CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 50605/S-032

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50605/S032

Trade Name: Ceftin Tablets

Generic Name: (cefuroxime axetil)

Sponsor: Glaxo Wellcome, Inc.

Approval Date: August 24, 1999

Indication: Provide for the use of Ceftin (cefuroxime axetil) Tablets and Oral Suspension for the treatment of acute bacterial maxillary sinusitis in pediatric patients.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 50605/S-032

APPROVAL LETTER

NDA 50-605/S-032
NDA 50-672/S-014

Glaxo Wellcome Inc.
Attention: Anne N. Stokley, M.S.P.H.
Product Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

AUG 2 4 1999

Dear Ms. Stokley:

Please refer to your supplemental new drug applications dated September 14, 1998, received September 15, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ceftin® (cefuroxime axetil) Tablets (NDA 50-605) and Ceftin® (cefuroxime axetil) for Oral Suspension (NDA 50-672). We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated March 18, 1999, July 21, 1999, and August 10, 1999.

These supplemental new drug applications provide for the use of Ceftin® (cefuroxime axetil) Tablets and Oral Suspension for the treatment of acute bacterial maxillary sinusitis in pediatric patients as follows:

1. In the **Pediatric Use** subsection of the **PRECAUTIONS** section, addition of the following sentences:

2. In the **DOSAGE AND ADMINISTRATION** section, addition of dosing information for pediatric patients (who can swallow tablets whole) as follows:

3. In the **DOSAGE AND ADMINISTRATION** section, addition of dosing information for pediatric patients (3 months to 12 years) using oral suspension as follows:

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). However, in accordance with the final rule for "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling", published December 13, 1994, please replace the words
with the words in the **DOSAGE AND ADMINISTRATION** section your labeling. Please include these revisions in your FPL submission.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 50-605/S-032, 50-672/S-014." Approval of these submissions by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50605/S-032

MEDICAL REVIEW(S)

Clinical Review of NDAs 50-672 and 50-605, S-014: Ceftin® (cefuroxime axetil) Powder for Oral Suspension and Tablets for the Treatment of Pediatric Acute Maxillary Sinusitis

Applicant:	GlaxoWellcome Five Moore Drive PO Box 13398 Research Triangle Park, North Carolina 27709
Contact:	Anne N. Stokley, M.S.P.H., Product Director, Regulatory Affairs
Date of Submission:	September 14, 1999
CDER Stamp Date:	September 15, 1999
Date Review Completed:	July 15, 1999; revised July 30, 1999
Drug & Formulation:	Ceftin® for Oral Suspension (cefuroxime axetil powder for oral suspension) Ceftin® Tablets (cefuroxime axetil tablets)

Proposed labeling submitted by Applicant:

The Applicant requests that the following labeling be added to the PRECAUTIONS Pediatric Usage section:

The Applicant proposes that the following labeling be added to the DOSAGE AND ADMINISTRATION section:

Current Labeling Relevant to this Application:

Ceftin is currently labeled for acute bacterial maxillary sinusitis in adults. The **INDICATIONS AND USAGE SECTION** contains the following section:

3. **Acute Bacterial Maxillary Sinusitis** caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-beta-lactamase-producing strains only). (See CLINICAL STUDIES section).

NOTE: In view of the insufficient numbers of isolates of beta-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* that were obtained from clinical trials with CEFTIN tablets for patients with acute bacterial maxillary sinusitis, it was not possible to adequately evaluate the effectiveness of CEFTIN Tablets for sinus infections known, suspected, or considered potentially to be caused by beta-lactamase-producing *Haemophilus influenzae* or *Moraxella catarrhalis*.

The **DOSAGE AND ADMINISTRATION** section provides the following information for CEFTIN Tablets:

Population/Infection	Dosage	Duration (days)
Adolescents and Adults (13 years and older)		
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10

The following information is contained in the **CLINICAL STUDIES** section:

CEFTIN Tablets: ***Acute Bacterial Maxillary Sinusitis***: One adequate and well-controlled study was performed in patients with acute bacterial maxillary sinusitis. In this study each patient had a maxillary sinus aspirate collected by sinus puncture before treatment was initiated for presumptive acute bacterial sinusitis. All patients had to have radiographic and clinical evidence of acute maxillary sinusitis. As shown in the following summary of the study, the general clinical effectiveness of CEFTIN Tablets was comparable to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor in treating acute maxillary sinusitis. However, sufficient microbiology data were obtained to demonstrate the effectiveness of CEFTIN Tablet in treating acute bacterial maxillary sinusitis due only to *Streptococcus pneumoniae* or non-beta-lactamase-producing *Haemophilus influenzae*. An insufficient number of beta-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* isolates were obtained in this trial to adequately evaluate the effectiveness of CEFTIN Tablets in the treatment of acute bacterial maxillary sinusitis due to these two organisms.

