reviewer, of updating the label. This is due to the fact that the original label was developed prior to the recognized need to subdivide the microbiology section of the label into non-fastidious and fastidious organism portions.

CURRENT INDICATIONS IN 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 Maxillary Sinusitis" (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-sensitive 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. The literature reports that over 95% of *M. catarrhalis* strains isolated from clinical infections produce beta-lactamase (1). Cefpodoxime has been shown in the literature to have activity against beta-lactamase producing strains of *M. catarrhalis* (1, 2). These reports indicate MIC 90s (μg/mL) for non beta-lactamase producing strains of 0.25μg/mL and for beta-lactamase producing strains 2.0μg/mL.

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 (5) of the literature in relation to the organisms which the sponsor wishes to include in the labeling for "Acute Maxillary Sinusitis" 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. aureus - (methicillin-resistant) - 30% (9)
S. pyogenes - No evidence in the literature suggesting that there are strains of this organism resistant to penicillin.
S. pyogenes - Erythromycin resistant - 10% (1)

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 maxillary sinus infections 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 Maxillary Sinusitis" 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 in the currently approved package insert and by the NCCLS at the time of this review 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	
Neisseria gonorrhoreae ATTC® 49226	
Streptococcus pneumoniae ATTC® 49619	

*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	
Neisseria gonorrhoeae ATTC® 49226	
Streptococcus pneumoniae ATTC® 49619	

*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 (0108 and 0045) 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 Maxillary Sinusitis" to their label were originally determined from data submitted in support of their original label claims. These disc diffusion interpretive criteria were:

Disc Diffusion (10µg) 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 Maxillary Sinusitis" 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 Maxillary Sinusitis".

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:

No information presented in this NDA supplement as to the concentrations of cefpodoxime achieved in the maxillary sinuses when given the dosages which are being requested for patient treatment by the sponsor. The clinical efficacy study results were based on clinical response. In a study of the bioavailability of cefpodoxime proxetil from a tablet relative to an oral solution it was found that the bioavailability from a tablet was 82% relative to an oral suspension (13).

CLINICAL EFFICACY

CLINICAL MICROBIOLOGY:

Isolates - Relevance to Proposed Indications

Acute Maxillary Sinusitis:
Haempohilus influenzae (including beta-lactamase producing strains)
Streptococcus pneumoniae
Moraxella catarrhalis (including beta-lactamase producing strains)
Staphylococcus aureus (including penicillinase producing strains and methicillin-susceptible strains)
Streptococcus pyogenes

These organisms have been shown to be associated with acute maxillary sinusitis and are thus appropriate for this indication (14, 15).

Overall Correlation of Therapeutic Data with Susceptibility Test Results

Acute Maxillary Sinusitis Study Results

Clinical trial results for three clinical studies were submitted to support the sponsors request for use of cefpodoxime for the treatment of "acute maxillary sinusitis". These were:

Protocol 0045: A multicenter, randomized, observer-blind, parallel group study with maxillary sinus aspiration at baseline to compare the efficacy and safety of cefpodoxime and amoxicillin/clavulanate in the treatment of adult (18 to 79 years) outpatients with signs and symptoms of acute maxillary sinusitis. Patients were assigned to receive cefpodoxime 200 mg every 12 hours or amoxicillin/clavulanate 500 mg every 8 hours for 10 days.

Protocol 0108: A multicenter, uncontrolled, open-label single agent study (cefpodoxime) with maxillary sinus aspiration at baseline to establish clinical cure and pathogen

eradication. Patients received cefpodoxime 200 mg every 12 hours, without regard to meals, for 10 days.

Protocol 0109: A multicenter, randomized, double-blind, parallel group study to compare the efficacy and safety of cefpodoxime and loracarbef in the treatment of adult (≥18 years) outpatients. No maxillary sinus aspirates were obtained at baseline in this study. Patients were assigned to receive cefpodoxime 200 mg every 12 hours or loracarbef 400 mg every 12 hours, one hour before meals, for 10 days.

Two measures of efficacy were employed in the analyses of these studies. Clinical efficacy, the abatement of clinical signs and symptoms, was assessed in all three studies at the post-treatment visit and follow-up. Bacteriologic efficacy, the eradication of infecting organisms, was assessed in studies 0045 and 0108 at the post-treatment visit and final follow-up (0108 only).

Susceptibility testing interpretive criteria for those cases where a study pathogen was isolated and susceptibility testes were as noted under "INTERPRETIVE CRITERIA FOR SUSCEPTIBILITY TESTING USED DURING THE CLINICAL TRIALS FOR THIS NDA SUPPLEMENT".

STUDY RESULTS

Following are the data as provided by the sponsor to support their request for inclusion of "Acute Maxillary Sinusitis" in the Vantin label.
BACTERIOLOGIC OUTCOME RESULTS:
STUDY 045: In this study only 3 of 44 evaluable patients had a culture taken at the post-treatment visit thus all bacteriologic outcomes are based on clinical outcomes.

