CENTER FOR DRUG EVALUATION AND RESEARCH

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

MEDICAL REVIEW(S)

Medical and Statistical Review of NDAs 50-674 and 50-675, S-012: Vantin® (cefpodoxime proxetil) Tablets for the Treatment of Acute Maxillary Sinusitis

Applicant: Pharmacia & Upjohn
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Date of Submission: January 20, 1998
CDER Stamp Date: January 22, 1998
Date Review Completed: September 17, 1998

Drug, Formulation & Route of Administration: Vantin® (cefpodoxime proxetil) tablet, oral administration
Vantin® Oral Suspension, oral administration

Proposed labeling submitted by Applicant:

Materials Reviewed:

- ◊ Volumes 1 through 28 and supplements submitted by applicant
- ◊ NDAs 20-634 Levaquin® (levofloxacin) and 19-537, supplement 29 CIPRO® (ciprofloxacin)
- ◊ Advisory Committee Minutes, March 3, 1998, Acute Sinusitis, pp.158-219
- ◊ DAIDP's Evaluability Criteria for Acute Maxillary Sinusitis (DRAFT)
- ◊ DAIDP's Points to Consider document
- ◊ "Sinusitis" in Evaluation of New-Anti-Infective Drugs for the Treatment of Respiratory Tract Infections by Chow AC, Hall CB, Klein JO, Kammer, Meyer RD, Remington JS. CID 1992;15(suppl 1):S73-S77.
- ◊ Chow AC. "Infections of the Sinuses and Parameningeal Structures" in Infectious Diseases, eds. Gorbach SL, Bartlett JG, Blacklow NR (WB Saunders Co: Philadelphia), 2nd ed., 1998, pp. 517-529.
- ◊ Gwaltney JM Jr., "Sinusitis" in Principles and Practice of Infectious Diseases, eds. Mandell GL, Bennett JE, Dolin R (Churchill Livingstone: New York), 4th ed., 1995, pp. 585-590.
- ◊ Gwaltney JM Jr. Acute Community-Acquired Sinusitis, CID 1996;23:1209-25.

Regulatory Background and Current Relevant Labeling:

NDA 50-674 & 50-675 was approved on August 7, 1992 for the following indications: Lower Respiratory Tract, Sexually Transmitted Diseases, Skin and Skin Structures, Upper Respiratory Tract, and Urinary Tract. Relevant to this application, the current label lists the following infections and organisms:

- ◊ Community-acquired Pneumonia caused by *S. pneumoniae* and *H. influenzae* (including beta-lactamase-producing strains),
- ◊ Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae* and *H. influenzae* (non-beta-lactamase-producing strains) [1], or *M. catarrhalis*.,
- ◊ Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *Streptococcus pyogenes*,
- ◊ Acute otitis media caused by *Streptococcus pyogenes* , *H. influenzae* (including beta-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis*.,
- ◊ Pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes*.

For the tablet formulation , the recommended dosages and durations for the above relevant indications are:

- ◊ Community-acquired pneumonia, 200 mg Q 12 hours for 14 days
- ◊ Acute exacerbation of chronic bronchitis, 200 mg Q 12 hours for 10 days.
- ◊ Skin and skin structure, 400 mg Q 12 hours for 7 to 14 days
- ◊ Pharyngitis and/or tonsillitis, 100 mg Q 12 hours for 5 to 10 days

For adults, the dosages and durations for the oral suspension are equivalent to the tablets.

[1] It was noted in the label that the exclusion of beta-lactamase-producing strains for the indication of Acute bacterial exacerbation of chronic bronchitis was because the data submitted was insufficient. There was no suggestion that the data was inadequate.

For infants and children aged 5 months through 12 years, the current label recommends the following:

Type of Infection	Total Daily Dose	Dose Frequency	Duration
Acute Otitis Media	10 mg/kg/day (Max 400 mg/day)	10 mg/kg/24 h (Max 400 mg/dose) or 5 mg/kg/12 h (Max 200 mg/dose)	10 days
Pharyngitis and/or tonsillitis	10 mg/kg/day (Max 200 mg/day)	5 mg/kg/12 h (Max 100 mg/dose)	5 to 10 days

Although an application for Acute Maxillary Sinusitis was submitted with the original NDA, it was rejected because too few subjects were studied. The Applicant contacted DAIDP on August 21, 1996 to arrange a teleconference to discuss the current supplement, to seek clarification of Points to Consider, and to review the data presentation plan. The topics discussed and DAIDP's recommendations for the submission were described in a letter from the Applicant to DAIDP dated September 27, 1996. A letter from the Applicant to DAIDP dated December 30, 1996 summarizes the studies to be submitted. An additional letter dated February 12, 1997 requests acknowledgment from DAIDP that the application would be accepted with only 13 isolates of *Moraxella catarrhalis* and if that data was found convincing, would serve as the basis for a claim.

Clinical Studies:
In support of this application, the following studies were submitted:

Chart 1: Studies Submitted in support of NDA 50-674

Protocol	Study Type	Dose Frequency and Duration	Number of Patients Enrolled and Evaluable
M/1140/0109	Multicenter, randomized, double-blind, controlled trial	Cefpodoxime 200 mg bid for 10 days	cefpodoxime 188 enrolled, 163 evaluable
		loracarbef 400 mg bid for 10 days	loracarbef 189 enrolled, 170 evaluable
M/1140/0108	Multicenter, open-label, uncontrolled trial	Cefpodoxime 200 mg bid for 10 days	cefpodoxime 488 enrolled, 126 evaluable
M/1140/0045	Multicenter, randomized, observer-blind, controlled trial	Cefpodoxime 200 mg bid for 10 days	cefpodoxime 78 enrolled, 26 evaluable
		amoxicillin/clavulanate 500 mg tid for 10 days	amoxicillin/clavulanate 75 enrolled, 18 evaluable

Study Title: Comparison of Oral Cefpodoxime Proxetil (Vantin®) with Oral Loracarbef (Lorbid™) in the Treatment of Acute Maxillary Sinusitis in Adults (Protocol M/1140/109)

Study dates: February 1, 1995 to May 10, 1996

Study objectives: To compare the clinical efficacy and safety of orally administered cefpodoxime proxetil with loracarbef in the treatment of acute maxillary sinusitis in adults.