This study enrolled 317 adult patients, 132 in the United States and 185 in South America. Patients were randomized in 1:1 ratio of cefuroxime axetil 250 mg b.i.d. or an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. An intent-to-treat analysis of the submitted clinical data yielded the following results:

Clinical Effectiveness of CEFTIN Tablets Compared to Beta-Lactamase Inhibitor-Containing Control Drug in the Treatment of Acute Bacterial Maxillary Sinusitis

	US Patients*		South American Patients†	
	CEFTIN n=49	Control n=43	CEFTIN N=87	Control n=89
Clinical success (cure + improvement)	65%	53%	77%	74%
Clinical cure	53%	44%	72%	64%
Clinical improvement	12%	9%	5%	10%

* 95% Confidence interval around the success difference [-0.08, +0.32].
† 95% Confidence interval around the success difference [-0.10, +0.16].

In this trial and in a supporting maxillary puncture trial, 15 evaluable patients had *Haemophilus influenzae* as the identified pathogen. Ten (10) of these 15 patients (67%) had their pathogen (non-beta-lactamase-producing *Haemophilus influenzae*) eradicated. Eighteen (18) evaluable patients had *Streptococcus pneumoniae* as the identified pathogen. Fifteen (15) of these 18 patients (83%) had their pathogen (*Streptococcus pneumoniae*) eradicated.

Reviewer's note: *The current label also contains an Indications section for Ceftin oral suspension. This lists the three pediatric indications approved for this formulation and the organisms because approval was based on clinical data. Thus, the following appears in the current label:*

1. **Pharyngitis/Tonsillitis** caused by *Streptococcus pyogenes*.
2. **Acute Bacterial Otitis Media** caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including beta-lactamase-producing strains), *Moraxella catarrhalis* (including beta-lactamase-producing strains), or *Streptococcus pyogenes*.
3. **Impetigo** caused by *Staphylococcus aureus* (including beta-lactamase-producing strains) or *Streptococcus pyogenes*.

The Applicant's proposed labeling does not add acute bacterial maxillary sinusitis in this indication section. This is appropriate because the above labeling was obtained from clinical studies and no clinical studies support this application. Nonetheless, the pediatric rule provides that only the clinical data obtained in adult clinical studies can be extrapolated to the requested pediatric labeling. Thus, the limitations on the adult acute bacterial maxillary sinusitis indication would be extrapolated to the pediatric indication. However, the data supporting the indication of acute bacterial otitis media contains more complete labeling of the common pathogens and was derived from clinical data.

Regulatory History: The original NDA review for Ceftin denied the indication of Acute Bacterial Maxillary Sinusitis in adults. An efficacy supplement to amend the label in support of this indication was submitted on 7/31/89. The FDA issued a non-approvable letter for the indication of sinusitis on 8/29/89. The Applicant responded to the nonapprovable letter on 7/10/91. Several queries and responses were made prior to an additional submission, with a second non-approval letter issued on 7/17/92. Once again, queries and responses ensued. The Agency issued an approvable letter for the indication of sinusitis on 9/14/95, and the Applicant responded on 12/7/95. The label reprinted above was agreed upon by DAIDP and the Applicant on 3/13/96.

The Medical Officer's review that recommended non-approval for the first supplemental application in support of Acute Bacterial Maxillary Sinusitis states the following "insufficient evaluable data to support an indication for CEFTIN in the treatment of acute bacterial sinusitis at this time" (Medical Officer's Review).