Bacteriologic Eradication Rates

	Cefpodoxime	Amoxicillin/clavulanate
Number Evaluable	26	18
Pathogen	E/N [1] (%)	E/N (%)
S. pneumoniae	8/8 (100)	5/5 (100)
H. influenzae	7/7 (100)	5/5 (100)
M. catarrhalis	1/1 (100)	3/3 (100)
S. aureus	4/5 (80.0)	2/2 (100)
S. pyogenes	0/0	0/0
Fusobacterium sp.	1/1 (100)	0/0

Haemophilus sp.	1/1 (100)	0/0
Klebsiella pneumoniae	2/2 (100)	0/1 (0)
Staphylocccus coag. neg. beta-lac +	2/2 (100)	0/0
Streptococcus agalactiae	0/0	1/1 (100)
Streptococcus constellatus	0/0	1/1 (100)
Streptococcus intermedius	1/1 (100)	1/1 (100)
Streptococcus sanguis	0/0	1/1 (100)
Streptococcus viridans	0/0	2/2 (100)
Streptococcus viridans #2	0/0	1/1 (100)
Streptocccus, Grp C	0/1 (0.0)	0/0
TOTAL Response	27/29 (93.1)	22/23 (95.7)

1. E = patients from whom pathogen eradicated; N = evaluable patients (patients with initial pathogen and assessable response at postreatment).

STUDY 108

Bacteriologic Eradication Rates = E/N [1] (%)

Cefpodoxime
Number Evaluable = 126

Pathogen	
S. pneumoniae	36/38 (94.7)
H. influenzae	35/37 (94.6)
M. catarrhalis	13/13 (100)
S. aureus	40/45 (88.9)
S. pyogenes	6/7 (85.7)
TOTAL Response	130/140 (92.9) [2]

1. E = patients for whom pathogen was eradicated; N = evaluable patients (patients with initial pathogen and assessable response at posttreatment)
2. Includes only the five pathogens which were evaluated in Study 108

CEFPODOXIME ERADICATION RATES
Including Clinical Success if No Culture Obtained Posttreatment
Studies M/1140/0108 and M1140/0045

Pathogen	Cefpodoxime N=152 E/N [1.] (%)
S. pneumoniae [a.]	44/46 (95.7)
H. influenzae [b.]	42/44 (95.5)
M. catarrhalis [c.]	14/14 (100.0)
S. aureus	44/50 (88.0)
S. pyogenes	6/7 (85.7)

1. E = Patients from whom pathogen is eradicated; N = evaluable patients (patients with initial pathogen and assessable pathogen response at posttreatment)
a. Number of penicillin intermediate and resistant isolates not noted by sponsor
b. Sixteen (16) isolates were shown to be beta-lactamase producers
c. Twelve (12) isolates were shown to be beta-lactamase producers

Bacteriologic Outcome by Patient
(Based on eradication including clinical success if no culture obtained post-treatment)

Study	108 (Cefpodoxime) N [1.] = 126 n [2.] (%)	045 (Cefpodoxime) N = 26 n (%)	108 + 045 (Cefpodoxime) N = 152 n (%)	045 (Amoxicillin/clavulanate) N = 18 n (%)
Response				
Cured	115 (91.3)	24 (92.3)	139 (91.4)	17 (94.4)
Failure	10 (7.9)	2 (7.7)	12 (7.9)	1 (5.6)
Superinfection [3.]	1 (0.8)	not avail.	not avail.	not avail.

1. N = evaluable patients
2. n = patients with outcome
3. This category not available in study 045.

CLINICAL OUTCOME RESULTS:

The following tables indicate the combined clinical outcome for trials 045, 108 and 109 posttreatment and follow-up.

Clinical Outcomes - All Studies - Posttreatment

	Cefpodoxime	Loracarbef	Amoxicillin/clavulanate
Total Number [1.]	315	170	18
Results [2.]			
Success [3.]	286 (90.8%)	142 (83.5%)	17 (94.4%)
Cured	174 (55.2%)	75 (44.1%)	9 (50%)
Improved	112 (35.6%)	67 (39.4%)	8 (44.4%)
Failure [4.]	29 (9.2%)	28 (16.5%)	1 (5.6%)
Missing	0	0	0

1. Total number = cured, improved and failure
2. It should be noted that the clinical cure rates presented in this table do not include in the calculation those patients who were failures at the posttreatment assessment. When these patients are returned to the demominators, the final clinical cure rates at final follow-up are as follows: Cefpodoxime = 64.7%, Loracarbef = 60.6%, Amoxicillin/clavulanate = 55.6%.
3. Cured or Improved
4. Includes Unchanged, Worsened, Failure, Side Effect Failure, and recurrence/Relapse, as applicable.

Clinical Outcomes - All Studies - Follow-up [1.]