Study design: This is an prospective, randomized, double-blind, controlled, multicenter study. See Chart 2 (following) for specifics of study design, observations and measurements.

Dosage: cefpodoxime proxetil 200 mg orally every 12 hours for 10 days or loracarbef 400 mg orally every 12 hours for 10 days

Chart 2: Observations and Measurements, Study M/1140/0109

Enrollment/Day 0 Day 0	Interim Visit Days 3-6, inclusive	Posttreatment Visit Days 12-18, inclusive	Final Follow-up Visit (Phone) Days 25-42, inclusive
• Informed Consent			
• Medical History & Physical Exam			
• Maxillary Sinus Imaging		• Repeat maxillary sinus imaging	• Repeat maxillary sinus imaging – if needed
• White blood cell count		• White blood cell count	
• Clinical examination (including vital signs)	• Clinical examination (including vital signs)	• Clinical examination (including vital signs)	• Clinical examination (including vital signs)
	• Sinus aspiration & culture – if needed	• Sinus aspiration & culture – if needed	• Sinus aspiration & culture – if needed
• Concomitant medications	• Any change in medications	• Any change in medications	• Any change in medications
	• Medical events, if any	• Medical events, if any	• Medical events, if any
		• Clinical evaluation	• Clinical evaluation

***Reviewers' note**: The time points are the same as the large microbiologic study (M/1140/108) submitted in support of this application. As the latter is uncontrolled, clinical therapeutic efficacy will be grossly compared across the studies. These reviewers can find no record of discussions with the Sponsor regarding an appropriate time frame for a test of cure visit. ODE IV's current Evaluability Criteria for acute sinusitis recommends that a post-therapy test of cure visit, which will be the primary outcome measure occur approximately 1 to 2 weeks after the completion of therapy. In this protocol that would be days 17 to 24. Days 17 to 24 falls between posttreatment visit and final follow-up visit as designed by the sponsor. Equivalence to the comparator arm will be accepted as an acceptable outcome measure, but the time frame for determining "cure" is too short and the cure rates will be probably be inflated due to early follow-up. Thus, these reviewers are resistant to allow promulgation of the post-therapy test-of-cure rates. Should they be disclosed, fairness would require that presentation of final follow-up cure rates in addition: this will provide a more reliable reflection of the actual cure rate in comparison to other studies.*

Investigators: The following fifteen investigators participated in study M/1140/0109

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Reviewers' note: *The reviewers find the above list of investigators acceptable.*

Inclusion criteria:
- age ≥ 18 years
- signs and symptoms compatible with acute maxillary (facial pain, purulent nasal discharge, or tenderness over sinus)
- abnormal radiographic/ultrasonic study compatible with acute maxillary sinusitis (opacification, mucosal thickening ≥ 4 mm, or air-fluid level)
- signed informed consent

Exclusion criteria:
- allergy to penicillin or cephalosporin
- postoperative sinusitis (sinus infection related to surgery on contiguous structures)
- antibiotic treatment within previous 4 days
- pregnant or nursing women
- chronic sinusitis (symptoms longer than 4 weeks or more than 3 episodes of acute sinusitis in the past year)
- severe sinusitis requiring intravenous antibiotics
- the presence of significant neoplastic disease, immunosuppressive therapy or seropositive HIV status
- females of childbearing potential not on acceptable birth control method (e.g., oral contraceptive pills, diaphragm)
- current enrollment in another investigational protocol, previous enrollment in this study, or participation in any other clinical investigational protocol within the past 30 days
- known elevation of serum creatinine (>2.0 mg/dL) or history of renal insufficiency

Treatment discontinuation:
The Sponsor removed patients in the following categories from the study, and listed them as nonevaluable for efficacy, but were to be included in the safety analysis:

- patients receiving concomitant antibiotic therapy
- patients receiving less than 80% of therapy or missed two or more consecutive doses of study drug

Reviewers' note: *The inclusion and exclusion criteria are acceptable and similar to M/1140/108. However, this study, M/1140/109 does not require sinus aspiration because it is designed as a clinical efficacy study and has not planned microbiologic component. The discontinuation allowances are only acceptable with the following clarifications—*
- *patients receiving concomitant antibiotic therapy for reasons other than sinusitis will be eliminated from efficacy analysis; those patients who are treatment failures and receive another antibiotic for additional sinusitis will be* ***evaluable*** *and carried forward as* ***failures***
- *patients who receive less than 80% of therapy and are failures before completing therapy or who discontinue the course of therapy due to failing therapy will be* ***evaluable*** *and carried forward as* ***failures***

Endpoints defined: The Sponsor defined the primary measure of efficacy as clinical efficacy at the posttreatment visit (visit at Days 12-18, inclusive. See Chart 2 above and accompanying Reviewers' note). Secondary measures of efficacy as analyzed by the Sponsor were clinical efficacy at the final follow-up and WBC count at the posttreatment visit. Changes in maxillary sinus images and body temperature were also added as secondary efficacy parameters during analysis by the sponsor.