The application contained the following isolates of critical pathogens for sinusitis pooled from two trials:

	Clinical Outcome*		**Bacterial Outcome***	
	Ceftin	Comparator	Ceftin	Comparator
Streptococcus pneumoniae	6/6(100%)	6/6(100%)	6/6(100%)	5/5(100%)
Haemophilus influenzae	7/8 (88%)	7/7(100%)	7/8(88%)	3/4(75%)
β lactamase +	4/4(100%)	N/A	4/4(100%)	N/A
β lactamase -	3/3(100%)	1/1(100%)	2//2(100%)	1/1(100%)
Moraxella catarrhalis	2/2(100%)	2/2(100%)	2/2(100%)	2/2(100%)
β lactamase +	N/A	N/A	N/A	N/A
β lactamase -	N/A	N/A	N/A	N/A

These numbers were deemed inadequate to support evidence of efficacy. In addition, the numbers are inadequate with respect to the Points-To-Consider Guidelines that were adopted by DAIDP on 10/26/92.

Reviewers' note: *The regulatory history provides the context for the wording adopted in this indication. Current published literature and treatment guidelines recognize Ceftin as effective in the treatment of acute bacterial maxillary sinusitis in adults (see section below discussing this issue).*

The Applicant submitted the current application on 9/14/98 under the final rule on the Pediatric Use subsection of labeling that was published in 12/94. This rule allows that the Applicant can obtain pediatric

labeling based on (1) completion of adequate and well-controlled trials in adults to demonstrate the safety and efficacy of the drug in adults with a specific indication and (2) other information supporting pediatric use. The final rule states that the "other information" supporting pediatric use must ordinarily include (1) data on the pharmacokinetics of the drug in the pediatric population to enable determination of the appropriate dosage; (2) data to show that the drug can be used safely in pediatric patients; and (3) evidence that the course of the disease and effects of the drug are sufficiently similar in pediatric and adult patients to permit extrapolation from the adult data to pediatric patients.

Reviewers' note: *The Applicant has submitted information under the Pediatric Rule for review. The nature of the adult label would allow for pediatric labeling with additional supporting data. The current adult label also limits the microorganisms for which efficacy has been demonstrated. It is unfortunate that the original application contained sparse microbiologic data. However, at the time the studies were designed and the data collected, DAIDP's requirements for approval were not as stringent. In addition, much additional information has appeared supporting the efficacy of Ceftin in the treatment of acute bacterial maxillary sinusitis, both pediatric and adult. See below.*

Sponsor Submitted Application: The Applicant requests, in accordance with the Pediatric Rule CFR 201.57(f)(9), the above labeling. The request is based on the following information that the Applicant has submitted:

1. The substantial evidence of efficacy of a regimen of 250 mg BID of cefuroxime axetil in adequate and well-controlled trials in adults with acute bacterial maxillary sinusitis.
2. The sufficient degree of similarity between sinusitis in adult and pediatric patients.
3. The clinical and bacterial efficacy of Ceftin for Oral Suspension and Ceftin Tablets against *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta-lactamase-producing strains) and *Moraxella catarrhalis* (including beta-lactamase-producing strains), established in pediatric patients with acute otitis media.
4. The clinical and bacteriological efficacy established in a suspension dose of cefuroxime axetil (15 mg/kg BID) whose pharmacokinetic properties have been characterized in pediatric patients.
5. Data demonstrating the penetration of cefuroxime into the middle ear fluid of pediatric patients with acute otitis media.
6. The clinical safety and efficacy profiles of the two regimens (15 mg/kg BID for Ceftin for Oral Suspension and 250mg BID for Ceftin Tablets) have been established in pediatric patients with acute otitis media.
7. Serum pharmacokinetic studies.

Reviewers' note: *The following data will be discussed item by item with respect to the strength of the supporting data in this review.*

!. The substantial evidence of efficacy of a regimen of 250 mg BID of cefuroxime axetil in adequate and well-controlled trials in adults with acute bacterial maxillary sinusitis.