	Cefpodoxime	Loracarbef	Amoxicillin/clavulanate
Total Number	280	137	17
Results			
Success	NA [a.]	NA	NA
Cured	200 (71.4%)	100 (73.0%)	10 (58.8%)
Improved	9 (3.2%) [b.]	not available	5 (29.4%) [b.]
Failure	71 (25.4%)	36 (26.3%)	2 (11.8%)
Missing	0	1 (0.7%)	0

1. Includes only patients who were a Clinical Success at posttreatment
a. NA = not applicable
b. Study/0045 only

SUMMARY

The "Bacteriologic Eradication" and the "Clinical Outcome" results, as provided by the sponsor, have been determined by this Reviewer to indicate that when cefpodoxime proxetil tablets are given as proposed this product appears efficacious in treating "Acute Maxillary Sinusitis" caused by the following organisms:
Haemophilus spp.(including beta-lactamase producing strains), *M. catarrhalis* (including beta-lactamase-producing strains), *S. pneumoniae*, *S. aureus* (methicillin-susceptible strains), and *S. pyogenes*. The numbers of *S. pyogenes* isolates is very small and based on numbers alone granting indications for this organism is not recommended.

The percentages of *M. catarrhalis* and *H. influenzae* isolated in these studies that were beta-lacatamase 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).

The disc diffusion interpretive criteria used in 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.

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 Maxillary Sinusitis" caused by the following organisms to be included in the label: *Haemophilus influenzae* (including beta-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), *Moraxella* (*Branhamella*) *catarrhalis* (including beta-lactamase producing strains), and *Staphylococcus aureus* (including penicillinase producing strains).

It is necessary, however, to add to all *Streptococcus pneumoniae* claims "penicillin-susceptible strains only".

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

REFERENCES

1. Doern, GV, AB Brueggemann, G Pierce, T Hogan, H Preston Holley, Jr., and A Pauch. 1996. Prevalence of antimicrobial resistance among 723 outpatient clinical isolates of *Moraxella catarrhalis* in the United States in 1994 and 1995; Results of a 30-center national surveillance study. Antimicrob Agents Chemo **40**:2884 - 2886.
2. Schatz, BS, KT Karavokiros, MA Taeubel, and GS Itokazu. 1996. Comparison of cefprozil, cefpodoxime proxetil, loracarbef, and ceftibuten. Annals of Pharmacotherapy **30**: 258 - 268.
3. Doern, GV, A Brueggemann, HP Holley, Jr., and AM Rauch. 1996. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients during the winter months of 1994 to 1995: Results of a 30-center national surveillance study. Antimicrob Agents Chemother **40**:1208 - 1213.
4. Urbaskova, P, J Trupl, H Hupkova, PC Appelbaum, and MR Jacobs. 1996. In vitro susceptibility of pneumococci to trovafloxacin, penicillin G, and other antimicrobial agents in the Czech Republic and Slovakia. Eur J Clin Microbiol Infect Dis **15**:686 - 688.
5. Balow, CH, RN Jones, DM Johnson, JA Deinhart, JJ Schentag, and the SPAR Study Group. 1997. Comparative in vitro assessment of sparfloxacin activity and spectrum using results from over 14,000 pathogens isolated at 190 medical centers in the USA. Diagn Microbiol Infect Dis **29**:173 - 186.
6. Thomson, KS, SA Chartrand, CC Sanders, and SL Block. 1997. Trovafloxacin, a new fluoroquinolone with potent activity against *Streptococcus pneumoniae*. Antimicrob Agents Chemother **41**:478 - 480.
7. Sanders, CC, and WE Sanders, Jr. 1992. ß-lactamase resistance in gram-negative bacteria: global trends and clinical impact. Clin Infect Dis **15**:824-839.
8. Doern, GV, AB Brueggemann, G Pierce, HP Holley, Jr., and A Rauch. 1997. Antibiotic resistance among clinical isolates of *Haemophilus influenzae* in the United States in 1994 and 1995 and detection of β-lactamase-positive strains resistant to amoxicillin-clavulanate: Results of a national multicenter surveillance study. Antimicrob Agents Chemother **41**:292 -297.
9. Panililio, A, DH Culver, RP Gaynes. 1992. Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals, 1975-1991. Infect Control Hosp epidemiology **13**:582-586.
10. 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.
11. NCCLS. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - fourth edition; Approved standard. NCCLS document M7-A4 (ISBN 1-56238-309-4). NCCLS, 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898, 1997.

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.
13. Borin, MT, KK Forbes, and GS Hughes. 1995. The bioavailability of cefpodoxime proxetil tablets relative to an oral solution. Biopharmaceuticals & Drug Disposition 16: 295 - 302.
14. Sydow, CV, S Savolainen, and A Soderqvist. 1995. Treatment of acute maxillary sinusitis - comparing cefpodoxime proxetril wit amoxicillin. Scand J Infect Dis **27**:229 - 234.
15. Gwaltney, Jr., JM, WM Scheld, MA Sande, and A Syndor. 1992. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: A fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy and Clin Immunology **90**:457 - 462.