Reviewers' note: *The reviewers find the primary measure of efficacy acceptable. Clinical efficacy at final follow-up is an adequate secondary outcome measure. Analysis of the other parameters, with the exception of radiologic findings, is important to corroborate these outcomes, but are not outcome measures themselves. The radiologic findings may lag clinical recovery and these reviewers do not believe they constitute a valid outcome measure at the posttreatment time frame. However, the other variables will be*

evaluated merely to support the primary and secondary efficacy outcome measures. The primary measures of safety as defined by the Sponsor are acceptable.

Outcome measures

Clinical efficacy at the posttreatment visit was recorded as follows
- Cured -- Disappearance of all clinical signs and symptoms
- Improved -- Disappearance of most, but not all, clinical signs and symptoms
- Unchanged -- No or little improvement in clinical signs and symptoms
- Worsened -- Worsening of clinical signs and symptoms

The secondary outcome measures were clinical efficacy at the final follow-up visit, and white blood cell count at posttreatment and final visits.

Clinical efficacy at the final follow-up visit was recorded as follows
- Cured -- Disappearance of all clinical signs and symptoms
- Failure -- Little or no improvement in clinical findings
- Recurrence/Relapse -- Return of signs and symptoms at late follow-up after cure at post-treatment evaluation. For purpose of analysis, recurrence relapse will be combined with failure.
- Side Effect Failure -- Unable to complete protocol therapy due to an adverse reaction. For purposes of analysis, side effect failure will be combined with failure.

Reviewers' note: *An "Improved" outcome is not desirable (ODE IV's Evaluability Criteria for acute sinusitis); unfortunately, this was included as an outcome measure and is difficult to evaluate. "Unchanged" and "Worsened" will be treated as failures. The clinical efficacy assignments at final follow-up visits are acceptable.*

Patient populations analyzed:

Intent to Treat Population (ITT) -- All patients who took at least one dose of study medication constitute this population. Subjects lost to follow-up prior to the posttreatment visit will be considered failures.

Evaluable Patient Population -- All subjects who meet protocol requirements and have the posttreatment evaluation. In addition, subjects considered treatment failures prior to the posttreatment visit will be included in the analysis.

Safety Patient Population -- All patients who received one or more doses of study medication will be included in all safety analyses.

Reviewers' note: *The above populations are acceptable for analysis.*

Statistical methods: Sample size determination utilized a binomial test of equivalence. A one-side test was employed with an alpha = 0.05 and a power of 80%. A 90% cure rate and a 90% evaluability rate were assumed. A sample size of 312 patients (156 per treatment arm) could demonstrate equivalence, which was defined as a difference of no greater than 10%.

Statistical evaluation of efficacy is primarily based upon the two-tailed 95% confidence interval of difference of clinical cure rates and clinical success (cure + improvement) rates at posttreatment in the evaluable subjects between cefpodoxime and loracarbef. The confidence intervals are computed using a normal approximation to binomial, and include a continuity correction. The evaluation of whether the treatment groups are considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-side Fisher's exact test.

Reviewers' note: *The analysis is a fairly standard analysis for a clinical trial submitted to DAIDP..*

Study Results

Demographics, Evaluability:

Chart 3: Patient Populations

Treatment Group	cefpodoxime	loracarbef
Intent to Treat (ITT)	188(100%)	189(100%)
Evaluable	163(86.7%)	170(90.0%)

Chart 4: Demograhic Distribution of Patients in ITT Population

Demographic feature	cefpodoxime (n=188)	loracarbef (n=189)	p-value*
Mean age (years)	42.0±13.6	43.3±13.6	0.346
18-65 years	175(93.1%)	175(92.6%)	1.00
>65 years	13(6.9%)	14(7.4%)	
Mean weight (kg)	79.2±18.2	80.7±20.2	0.445
Race (N(%))			
White	168(89.4%)	161(85.2%)	0.123
Hispanic	14(7.5%)	11(5.8%)	
Black	6(3.2%)	14(7.4%)	
Other	0(0%)	3(1.6%)	
Women (N(%))	112(59.6%)	109(57.7%)	
Men (N(%))	76(40.4%)	80(42.3%)	0.754
Smoking status			
None	114(60.6%)	102(54.0%)	0.417
Past	37(19.7%)	45(23.8%)	
Current	37(19.7%)	42(22.2%)	

p-value is obtained by t-test in data carrying the assumption of normal distribution and by Fisher's exact test in categorical data.

Chart 5: Demograhic Distribution of Patients in Evaluable Population

Demographic feature	cefpodoxime (n=163)	loracarbef (n=170)	p-value*
Mean age (years)	42.3±13.8	43.6±13.9	0.396
18-65 years	151(92.6%)	156(91.8%)	0.840
>65 years	12(7.4%)	14(8.2%)	
Mean weight (kg)	79.8±18.1	80.7±20.7	0.646
Race (N(%))			
White	145(89.0%)	143(84.1%)	0.156
Hispanic	12(7.4%)	11(6.5%)	
Black	6(3.7%)	14(8.2%)	
Other	0(0%)	2(1.2%)	
Women (N(%))	98(60.1%)	109(58.8%)	0.824
Men (N(%))	65(39.9%)	80(41.2%)	
Smoke			
None	100(61.4%)	94(55.3%)	0.466
Past	30(18.4%)	40(23.5%)	
Current	33(20.3%)	36(21.2%)	

p-value is obtained by t-test in data carrying the assumption of normal distribution and by Fisher's exact test in categorical data.