Clinical studies section of current label (see page 2 above) describes the studies that served the basis of approval for the adult indication. The Applicant offers no other data in this application, but later submitted a publication of a therapeutic trial employing cefuroxime axetil as a comparator arm in a clinical trial.[1] This trial was a double-blind, multicenter trial in which 382 patients with a diagnosis of acute purulent sinusitis were randomized to receive sparfloxacin, 200 mg daily for 5 days followed by 400 mg once on day 1, or cefuroxime axetil, 250 mg twice daily for 8 days. The study enrolled 382 patients, of whom the intent-to-treat population was 374 and evaluable population was 304. The study would not have met the DAIDP's current requirements for a clinical trial to demonstrate efficacy, but presumed or definite

[1] Gehano P, Berche P, and the Sinusitis Study Group. Sparfloxacin versus cefuroxime axetil in the treatment of acute purulent sinusitis. Journal of Antimicrobial Chemotherapy (Suppl A) 1996;37:105-114.

bacterial eradication was achieved in 93.6% of patients treated with sparfloxacin and 89.2% of those treated with cefuroxime.

The Applicant also submitted a pediatric study.[2] The study enrolled 39 patients between the ages of 5 and 14 who received cefuroxime axetil, 20 mg/kg/day in two doses for 7 days. Patients were enrolled based on history, physical examination and radiologic findings. For microbiologic evaluation, throat cultures were performed. Resolution of clinical symptoms with radiologic evidence of improvement was defined as cure, improvement of clinical symptoms and radiographic evidence of residual sinus congestion was defined as improved. Failure was defined as no improvement of clinical symptoms with persistence of radiologic findings. Patients were followed up for 3 months. At the end of treatment 36 (92%) of patients were cured or improved. Of the 3 patients who did not respond to treatment, 2 patients were cured with an additional week of therapy. No further information is available with respect to whether any patients relapsed or required additional therapy in the ensuing 3month follow-up.

Reviewer's note: The Reviewer is also aware of other clinical trials where cefuroxime has been evaluated.[3,4,5] Unfortunately, these trials would not meet DAIDP's current requirements for demonstrating efficacy in treating acute maxillary bacterial sinusitis. However, the bulk of the evidence overwhelmingly supports the efficacy in the treatment of this indication. Finally, many experts and treatment guidelines recognize the efficacy of cefuroxime in the treatment of acute maxillary sinusitis (see summary of this at end of the review).

The requested pediatric regimen is based on what is efficacious in treating acute otitis media. The pediatric study submitted in support of this application does not meet DAIDP's requirements. The entry criteria and study design were not rigorous enough, the dose and duration are not that requested in labeling, and throat cultures are not acceptable in lieu of sinus puncture cultures. However, a 92% cure or improved outcome at end of therapy, with an additional 5.2% being cured with an additional 7 days of therapy provides some comfort.

2. **The sufficient degree of similarity between sinusitis in adult and pediatric patients.**

The Applicant presents and supports with references the following arguments for similarities of acute bacterial sinusitis:

- The anatomic nature of the maxillary sinuses is similar in adult patients and pediatric patients.
- The pathophysiology and pathology of acute maxillary sinusitis are similar in adult and pediatric patients.
- The major signs and symptoms of sinusitis in adult and pediatric patients are similar, except for very young children when symptoms are less clearly related to the sinuses.
- The causative bacterial pathogens in sinusitis in adults and pediatric patients are similar.

***Reviewers' note:** The Reviewer agrees with these points.*

3. **Similarity of Acute Maxillary Sinusitis and Acute Otitis Media in Pediatric Patients**
4. **The clinical and bacterial efficacy of Ceftin for Oral Suspension and Ceftin Tablets against *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta-lactamase-producing strains) and *Moraxella catarrhalis* (including beta-lactamase-producing strains), established in pediatric patients with acute otitis media.**

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[2] Gürses N., Kalayci, Islek I. Uysal S. Cefurxoime axetil in the treatment of acute sinusitis in childhood. Journal of Antimicrobial Chemotherapy. 1996;38:547-550.

[3] Camacho AE, Cobo R, Otte J, Spector SL, Lerner CJ, Garrison NA, et al. Clinical comparison of cefuroxime axetil and amoxicillin/clavulanate in the treatment of patients with acute bacterial maxillary sinusitis. Am J Med 1992;93:271-276.

[4] Brodie DP, Knight S, Cunningham K. Comparative study of cefurxoime axetil and amoxycillin in the treatment of patients with acute sinusitis in general practice. Journal of International Medical Research 1989; 17, 547-551.