PROPOSED CEFPODOXIME PROXETIL TABLET 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 SUSCEPTIIBILITY 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) [j]	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 SUSCEPTIIBILITY 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

REFERENCES

1. NCCLS. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - fourth edition; Approved standard. NCCLS document M7-A4 (ISBN 1-56238-309-4). NCCLS, 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898, 1997.
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
Frederic J. Marsik, Ph.D.
Review Microbiologist

cc: Original 50-674
HFD -520 Divisional File
HFD-520/MO/H. Hamilton
HFD-520/Micro/F. Marsik
HFD-520/MO/R. Viraraghavan
HFD-520/Stats/J. Jiang
HFD-520/Bio/J. Zheng

Concurrence Only

HFD-520/Dep/Dir/L. Gavrilovich

HFD-520/TLMicro/A.T.Sheldon
BD#1 Initialed 9/30/98, Final 10/27/98 ATS
10/27/98
10/28/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-674/S-012 & NDA 50-675/S-015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVEIW

NDA number:	50-674/S012, 50-675/S015
Submission date:	January 22, 1998
Product	Vantin® (cefpodoxime proxetil)
Sponsor:	Pharmacia & Upjohn Trading Corporation
Type of submission:	Efficacy supplement
Reviewer:	Jenny Zheng, Ph.D.
Date received for reviewing:	March 25, 1998

BACKGROUND:
This supplement (NDA 50-754) proposed the treatment of acute maxillary sinusitis in both adult and pediatric patients by Vantin®. Three clinical trials were conducted in adult patients and the sponsor requests approval for pediatric patients also based on the similarity of the course of disease and the drug efficacy between adult and pediatric patients as well as two bioequivalence studies and one PK study in pediatric patients.

The three pharmacokinetic studies were reviewed by Dr. Safaa Ibrahim dated March 21, 1991 in original review (NDA 50-674 & 50-675).

1. Borin MT, Forbes KK, Hughes GS. Bioequivalence study of cefpodoxime proxetil flavored granules and tablets. Upjohn Technical Report 7215-90-030, Dec.20, 1990.
2. Borin MT, Forbes KK, Hughes GS. Bioequivalence study of two formulations of cefpodoxime proxetil flavored granules. Upjohn Technical Report 7215-90-037, Dec. 28, 1990.
3. Borin MT, Forbes KK, Hughes GS. The pharmacokinetics of cefpodoxime in pediatric patients following administration of cefpodoxime proxetil oral suspension. Upjohn Technical Report 7215-94-012, May 13, 1994. Subsequently published as Kearns GL, Durville T, Wells TG, Jacobs RF, Hughs GS, Borin MT. Single-dose pharmacokinetics of cefpodoxime proxetil in infants and children. Drug Invest, 1994; 7:221223.

It was found that cefpodoxime proxetil suspension is bioequivalent with tablet.

Pharmacokinetic parameters obtained from pediatric patients and adults are tabulated in table 1. The concentration vs time profiles are also attached. The results indicate that C_{max} and AUC of pediatric subjects from age 7 to 18 are comparable to that of adults although the half-life is slightly shorter in that group of children. The short half-life may result from the truncated sampling schedule in the pediatric study. Plasma samples were collected until 12 and 24 hours for pediatric and adult study, respectively. For the children who are less than 6 years old, the C_{max} is lower and the clearance is higher after normalized by body weight. In this case, children who are less than 6 years old may have less exposure.

The profiles of mean plasma concentration vs. time in pediatric patients and adults are shown in figures 1 and 2. It is known that for the cephalosporin class agents the efficacy

can be well predicted by the parameter of time above minimal inhibitory concentration (MIC) within dose interval. The MIC_{90} values are 0.05, 0.24 and 0.63 μg/mL for penicillin-susceptible *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, respectively. The values of time above MIC_{90} within 12 hours are extrapolated from profiles of mean plasma concentration vs. time and listed in table 2. It should be emphasized that the values are extrapolated using **MEAN** plasma concentration vs. time profiles. Some patients may have higher values and some patients may have lower values.