Reviewers' note: *Distribution of features is similar in the ITT and Evaluable populations. There appears to be no bias with respect to treatment arm.*

Chart 6: Reasons for Discontinuance in ITT subjects and Evaluable Subjects

	ITT population		Evaluable population	
	cefpodoxime	loracarbef	cefpodoxime	loracarbef
Discontinued				
Lack of efficacy	24(12.8%)	23(12.2%)	22(13.5%)	22(12.9%)
Medical event				
Serious medical event	0(0%)	0(0%)	0(0%)	0(0%)
Nonserious medical event	7(3.7%)	7(3.7%)	2(1.2%)	4(2.4%)
Protocol violation	11(5.9%)	8(4.2%)	5(3.1%)	5(2.9%)
Other				
Ineligible after medication started	0(0%)	0(0%)	0(0%)	0(0%)
Subject request	3(1.6%)	1(0.5%)	2(1.2%)	0(0%)
Lost to follow-up	2(1.1%)	4(2.1%)	0(0%)	2(1.2%)
Total discontinued & completed study	188(100%)	189(100%)	163(100%)	170(100%)

Reviewers' note: *The above reasons for discontinuance appear reasonable and not biased by treatment arm.*

Chart 7: Reasons for Nonevaluability

	cefpodoxime	loracarbef
Evaluable	163	170
Nonevaluable (total)	25	19
Failed to meet entry criteria	0(0%)	0(0%)
Failed to follow protocol	5(20.0%)	4(21.1%)
Concomitant Antibiotic Therapy	0(0%)	0(0%)
Missed ≥ 2 consecutive doses of drug	3(12.0%)	2(10.5%)
Received < 16 doses of drug	4(16.0%)	1(5.3%)
Other	13(52.0%)	12(63.0%)

Reviewers' note: *The above reasons for nonevaluability appears reasonable and not biased by treatment arm. Overall, 86% enrolled in the cefpodoxime arm and 90% enrolled in the loracarbef arm are evaluable.*

Chart 8: Medical History

	ITT population		Evaluable population	
Medical history	cefpodoxime	loracarbef	cefpodoxime	loracarbef
Allergic rhinitis	65(34.6%)	59(31.2%)	53(32.5%)	54(31.8%)
Nasal polyps	7(3.7%)	12(6.4%)	6(3.7%)	11(6.5%)
Septal deviation	18(9.6%)	21(11.1%)	15(9.2%)	20(11.8%)
Previous ENT surgery	38(20.2%)	41(21.7%)	31(19.0%)	37(21.8%)
Previous dental infection	7(3.7%)	6(3.2%)	6(3.7%)	6(3.5%)

Reviewers' note: *The medical histories appear to be fairly evenly distributed with respect to treatment arm and no bias evident with respect to evaluable and ITT populations.*

Chart 9: Physical findings in ITT population

	At enrollment		At posttreatment	
Physical findings	cefpodoxime	loracarbef	cefpodoxime	loracarbef
Body temperature ^	98.3±0.9	98.2±0.8	98.1±0.8	98.0±0.8
White blood cell count ^	7.8±2.6	7.6±2.2	7.1±2.1	7.0±1.8
Purulent nasal discharge*	178(94.7%)	177(93.7%)	56(29.8%)	79(41.8%)
Facial pain*	160(85.1%)	169(89.4%)	42(22.3%)	44(23.3%)
Tenderness over sinus*	178(94.7%)	179(94.7%)	47(25.0%)	52(27.5%)
Malaise*	130(69.1%)	134(70.9%)	37(19.7%)	39(20.6%)
Aching of teeth*	78(41.5%)	78(41.3%)	11(5.9%)	24(12.7%)
Headache*	152(80.9%)	149(78.8%)	43(22.9%)	54(28.6%)
Fever	35(18.6%)	18(9.5%)	4(2.1%)	2(1.1%)
Other	108(57.4%)	120(63.5%)	38(20.2%)	48(25.4%)

^ mean value and standard deviation

* Treated as dichotomous values. Among those with findings at posttreatment, almost all were assessed as "mild" by the investigator.

Chart 10: Physical findings in Evaluable population

Physical findings	At enrollment		At posttreatment	
	cefpodoxime	loracarbef	cefpodoxime	loracarbef
Body temperature ^	98.3±0.9	98.2±0.8	98.1±0.8	98.0±0.8
White blood cell count ^	7.8±2.6	7.7±2.2	7.1±2.1	7.1±1.9
Purulent nasal discharge*	155(95.1%)	158(92.9%)	49(30.1%)	71(41.8%)
Facial pain*	144(88.3%)	153(90.0%)	38(23.3%)	39(22.9%)
Tenderness over sinus*	156(95.7%)	161(94.7%)	44(27.0%)	48(28.2%)
Malaise*	114(69.9%)	119(70.0%)	33(20.2%)	35(20.6%)
Aching of teeth*	67(41.1%)	68(40.0%)	10(6.1%)	20(11.8%)
Headache*	134(82.2%)	133(78.2%)	40(24.5%)	46(27.1%)
Fever	31(19.0%)	16(9.4%)	4(2.5%)	2(1.2%)
Other	88(54.0%)	104(61.2%)	31(19.0%)	41(24.1%)

^ mean value and standard deviation

* Treated as dichotomous values. Among those with findings at posttreatment, almost all were assessed as "mild" by the investigator.