[5] Sydnor A, Gwaltney JM, Cochetto D, Scheld WM. Comparative evaluation of cefuroxime axetil and cefaclor for treatment of a cute bacterial maxillary sinusitis. Archives Otolaryngology – Head & Neck Surgery. 1989; 115:1430-1433.

As mentioned above, the Applicant received the existing pediatric indications with clinical trials in pediatric patients. Thus, the Applicant attempts to apply this evidence of efficacy to efficacy against pediatric acute bacterial maxillary sinusitis. The Applicant presents the following arguments, with references, to support these claims:

- Both diseases are closed space infections when the drainage of the maxillary sinus, in the case of acute maxillary sinusitis, or of the middle ear, in the case of acute otitis media, is obstructed.
- The primary bacterial pathogens of acute maxillary sinusitis and acute otitis media in children are exactly the same: *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.
- The two diseases can occur simultaneously in children and treatment is similar because of the similar etiology of the two diseases.
- Untreated, both diseases can potentially lead to serious sequelae such as orbital celluitis, osteomyelitis of the skull, cavernous sinus thrombosis, brain abscess, and meningitis.

***Reviewer's note**: The reviewers recognize that there are extensive similarities between the middle ear cavity and sinus cavity[6], but DAIDP has not extrapolated efficacy from one site of infection to the other. References cite that therapy adequate for acute otitis media would be effective for sinusitis.*[6, 7, 8]

The Applicant has suggested that the efficacy of Ceftin in the treatment of acute otitis media (AOM) should provide support for this pediatric sinusitis supplement, both clinically and microbiologically. These data are indeed important, as are the sinusitis efficacy data in adults treated with Ceftin. Finally, the pharmacokinetic profile of cefuroxime axetil in adults and children potentially provides bridging data.

5. **The clinical and bacteriological efficacy established in a suspension dose of cefuroxime axetil (15 mg/kg BID) whose pharmacokinetic properties have been characterized in pediatric patients.**
6. **Data demonstrating the penetration of cefuroxime into the middle ear fluid of pediatric patients with acute otitis media.**
7. **Serum pharmacokinetic studies.**

As mentioned earlier in this review, the current pediatric indications were supported by studies with both clinical and microbiologic data. The serum pharmacokinetic studies submitted with this pediatric use supplement date back to 1989. These data (from protocol CAE-226, submitted to IND on January 18, 1989; final report submitted in NDA 50-672, Volume 4, page 042) evaluated a single dose of cefuroxime axetil 15 mg/kg. It revealed a peak plasma concentration (C_{max}) of 5.1 mcg/mL with a mean elimination half-life of 1.9 hours. The selection of a 15 mg/kg BID dose of cefuroxime axetil to treat pediatric sinusitis is based on dose selection for acute otitis media. Dose selection for this indication is based on penetration of cefuroxime axetil in the middle ear fluid of pediatric patients with acute otitis media with purulent effusion.[9] This single center study randomized 20 patients, aged 1 to 4 years, to 1 of 3 sample intervals (2-3 hours, 3-4 hours, or 4-5 hours) after administration of a single oral dose of cefuroxime axetil, 15 mg/kg. Cefuroxime was detected in 14/17 (82%) of evaluable subjects, and ranged in concentration from μg/mL. The concurrent serum concentrations varied from μg/mL, with little evidence of decrease between 2 and 5 hours post-dosing. The ratio of concentration of

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[6] Parsons, DS, Wald, ER. "Otitis Media and Sinusitis" in Otolaryngologic Clinics of North America 1996; 29:11-25.

[7] Nelson Textbook of Pediatrics, 15th ed., eds. Berm Kliegman R, Arvin A. (Philadelphia: WB Saunders Co.) Chapter 327.8 Sinusitis, 1996.

[8] American Academy of Pediatrics. Section 3: Summaries of Infectious Diseases. In: Peter B, ed. 1997 Red Book: Report on the Committee on Infectious Diseases. 24th ed. Elk Grove Village, IL: American Academy of Pediatrics; 1997: 222, 365, 416.