Table 1. Mean (SD) Cefpodoxime Pharmacokinetic Parameters in Pediatric Patients After a Single 5 mg/kg (200 mg Maximum) Dose of Cefpodoxime Proxetil Oral Suspension in Protocol P/1140/0032 and in adults after 200 mg Dose of Cefpodoxime Proxetil Tablet in Protocol R/1140/4900 and Protocol R/1140/4901

Projected age	0.5-2 years	3-6 years	7-12 years	13-18 years	Adult[b]	Adult[c]
Observed age	1-2.75 years	4.08-6.75 years	7.75-12.8 years	13.2-17.2 years		
	A[a] (n=5)	B (n=8)	C (n=9)	D (n=7)	n=8	n=8
C_{max} (μg/mL)	1.83 (0.30)	1.91 (0.49)	2.76 (0.64)	2.27 (0.48)	2.34 (0.76)	2.34 (0.88)
T_{max} (h)	2.8 (0.45)	2.6 (0.74)	2.4 (0.73)	2.4 (0.54)	2.25 (0.46)	2.38 (0.84)
λ_z (h^{-1})	0.45 (0.11)	0.37 (0.03)	0.42 (0.05)	0.35 (0.05)	NA	NA
Half life (h)	1.5	1.9	1.7	2.0	2.45	2.29
$AUC_{0-\infty}$ (μg•h/mL)	9.62 (1.86)	9.99 (2.48)	13.4 (2.99)	12.3 (2.50)	13.1 (3.64)	13.5 (5.26)
CL_{po} (mL/min)	95.5 (33.5)	191 (62.3)	232 (93.3)	280 (52.2)	268 (62)	279 (101)
CL_{po} (mL/min/kg)	8.93 (1.81)	8.91 (2.88)	5.96 (1.37)	4.80 (1.21)	NA	NA
V_β/F (L)	13.0 (4.43)	30.9 (10.0)	24.8 (20.3)	48.8 (12.5)	NA	NA
V_β/F (L/kg)	1.22 (0.248)	1.45 (0.476)	0.88 (0.348)	0.84 (0.32)	NA	NA
f_e	34.1	24.4 (6.5)	31.1 (13)	24.3 (10)	NA	Na
CLr (mL/min)	35.1	43.3 (13.4)	69.3 (35.9)	70.9 (26.6)	84.4 (17)	78.7 (16)
CLr (mL/min/kg)	2.81	2.04 (0.497)	1.83 (0.835)	1.22 (0.385)	NA	NA

a. one subject spat out ~1/3 of administered dose.
b. Retrieved from Dr. Safaa Ibrahim's review (Protocol R/1140/4900).
c. Retrieved from Dr. Safaa Ibrahim's review (Protocol R/1140/4901).

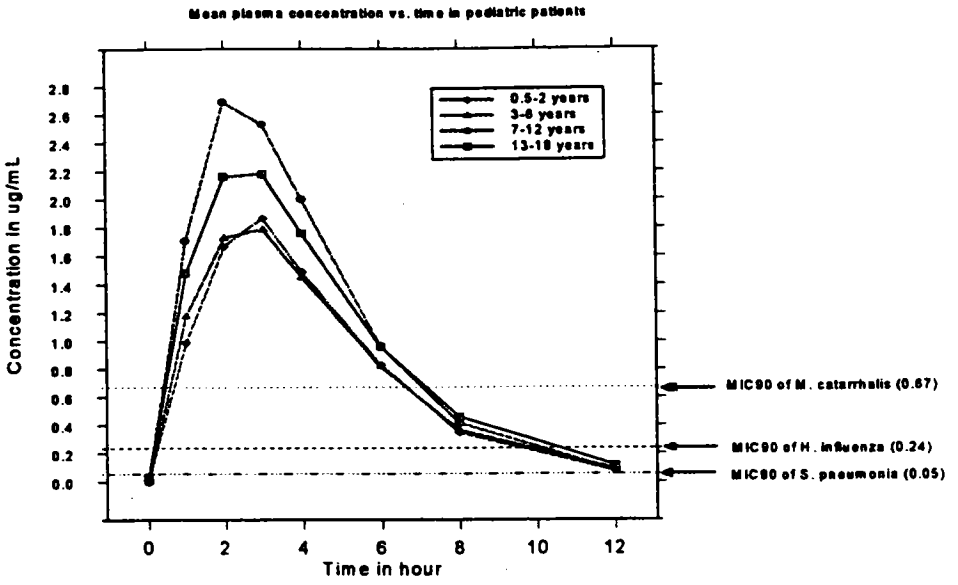


Table 2. The Values of Time above MIC_{90} for the Common Pathogens of Sinusitis

		Time above MIC_{90} within 12 hours (%)				
	MIC_{90}(μg/mL)	**0.5-2 years**	**3-6 years**	**7-12 years**	**13-18 years**	**Adults**
S. pneumoniae	0.05	>90	>90	>90	>90	>90
H. influenzae	0.24	>75	>75	>80	>80	>80
M. catarrhalis	0.67	~50	~50	~60	~60	~60

As shown in table 2, for the pathogens of *S. pneumoniae* and *H. influenzae*, the values of time above MIC_{90} within dose interval are similar between the pediatric patients and adults. However, for the *M. catarrhalis*, the value of time above MIC_{90} is slightly lower in children who are 0.5- 6 years old. It becomes a concern when considering the causative pathogens for acute sinusitis in children and adults. In adults, approximately 2% of infections are due to *M. catarrhalis*. However, in children, *M. catarrhalis* is the causative organism in 20%-25% of childhood maxillary sinus infections. Therefore, due to the lower value of time above MIC_{90} for *M. catarrhalis* and more frequent infection caused by *M. catarrhalis* in children, the probability of failing cefpodoxime treatment is higher in children.