Reviewers' note: *The above suggests a reasonable distribution of physical findings among those enrolled and those evaluable. In addition, adequate resolution of these findings is evident at posttreatment.*

Chart 11: Radiologic Findings

Radiologic findings	cefpodoxime	loracarbef
Opacification	85(46.5%)	94(51.6%)
Fluid level	27(26.2%)	35(35.7%)
Mucosal swelling ≥ 4mm	119(69.1%)	122(61.1%)

Reviewers' note: *The reviewers accept this as an entry criteria, but radiologic findings may lag behind a clinical cure. Thus, the reviewers do not consider this an appropriate outcome measure.*

Chart 12: Clinical outcomes

	ITT population		Evaluable population	
	cefpodoxime	loracarbef	cefpodoxime	loracarbef
Cured	99(52.7%)	80(42.3%)	87(53.4%)	75(44.1%)
Improved	62(33.0%)	71(37.6%)	59(36.2%)	67(39.4%)
Failure	27(14.4%)	38(20.1%)	17(10.4%)	28(16.5%)
Success (Cured + Improved)	161(85.6%)	151(79.9%)	146(89.6%)	142(83.5%)
Failure	27(14.4%)	38(20.1%)	17(10.4%)	28(16.5%)
Cured	99(52.7%)	80(42.3%)	87(53.4%)	75(44.1%)
Failure (Failure + Improved)	89(47.3%)	109(57.7%)	76(46.6%)	95(55.9%)
Cefpodoxime vs Loracarbef by Cure	10.3% 95%CI	(-0.2%,20.9%)	9.3% 95%CI	(-2.0%,20.6%)
Cefpodoxime vs Loracarbef by Success	5.7% 95%CI	(-2.4%,13.9%)	6.0% 95%CI	(-1.8%,13.9%)

Reviewers' note: *The cure and success rates are acceptable. The confidence intervals meet equivalence. The large "improved" category is difficult to interpret, but analysis by "cure" and "success" supports equivalence. The uncertainty contributed by the "improved" makes it impossible for these reviewers to believe any superiority exists.*

The test-of-cure visit occurred very shortly after completion of therapy. This is unfortunate because the time frame would not meet ODE IV's current Evaluability Criteria for acute sinusitis. A test-of-cure visit intermediate between the current posttreatment and final follow-up would more accurately yield an appropriate cure rate.

Chart 13: Subset Analyses by Demographic Aspects of Clinical Success
Rate at Posttreatment in Evaluable Subjects

Subset	cefpodoxime	loracarbef	95% CI	P-value*
Male	57/65(87.7%)	65/70(92.9%)	(-16.7%, 6.3%)	0.018
Female	89/98(90.8%)	77/100(77.0%)	(2.8%, 24.9%)	
18-65 yrs	135/151(89.4%)	129/156(82.7%)	(-1.6%, 15.1%)	0.621
>65 yrs	11/12(91.7%)	13/14(92.9%)	(-29.6%, 27.2%)	
White	130/145(89.7%)	118/143(82.5%)	(-1.5%, 15.8%)	0.058
Black	4/6(66.7%)	13/14(92.9%)	NA	
Hispanic	12/12(100%)	9/11(81.8%)	(-13.3%, 49.7%)	
Other	0/0(NA)	2/2(100%)	NA	

* Breslow-Day's P-value.

Reviewers' note: *The cure rates posttreatment are acceptable in different demographic subsets: it is impossible to draw conclusions from the statistical analysis given the diminishment in sample size. Significant heterogeneity of treatment effect was detected between race and gender. With respect to race, small numbers make this an unreliable conclusion. Female sex is favored by cefpodoxime treatment and male sex is favored by loracarbef treatment; it is unclear whether this has any significance.*

Chart 14: Clinical Responses at Final Follow-up in ITT and Evaluable Subjects

	ITT		Evaluable	
Clinical Response	cefpodoxime	loracarbef	cefpodoxime	loracarbef
Cured	114(60.6%)	110(58.2%)	101(70.6%)	100(73.0%)
Failure	47(25.0%)	40(21.2%)	42(29.4%)	36(26.3%)
Missing	27(14.4%)	39(20.6%)	0(0%)	1(0.7%)
Cefpodoxime vs loracarbef by cure	2.4% 95% CI (-8.0%, 12.9%)		-2.4% 95% CI (-13.6%, 8.9%)	

Reviewers' note: *The above analyses demonstrates acceptable cure rates at the follow-up visit. Equivalence between the treatment arms is demonstrated.*

The patient population enrolled was not especially stringent. In order to evaluate response in a population more selected for acute maxillary bacterial sinusitis, patients with the finding of air-fluid level on radiologic study were stratified and evaluated and evaluated separately. The following is revealed:

Chart 15: Clinical Cure Rates among Sponsor Evaluable Patients with Air Fluid Levels and Opacification upon Radiologic Examination at Enrollment

	With opacification N/total(%)		With air-fluid levels N/total(%)		Total N/total(%)	
Clinical Outcome	loracarbef	cefpodoxime	loracarbef	Cefpodoxime	loracarbef	cefpodoxime
Cure	40/94(42.6)	44/85(51.8)	16/35(45.7)	14/27(51.9)	56/129(43.4)	58/112(52.8)
Improved	38/94(40.4)	35/85(41.2)	13/35(37.1)	10/27(37.0)	51/129(39.5)	45/112(40.2)
Failure	16/94(17.0)	6/85(7.0)	6/35(17.1)	3/27(11.1)	22/129(17.0)	9/112(8.0)

Reviewers' note: *The subset of patients with air-fluid levels and opacification on radiologic examination should provide a population enriched for the diagnosis of acute bacterial maxillary sinusitis. For the ITT population, the cure:improved:failure rates are as follows for the cefpodoxime and loracarbef populations, respectively, 52.7%:33.0%:14.4% and 42.3%:37.6%:20.1%. For the evaluable population, the cure:improved:failure rates are as follows for the cefpodoxime and loracarbef populations, respectively, 53.4%:36.2%:10.4% and 44.1%:39.4%:16.5%. It is perplexing that this analysis does not demonstrate improved cure rates because the subset should be more specific for a diagnosis of acute bacterial maxillary sinusitis.*