[9] Thoroddsen E, Marr C, Efthymiopoulos C, Thorarinsson H. Concentration of cefuroxime in middle ear effusion of children with acute otitis media. Pediatric Infectious Disease Journal 1997; 16:959-962.

cefuroxime axetil in middle ear effusion to that of serum ranged from These findings are supported by an earlier study.[10]

Reviewer's note: The Applicant does present a fairly strong argument for the similarity between acute otitis media and acute bacterial maxillary sinusitis in the pediatric population. Normally, the pediatric rule relies on serum pharmacokinetic data. The original studies for this drug date back to the 1980s. The pharmacokinetic reviewer discusses the following issues:

> *"The pharmacokinetics/dynamics information submitted represent two publications in the literature. Previous Clinical Pharmacology/Biopharmaceutics reviews of pediatric data concluded linear kinetics across doses 10, 15, and 20 mg/kg given as single doses. Patients had the following diagnoses: facial cellulitis, pneumonia, cervical adenitis, and otitis media. Pharmacokinetics were not sub-classified by diagnosis; however, those cases with predominantly otitis media appear to fit to the same concentration-time curves. Of particular note, one child was 12 years old and 4 children were 3-6 years old; due to this small number, conclusions about dosing in these age groups should be made with caution. In addition, the Biopharmaceutics reviewer noted that the analytical methods for determination of cefuroxime in plasma were not fully validated and the data were therefore unacceptable. Two points were used to determine ke and half-life and this was concluded to represent an unreliable method."*
>
> *(Pharmacokinetic review for this NDA)*

While the pharmacokinetic studies were imperfect, there was substantial evidence, clinical and microbiologic, to approve the use of Ceftin in pediatric patients with acute otitis media. All of these data, together with demonstrated efficacy in adults with maxillary sinusitis, preclude any need for additional pharmacokinetic studies.

8. **The clinical safety and efficacy profiles of the two regimens (15 mg/kg BID Ceftin Oral Suspension and 250mg BID Ceftin Tablets) have been established in pediatric patients with acute otitis media.**

Reviewer's note: DAIDP has granted three pediatric indications based on clinical and microbiologic data. Safety and efficacy have been established, and the labeling reflects this.

9. **Clinical Treatment Guidelines for Pediatric Acute Bacterial Maxillary Sinusitis**

Cefuroxime axetil is extensively recommended for the therapy of acute bacterial maxillary sinusitis, both adult and pediatric. The Consensus Meeting on Management of Rhinosinusitis in Children supports the use of cefuroxime axetil in the treatment of pediatric sinusitis.[11]

The following references vary from consensus statements, widely used pocket references to standard texts, and all endorse cefuroxime axetil for use in the treatment of acute bacterial maxillary sinusitis:

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[10] Powell DA, James NC, Ossi MJ, Nahata MC, Donn KH. Pharmacokinetics of cefuroxime axetil suspension in infants and children. Antimicrobial Agents and Chemotherapy. 1991;35:2042-2045.

[11] Clement PAR, Bluestone CD, Gordts F, Lusk RP, Otten FWA, Goosens H, et al. Management of rhinosinusitis in children: Consensus meeting, Brussels, Belgium, September 13, 1996. Archives of Otolaryngology, Head & Neck Surgery, 1998; 124(1):31-34.

"Because of the high incidence of β-lactamase—producing *H. influenzae* and *B. catarrhalis* in some communities, consideration may be given to the use of or an oral cephalosporin (e.g., cefaclor, **cefuroxime**, cefixime, cefpodoxime proxetil, loracarbef) in the mild or moderately ill child."[12]

" A number of antimicrobial agents have been shown to be effective against the major bacterial causes of community-acquired sinusitis in studies employing quantitative cultures of pre- and post-therapy sinus aspirates.... **Cefuroxime axetil** and amoxicillin-clavulanate are considerable [sic] more expensive than trimethoprim-sulfamethoxazole but are better tolerated."[13]

A widely used pocket reference lists **cefuroxime** along with amoxicillin, amoxicillin-clavulanate, levofloxacin, trovafloxacin, clarithromycin, azithromycin, cefpodoxime, and cefprozil as preferred therapies for acute sinusitis.[14]

A standard pediatric text states merely that therapies appropriate for AOM are acceptable for pediatric acute bacteria sinusitis.[7] Its companion pocket text states more specifically that acute sinusitis therapy is same as for acute otitis media but 14-21 days of therapy may be needed and lists **cefuroxime** along with trimethoprim-sulfamethoxazole, erythromycin, ampicillin, amoxicillin, amoxicillin-clavulanate, cefaclor, cefixime, cefprozil, loracarbef, ceftibuten, cefpodoxime, azithromycin and clarithromycin as therapies for acute otitis media.[15]