COMMENTS:

1. The pharmacokinetic data were obtained from children who are 1-18 years old. No information is available for the children who are younger than 1 years old. Therefore, it is recommended that a footnote should be added in the labeling to clearly state that no information is available for children who are less than 1 years old.

2. The pharmacokinetics of cefpodoxime proxitel is similar between adults and children who are older than 6 years old. Although C_{max} is smaller for the children who are younger than 6 years old, for the pathogens of *S. pneumoniae* and *H. influenzae*, the values of time above MIC_{90} within dose interval in the children are more than 80%. However, for the *M. catarrhalis*, the value of time above MIC_{90} is about 50%. If the value of 50% of time above MIC_{90} is marginal for efficacy, it can be problematic considering the fact that infections caused by *M. catarrhalis* are more frequent in children than adults (20-25% vs 2%).

RECOMMENDATION:
The application is acceptable.

/S/ 11-2-98

Jenny Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT initiated by F. PELSOR, Pharm.D., Team Leader /S/ 11/2/98

cc:
Division File: NDA 50-674/S012, 50-675/S015
HFD-520 (H. Hamilton, MO)
HFD-520 (C. Debellas, CSO)

HFD-340 (Viswanathan)
HFD-880 (Division File)
HFD-880 (F. Pelsor, TL)
HFD-880 (J Zheng, Reviewer)
CDR (attn: B. Murphy)

Protocol R/1140/4900

RESULTS:

Table 2
Mean(SD) Pharmacokinetic Parameters of Cefpodoxime After single oral doses To healthy Volunteers

	Dose, mg					
Parameter	100 mg	200 mg	400 mg	600 mg	800 mg	ANOVA
AUC mcg.h/ml	7.38 (2.85)	13.1 (3.64)	22.7 (4.90)	38.8 (6.04)	44.3 (7.55)	0.0001
AUC/Dose mcg.h/ml	7.38 (2.85)	6.56 (1.82)	5.67 (1.23)	5.96 (1.01)	5.54 (0.95)	NS*
Cmax mcg/ml	1.45 (0.46)	2.34 (0.76)	3.72 (0.97)	5.31 (1.20)	6.61 (1.64)	0.0001
Cmax/Dose mcg/ml	1.45 (0.46)	1.17 (0.38)	0.93 (0.24)	0.89 (0.20)	0.83 (0.21)	0.0023
Tmax h	2.00 (0.66)	2.25 (0.46)	2.56 (0.82)	3.25 (1.28)	2.86 (0.69)	0.0426
t1/2,h	2.09	2.45	2.84	2.75	3.15	
MRT h	4.12 (0.61)	4.76 (0.69)	5.31 (0.85)	5.71 (1.03)	5.68 (0.78)	0.0015
CLp/F ml/min	249 (71)	268 (62)	305 (58)	288 (56)	309 (54)	NS
CLr ml/min	97.6 (30)	84.4 (17)	96.0 (11)	84.7 (13)	81.2 (9.9)	NS
fe % Dose	39.53 (4.9)	23.3 (6.5)	23.3 (5.3)	30.0 (5.0)	26.8 (4.6)	0.0001

*(Not significant at P>.05)

Plots of mean cefpodoxime plasma concentrations (Cp) and mean Cp/Dose versus time profiles are presented in figure 1.

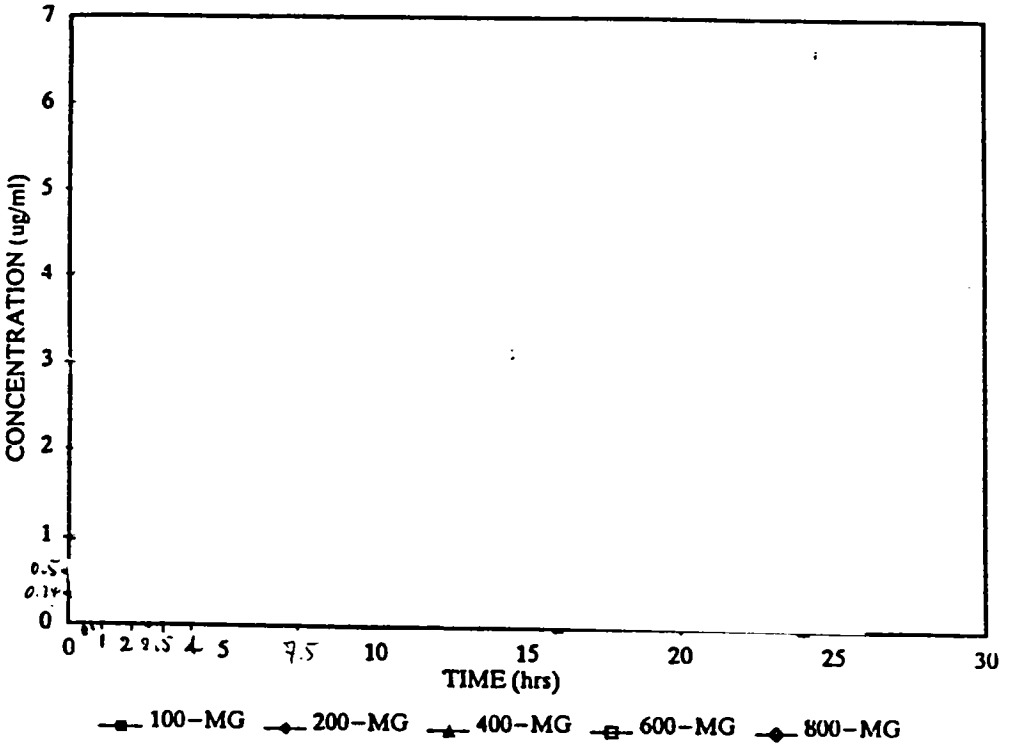
Statistically significant differences were observed in Cmax/Dose,, Tmax, t1/2, MRT and fe (table 2). Differences in AUC/Dose were not significant (12% to 33%). Linear regression analysis of AUC/Dose, Cmax/Dose and fe versus dose revealed statistically significant nonzero intecept terms.