Safety

Chart 16: Medical Event Rates

Adverse Event	cefpodoxime (N=188)	loracarbef (N=189)	Fisher's P-value
Subject with at least one adverse event not necessarily attributed to study drug	111(59.0%)	106(56.1%)	0.603
Body	67(35.6%)	70(37.0%)	0.831
Cardiovascular	3(1.6%)	5(2.7%)	0.724
Digestive	39(20.7%)	38(20.1%)	0.899
Metabolic & Nutritional	0(0%)	1(0.5%)	1.000
Musculo-Skeletal	1(0.5%)	2(1.1%)	1.000
Nervous	2(1.1%)	4(2.1%)	0.685
Respiratory	59(31.4%)	53(28.0%)	0.500
Skin	4(2.1%)	2(1.1%)	0.449
Special Senses	10(5.3%)	11(5.8%)	1.000
Urogenital	9(4.8%)	8(4.2%)	0.810
Subject with at least one adverse event attributed to study drug	34(18.1%)	22(11.6%)	0.084
Body	9(4.8%)	11(5.8%)	0.819
Cardiovascular	1(0.5%)	0(0%)	0.499
Digestive	22(11.7%)	9(4.8%)	0.015
Nervous	1(0.5%)	1(0.5%)	1.000
Respiratory	2(1.1%)	1(0.5%)	0.623
Skin	3(1.6%)	3(1.6%)	1.000
Urogenital	4(2.1%)	3(1.6%)	0.724
Subject with Serious AEs	2(1.1%)	0(0%)	0.248
Subject discontinued due to AEs	6(3.2%)	6(3.2%)	1.000

Diarrhea and nausea were the most common treatment related medical events. Both are known side effects of cefpodoxime and loracarbef treatment. The overall incidence of diarrhea in the cefpodoxime group was more than twice that in the loracarbef group: 9.0% versus 4.2%, respectively. The incidence of treatment related diarrhea was 6.4% in the cefpodoxime group and 1.1% in the loracarbef group.

Six patients (3.2%) in each treatment group discontinued because of medical events. In the cefpodoxime group, moderate to severe diarrhea and/or mild to severe nausea accounted for the discontinuation of four of the six patients. Tooth and mouth disorders, and fungal infection were responsible for the discontinuation of the fifth and sixth patients. All events that caused discontinuation resolved as of last patient contact.

In the loracarbef group, moderate abdominal cramping with severe headache or mild diarrhea was responsible for discontinuation in two patients. In a third, moderate nausea with moderate moniliasis caused discontinuation. Pruritis, fever, and headache, and skin eruption were responsible for discontinuation in the fourth, fifth and sixth patients, respectively. All events in the six patients were resolved at last contact.

No patient died during the study. Two patients in the cefpodoxime group had serious medical events. One patient had severe cholecystitis and cholelithiasis beginning 7 days after treatment ended. The second patient had severe abdominal pain beginning 16 days after treatment ended. Both events resolved without residual effects.

Reviewers' note: *There is a significant difference in adverse events related to the gastrointestinal tract with diarrhea and nausea much more frequent in the cefpodoxime group. However, it appears that the adverse events related to therapy with cefpodoxime are well reflected in the current label. Diarrhea is reported as occurring in 7.2% of recipients. Other events in the label whose incidence is reported as greater than 1% are: nausea (3.8%), vaginal fungal infections (3.1%), abdominal pain (1.6%), rash (1.4%), headache (1.1%), and vomiting (1.1%). Thus, it appears this clinical trial provides no new information with respect to frequency of adverse events.*

Conclusions:

(1) The 95% confidence intervals of the clinical cure rates at posttreatment in the evaluable population was $_{163,170}(-2.0\%, 20.6\%)_{53.4\%, 44.1\%}$, and the 95% confidence intervals of the clinical success rates at posttreatment in the evaluable population was $_{163,170}(-1.8\%, 13.9\%)_{89.6\%, 83.5\%}$. These analyses demonstrate that cefpodoxime is therapeutically equivalent in efficacy to loracarbef in the treatment of acute maxillary sinusitis.

(2) No significant differences were detected between the cefpodoxime and loracarbef treatment groups with respect to the rate of discontinuation due to adverse events or the rates of serious adverse events. There were, however, more adverse events related to the digestive tract (especially nausea and diarrhea) among the cefpodoxime treatment group than among the loracarbef treatment group.

Recommendations

Cefpodoxime, 200 milligrams orally every 12 hours for 10 days be approved for the treatment of acute maxillary sinusitis.

Study title: Oral Cefpodoxime proxetil (Vantin® Tablets in the Treatment of Acute Maxillary Sinusitis in Adults: Sinus Aspiration Study (Protocol M/1140/108))

Study dates: The first enrollment occurred January 20, 1995 and the date of completion was March 25, 1997.

Study objectives: To evaluate the clinical and bacteriologic efficacy and safety of orally administered cefpodoxime proxetil (200mg po q 12 hours for 10 days) in the treatment of acute maxillary sinusitis in adults.

Study design: This is an open label, domestic, multicenter, uncontrolled study. See Chart 16 (following) for specifics of study design, observations and measurements.

Chart 17: Observations and Measurements, Study M/1140/0108

Initial Visit: Day 0 Day 0	Interim Visit Days 3-5, inclusive	Posttreatment Visit Days 12-18, inclusive	Final Follow-up Visit (Phone) Days 25-42, inclusive
• History & Physical Exam			
• Maxillary Sinus Imaging		• Repeat maxillary sinus imaging	
• Sinus aspiration for culture	• Sinus aspiration, if failure	• Sinus aspiration, if failure	• Sinus aspiration, if failure
• Hematology parameters		• Hematology parameters	
• Clinical examination	• Clinical examination	• Clinical examination	• Clinical examination
• Concomitant medications	• Any change in medications	• Any change in medications	• Any change in medications
	• Medical events, if any	• Medical events, if any	• Medical events, if any
			• Follow-up of abnormal labs

Reviewers' note: This study fulfills the minimal microbiologic requirement stated in DAIDP's Points-to-Consider. The uncontrolled design limits conclusions that can be drawn; however, it is acceptable within our guidance documents.