Perhaps the most widely used "pocket guide" in the US states the following: "For acute sinusitis, primary therapy recommends amoxicillin clavulanate, **cefuroxime axetil**, or trimethoprim-sulfamethoxazole." [16]

Another standard textbook of infectious states that "a case may be made for the selection of a ß-lactamase—resistant antibiotic for initial empiric therapy" and lists cefuroxime axetil as one of the therapeutic options when this strategy is adopted.[17] A pocket guide by the some of the same authors lists the following as recommended therapies:

- "Standard agents": amoxicillin, doxycycline, and trimethoprim-sulfamethoxazole
- "Modernized list" based on in vitro activity vs. anticipated bacterial pathogens: cephalosporins (cefaclor, **cefuroxime axetil**, cefpodoxime, cefprozil), loracarbef, macrolides (clarithromycin, azithromycin), amoxicillin-clavulanate, fluoroquinolones (ofloxacin, ciprofloxacin, levofloxacin, and trovafloxacin). [18]

The Red Book recommends the following in the relevant stated sections:
"**Sinusitis**. Antibiotics effective in the treatment of acute otitis media are also likely to be effective in acute sinusitis and are recommended."
For otitis, amoxicillin is recommended as a first line therapy, and states "[e]ffective alternative drugs, especially for penicillin-resistant strains of *S. pneumoniae* or ampicillin-resistant strains of *H. influenzae*, include erythromycin sulfisoxazole, amoxicillin-clavulanic acid, extended spectrum cephalosporins, and clarithromycin... **Cefuroxime axetil**, cefpodoxime, and cefprozil are the only orally administered

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[12] Cherry JD & Newman Anita. Chapter 17, "Sinusitis" in Textbook of Pediatric Infectious Diseases, ed. 4, vol. 1, eds. Feigin RD, Cherry JD. (Philadelphia: WB Saunders Co.) 1998, p. 189.
[13] Gwaltney, Jr, JM. Chapter 44, "Sinusitis" in Principles and Practice of Infectious Diseases, 4th ed., eds. Mandell GL, Bennett JE, Dolin R. (New York: Churchill Livingstone) 1995, p. 589.
[14] Bartlett JG. 1998 Pocket Book of Infectious Disease Therapy. (Baltimore: Williams & Wilkins) p. 267.
[15] Nelson JD. 1998-1999 Pocket Book of Pediatric Antimicrobial Therapy. 13th ed. (Baltimore: Williams & Wilkins) p. 23.
[16] Gilbert DN, Moellering RC, Sande MA. The Sanford Guide to Antimicrobial Therapy 1998, 28th ed. (Vienna, VA: Antimicrobial Therapy, Inc.) p.35.
[17] Chow AW. "Infections of the Sinuses and Parameningeal Structures" in Infectious Diseases, 2nd ed., eds. Gorbach SL, Bartlett JG, Blacklow NR. (Philadelphia: WB Saunders Co.) 1998, p. 522.
[18] Gorbach SL, Bartlett JG, Falagas M, Hamer DH. 1999 Guidelines for Infectious Diseases in Primary Care. (Baltimore: Williams & Wilkins)

cephalosporins that have activity comparable to but not better than the activity of amoxicillin for highly resistant strains."

For *Moraxella catarrhalis*, it is recommended that "appropriate antibiotic choices include amoxicillin-clavulanate, cefixime, cefaclor, **cefuroxime**, erythromycin, clarithromycin, azithromycin, dirithromycin, and trimethroprim-sulfamethoxazole." [19]

Reviewer's note: *It is the opinion of various authoritative sources that cefuroxime axetil is an effective therapy for the treatment of acute bacterial maxillary sinusitis in both adult and pediatric populations. In addition, certain references relate efficacy in the treatment of acute otitis media with efficacy in the treatment of acute bacterial sinusitis in the pediatric populations.*

Conclusions and Recommendations:

Cefuroxime axetil has demonstrated efficacy and safety in adults with acute sinusitis and children with acute otitis media. Acute sinusitis in pediatric patients is an infectious disease entity considered very similar in its pathophysiology and microbiologic etiology to that of adults. While cefuroxime axetil is not as fully characterized with regard to pharmacokinetic profile in children as might be ideal, the preponderance of evidence supports its effectiveness in treating pediatric patients with acute sinusitis, and thus, labeling in the Pediatric Use sub-section of the package insert. Additionally, studies have appeared in the literature that support adequacy of this treatment and dosage regimen.