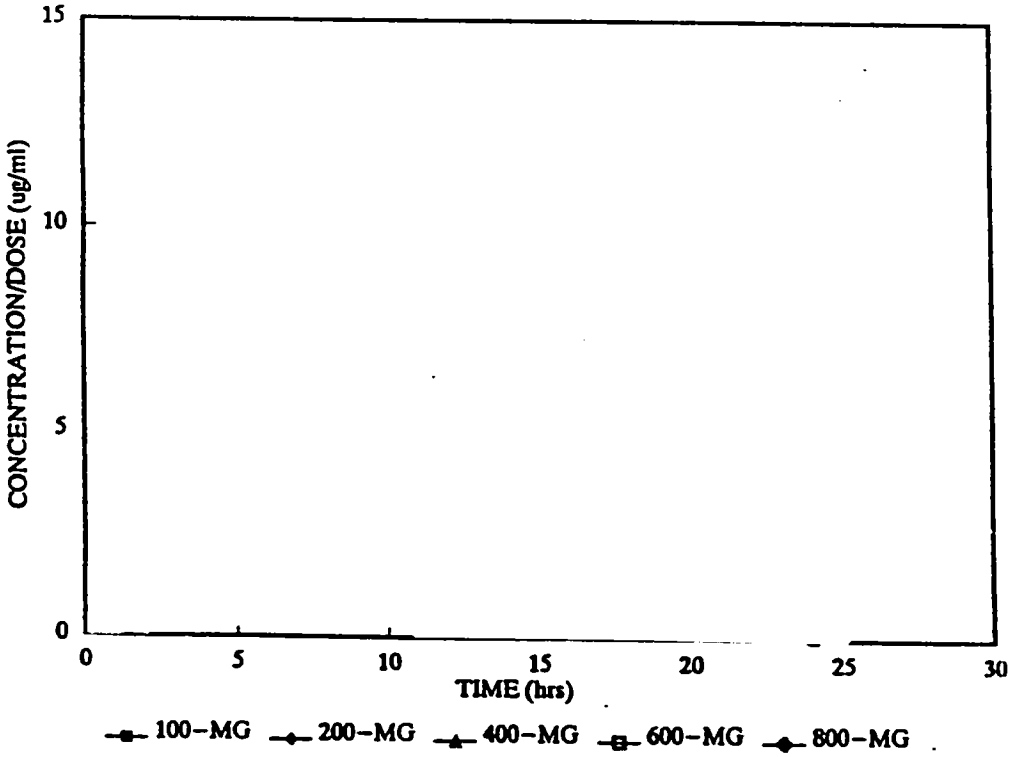
COMMENT: The sponsor attriputed the observed differences in the kinetic parameters as a function of dose to a slight dose-dependency in the pharmacokinetics of cefpodoxime. A full characterization of drug kinetics after an intravenous or oral solution administration is necessary in order to illustrate the dose-dependency cefpodoxime.

CONCLUSION: The observed differences in Cmax/Dose, AUC/Dose and Tmax among doses may be attributed to saturable mechanism involved in cefpodoxime absorption in the intestinal tract or due to solubility/dissolution limitation as the dose of cefpodoxime proxetil increased.