The time points are the same for all studies submitted in support of this application (M/1140/109 and M/1140/0045, in addition to this study). These reviewers can find no record of DAIDP discussions with the Sponsor regarding an appropriate time frame for a test of cure visit. ODE IV's current Evaluability Criteria for acute sinusitis recommends that the primary outcome measure, a post-therapy test of cure visit, occur approximately 1 to 2 weeks after the completion of therapy. In this protocol that would be days 17 to 24. Days 17 to 24 falls between posttreatment visit and final follow-up visit as designed by the sponsor. Because the study is uncontrolled, acceptable efficacy can only be concluded after comparison with other trials and a general sense of what an acceptable cure rate is. The time frame for determining "cure" is too short and the cure rates will be probably be inflated due to early follow-up. Thus, these reviewers are resistant to allow promulgation of the post-therapy test-of-cure rates. Should they be disclosed, fairness would require that presentation of final follow-up cure rates in addition: this will provide a more reliable reflection of the actual cure rate in comparison to other studies.

Inclusion criteria:
- acute maxillary sinusitis
- age ≥ 18 years
- symptoms and signs compatible with diagnosis (facial pain, purulent nasal discharge, or tenderness over sinus)

- abnormal radiographic/ultrasonic study compatible with diagnosis (opacification, mucosal thickening ≥ 4 mm, or air-fluid level)
- signed informed consent
- willingness to have sinus aspiration.

Exclusion criteria:
- allergy to penicillin or cephalosporin
- postoperative sinusitis (sinus infection related to surgery on contiguous structures)
- antibiotic treatment within previous 4 days
- pregnant or nursing women
- chronic sinusitis (symptoms longer than 4 weeks or more than 3 episodes of acute sinusitis in the past year)
- severe sinusitis requiring intravenous antibiotics
- the presence of significant neoplastic disease, immunosuppressive therapy or seropositive HIV status
- females of childbearing potential not on acceptable birth control method (e.g., oral contraceptive pills, diaphragm)
- current enrollment in another investigational protocol, previous enrollment in this study, or participation in any other clinical investigational protocol within the past 30 days
- known elevation of serum creatinine (>2.0 mg/dL) or history of renal insufficiency
- history of bleeding disorder or currently on anticoagulants

Evaluability criteria: Patients in the following categories were removed from the study and listed as nonevaluable for efficacy, but were included in the safety analysis:

- patients with a pathogen resistant to cefpodoxime
- patients with concomitant antibiotic therapy for indications other than upper respiratory diseases and whose sinusitis was determined to be clinically Cured or Improved
- patients who received less than 80% of the therapy or missed two or more consecutive doses of study drug

To clarify, patients for whom no pathogenic organism was on initial culture of sinus aspirate remained on the study, continued to receive study medication and had outcomes reported. Organisms considered pathogens in this study were *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *S. pyogenes*.

Patients who failed to have an adequate clinical response by the interim visit (Day 3-6) or who deteriorated after 2 full days of therapy were to be taken off protocol therapy and treated as indicated by the investigator. These patients are listed as evaluable and failures.

***Reviewers' note**: The above Inclusion, Exclusion and Evaluability criteria are acceptable.*

Endpoints defined: The Sponsor defined the primary measures of efficacy as clinical and bacteriologic efficacy at the posttreatment visit (visit at Days 12-18, inclusive. See Chart 16 above.). Secondary measures of efficacy as analyzed by the Sponsor were clinical and bacteriologic efficacy at the final follow-up and WBC count at the posttreatment visit and final follow-up. Changes in maxillary sinus images, clinical signs and symptoms and body temperature were also added as secondary efficacy parameters during analysis by the sponsor.

The Sponsor defined the primary measures of safety were assessed by monitoring change in vital signs, change in hematology values, reports of medical events, and exposure to study drug. All medical events, whether or not considered to be related to study drug, were recorded. The investigator was required to classify each event as serious or nonserious, related, or unrelated to study drug, and mild, moderate or severe in intensity.

Reviewers' note: *The reviewers find the primary measures of efficacy acceptable. Clinical and bacterial efficacy at final follow-up are adequate secondary outcome measures. Analysis of the other parameters, with the exception of radiologic findings, is important to corroborate these outcomes, but are not outcome measures themselves. The radiologic findings may lag behind clinical recovery and these reviewers do not believe they constitute a valid outcome measure at the posttreatment time frame. However, the other variables will be evaluated merely to support the primary and secondary efficacy outcome measures. The primary measures of safety as defined by the Sponsor are acceptable.*

Outcome measures

Clinical efficacy at the posttreatment visit was recorded as follows

- Cured -- Disappearance of clinical signs and symptoms
- Improved -- Disappearance of most, but not all, clinical signs and symptoms
- Unchanged -- No change in condition from enrollment
- Worsened -- Condition worsened from enrollment

Clinical efficacy at the final follow-up was recorded as follows

- Cure -- Disappearance of all clinical signs and symptoms
- Failure -- Little or no improvement in clinical symptoms
- Recurrence/Relapse -- Return of signs and symptoms at late follow-up after cure at posttreatment evaluation
- Side Effect Failure -- Unable to complete protocol therapy due to an adverse reaction caused by study medication

Bacteriologic efficacy at the posttreatment visit was recorded as

- Not clinically indicated
- No organism(s) isolated
- Organism(s) isolated (with a list of such organisms)

Reviewers' note: *The Reviewers considered the following outcomes in their analysis*

Clinical efficacy at the posttreatment visit

- *Cure -- Complete resolution of signs and symptoms*
- *Improved -- Disappearance of most, but not all, clinical signs and symptoms*
- *Failure -- Unsatisfactory resolution of signs and symptoms*