Protocol RL1-40/4900

Figure 2





Protocol R/1140/4901

RESULTS:

Mean(SD) Pharmacokinetic Parameters Derived For Cefpodoxime After Twice a Day Administration of Cefpodoxime Proxetil Tablets To Healthy volunteers

First Dose:

	DOSE (mg)			
PARAMETER	100	200	400	ANOVA
AUC,mcg.h/ml	6.90 (2.49)	13.5 (5.26)	23.9 (7.63)	0.0001
AUC/D,mcg.h/ml	6.90 (2.49)	6.74 (2.63)	5.97 (1.91)	NS*
Cmax,mcg/ml	1.23 (0.52)	2.34 (0.88)	3.76 (1.17)	0.0001
Cmax/D,mcg/ml	1.23 (0.52)	1.17 (0.44)	0.94 (0.29)	NS
Tmax,h	2.25 (0.54)	2.38 (0.84)	3.07 (0.02)	NS
t1/2,h	2.28	2.29	2.24	
CLp/F,ml/min	271 (97)	279 (101)	306 (102)	NS
CLr,ml/min	79.0 (19)	78.7 (16)	85.2 (9)	NS
fe,% Dose	29.5 (7.0)	29.5 (10)	28.7 (10)	NS
MRT,h	4.73 (0.67)	4.93 (0.66)	5.36 (0.65)	NS

*(Not Significant)

Last Dose (29th):

	DOSE (mg)			
Parameter	100	200	400	ANOVA
AUC,mcg.h/ml	6.56 (2.02)	11.8 (3.49)	20.5 (4.53)	0.0001
AUC/D,mcg.h/ml	6.56 (2.02)	5.90 (1.74)	5.12 (1.13)	NS*
Cmax,mcg/ml	1.19 (0.41)	2.23 (0.71)	3.62 (0.62)	0.0001
Cmax/D,mcg/ml	1.19 (0.41)	1.11 (0.35)	0.91 (0.16)	NS
Tmax,h	1.88 (0.52)	2.00 (0.27)	2.43 (0.61)	NS
t1/2,h	2.28	2.32	2.27	
CLp/F,ml/min	275 (79)	304 (86)	339 (74)	NS
CLr,ml/min	93.3 (22)	87.9 (16)	95.8 (18)	NS
fe,% Dose	35.3 (9.0)	30.3 (7.0)	29.2 (7.0)	NS
MRT,h	4.67	4.59	4.97	
R	1.04 (0.03)	1.05 (0.02)	1.06 (0.04)	

*(Not Significant)

Plots of mean cefpodoxime plasma concentrations (Cp) and mean Cp/Dose versus time profiles after 100-,200- and 400- mg doses bid of cefpodxime proxetil tablets are presented in figure 1.

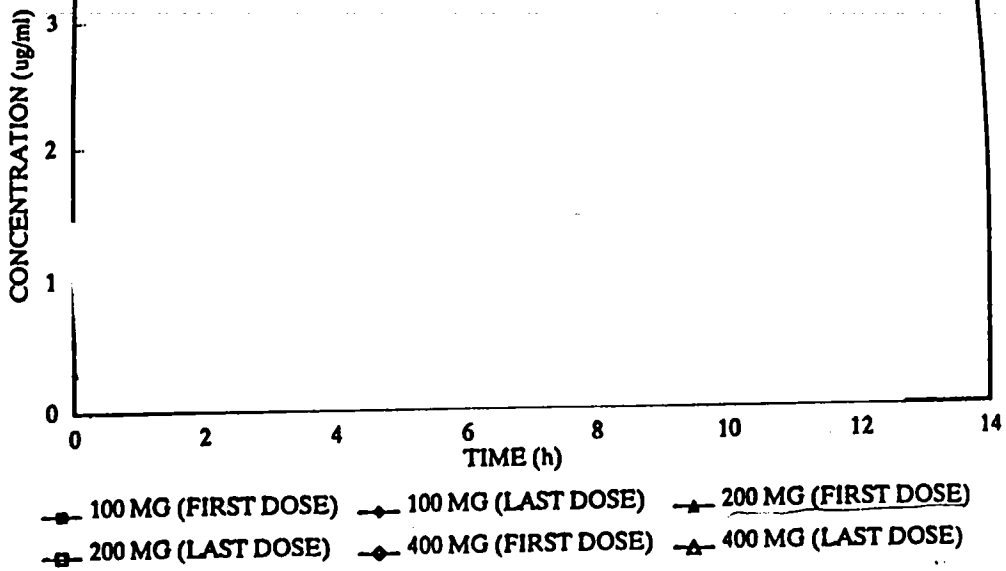
AUC/Dose and Cmax/Dose were not significantly different among dose groups after the first and last doses ($p>0.05$, ANOVA).

CLr was statistically significantly different ($p<0.05$, paired t-test) between the first and last dose.

Comments: The above observations may be attributed uncorrectly to a slight dose-dependency, intravenous data or data after oral

Protocol R/1140/4901

Figure 1



100 MG (FIRST DOSE) 100 MG (LAST DOSE) 200 MG (FIRST DOSE)
200 MG (LAST DOSE) 400 MG (FIRST DOSE) 400 MG (LAST DOSE)