Clinical efficacy at the final follow-up visit

- *Cure -- Continued resolution of signs and symptoms*
- *Failure -- Unsatisfactory resolution of signs and symptoms. Failures at posttreatment visit are failures at final follow-up*
- *Recurrence, Relapse -- Those with recurrence of signs and symptoms after resolution at posttreatment visit*

Bacteriologic efficacy was measured as

- *Eradication -- Documented eradication of pathogen by culture at posttreatment visit*
- *Presumed Eradication -- Eradication of pathogen assumed by clinical outcome of "Cure"*
- *Failure -- Documented failure to eradication pathogen by culture at the posttreatment visit*
- *Presumed Failure -- Presumed failure to eradicate pathogen by clinical outcome of "Failure"*

Patient populations analyzed:

Intent to Treat Population (ITT) -- All patients who took at least one dose of study medication were include in the ITT population. This was the Sponsor's population for safety analysis.

Reviewers' note: *The Reviewers also used this population to evaluate a clinical outcome (cure or failure) so that a gross clinical efficacy rate could be compared to the sponsor's other pivotal trial submitted in*

support of this application (M/1140/109). The Sponsor has, to the best of their ability, supplied us with the clinical outcomes of these patients. However, these patients are not the more scrutinized microbiologically evaluable population and the information gathered with respect to clinical outcome was not as complete as the microbiologically evaluable population.

Evaluable Patient Population -- The Sponsor's evaluable populations consisted patients who met the following requirements

- satisfied all inclusion criteria and had no exclusion criteria
- had one or more pathogenic organism(s) (*S. aureus, S. pneumoniae, S. pyogenes, H. influenzae,* or *M. catarrhalis*) on initial culture that were not resistant (disc zone diameter ≤ 17 mm) to cefpodoxime at enrollment
- did not receive antibiotic or intranasal steroid during the study
- took at least 80% of the tablets, did not miss 2 or more consecutive doses, and received drug for at most 13 days
- kept the posttreatment follow-up visit within 10-24 days after enrollment (treatment failures were exempt from this requirement as they were carried forward)
- having adequate follow-up at final visit (treatment failures were exempt from this requirement as they were carried forward)

Reviewers' note: *The above are acceptable with the following clarifications and amendments: (1) patients receiving additional antibiotics for sinusitis are carried forward as failures, (2) patients with posttreatment visits on days 10 and 11 will not be evaluable unless carried forward as failures because this visit is too close to end of therapy. The reviewers evaluated the Sponsor's submission to determine how many patients fall into these 2 categories. Only one patient received antibiotic for failed sinusitis: Number 322 will be an evaluable failure because patient was prescribed Augmentin on day 13 for sinusitis. Sponsor considers patient to be nonevaluable because of additional antibiotic therapy. Five evaluable patients were seen for follow-up on days 10 and 11 who had outcomes of cure or improved. The patient numbers were 185 (cure), 269 (cure), 1096 (improved), 1111(cure), and 807(improved). Failures seen on day 10 or 11 were carried forward as failures. There was only one patient who fell into this category (number 326).*

DAIDP requires that patients microbiologically evaluable for sinusitis have their cultures obtained by sinus aspirate. This criteria was met in this study. Because S. aureus can colonized the area in question and contiguous areas, it can be a contaminant on sinus aspirate cultures. Thus, the following criteria must be met for patients to be evaluable for acute sinusitis due to S. aureus.

- *Staphylococcus aureus isolated in pure, not mixed, culture*
- *adequate organism burden as demonstrated by a quantitation of 10^4 cfu/ml or semiquantitation of 3+ or 4+ of S. aureus*
- *PMNs present on gram stain*

Patients with organisms other that S. aureus could have more than one pathogen. There were 126 evaluable patients and of these, the sponsor forwarded 91 of the 126 culture reports. Review of these 91 reports revealed that only 4 patients with S. aureus cultures met the above criteria (numbers

Among the remaining 87, the following patients with S. aureus were removed from the fully evaluable patient population database for this analysis:

Patients had S. aureus and S. pneumoniae cultured – these patients were evaluable for S. pneumoniae but not S. aureus. Patients 269 and 1007 had S. aureus and H. influenzae cultured – these patients were evaluable for H. influenzae but not S. aureus.

Thirty-five culture reports were not forwarded by the Sponsor because they were not performed by a central laboratory and were not easily available. Among these 35 cultures, the Sponsor considered 11 patients with S. aureus cultures to be evaluable. The reviewers find these patients to be nonevaluable for S.

aureus because there was no documentation of PMNs on gram stain or pure culture semiquantitatively recorded at a density of 3+ or 4+. Those with mixed cultures of S. aureus and either S. pneumoniae, H. influenzae, M. catarrhalis or S. pyogenes were kept evaluable for the non-S. aureus isolate.

All patients enrolled were kept in the ITT analysis which reflects safety and clinical outcome.

Statistical methods: Because this was a non-comparative study, the Sponsor limited inferential tests to paired t-tests, using a two-sided test. The Sponsor considered the test result statistically significant if the $p \leq 0.05$, and marginally statistically significant if the $0.05 \leq p \leq 0.10$, unless otherwise noted. The Sponsor summarized demographic information for evaluable and ITT patients, using median, mean, SD, minimum, and maximum for continuous variables, and frequency tables for categorical variables.

Reviewers' note: *The reviewers considered the primary efficacy variables to be clinical cure rate and clinical success (cure + improvement) rates at posttreatment, and bacterial eradication rate at posttreatment in evaluable subjects. The reviewers' evaluable population is used in the analysis. Safety data came from all subjects receiving at least one dose of study medication.*

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