This Reviewer recommends approval of labeling changes, in accordance with the Pediatric Rule, for the use of cefuroxime axetil in the treatment of pediatric patients with acute sinusitis. These changes, as presented on the first page of this review, affect the PRECAUTIONS/ Pediatric Use and the DOSAGE AND ADMINISTRATION sections of the label.

/S/

Holli Hamilton, MD, MPH
Medical Officer
HFD-520

Concurrences:
HFD-520/DivDir/GChikami, MD /S/ 8/2/99
HFD-520/TL/JSoreth, MD /S/ 8/2/99

cc: Orig NDAs 50-672 & 50-605
HFD-520/Division File
HFD-520/CSO/BDuvallMiller
HFD-520/Microbiology/ASheldon
HFD-520/Chemistry/DKatague
HFD-520/Pharm/KUhl/FPelsor
HFD-520/MO/HHamilton
HFD-520/MTL/JSoreth

[19] 1997 Red Book: Report on the Committee on Infectious Diseases, pp. 222, 365,416.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50605/S-032

CHEMISTRY REVIEW(S)

NDA SUPPLEMENT REVIEW

CHEMIST'S REVIEW | **1. ORGANIZATION** DAIDP (HFD-520) | **2. NDA NUMBER** 50-605

3. NAME & ADDRESS OF APPLICANT

Glaxo Wellcome Inc.,
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

4. AF NUMBER

5. SUPPLEMENT(s) NUMBER(s) DATE(s)
SE1-032BC 7/21/99

6. NAME OF DRUG
Ceftin Tablets

7. NONPROPRIETARY NAME
Cefuroxime axetil Tablets

8. SUPPLEMENT(s) PROVIDES FOR:
Adding pediatric sinusitis to the package insert of Ceftin

9. AMENDMENTS AND OTHER (REPORTS, etc.) DATES
SE1-032BC 7/21/99

10. PHARMACOLOGICAL CATEGORY
Anti-bacterial

11. HOW DISPENSED
X
Rx OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM(s)
Tablet

14. POTENCY(ies)
125mg, 250mg, and 500 mg

15. CHEMICAL NAME AND STRUCTURE

$C_{20}H_{22}N_4O_{10}S$ MW: 510.48

(RS)-1-Hydroxyethyl(6R,7R)-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7^2-(Z)-(O-methyloxime),1-acetate 3-carbamate

16. RECORDS AND REPORTS

	Yes	No
CURRENT	X	
REVIEWED	X	

17. COMMENTS: EA categoric exclusion claimed.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend approval letter to issue for this supplement.

cc: Orig: NDA 50-605 HFD-520/Gavrilovich
HFD-520 HFD-520/Nambiar
HFD-520/Osterberg HFD-520/Duvall-Miller
HFD-520/Yu HFD-520/DKatague:R/D initialed DBK 8/2/99

NAME	REVIEWER SIGNATURE	DATE COMPLETED
Andrew Yu, PhD	/S/	30-JUL-1999

DISTRIBUTION ORIGINAL JACKET REVIEWER DIVISION FILE

NDA SUPPLEMENT REVIEW

CHEMIST'S REVIEW | **1. ORGANIZATION** DAIDP (HFD-520) | **2. NDA NUMBER** 50-672

3. NAME & ADDRESS OF APPLICANT

Glaxo Wellcome Inc.,
Five Moore Drive, PO Box 13398
Research Triangle Park
North Carolina 27709-3398

4. AF NUMBER

5. SUPPLEMENT(s)
NUMBER(s) DATE(s)
SE1-014BC 7/21/99

6. NAME OF DRUG
Ceftin for Oral Suspension

7. NONPROPRIETARY NAME
Cefuroxime axetil Powder for Oral Suspension

8. SUPPLEMENT(s) PROVIDES FOR:
Adding pediatric sinusitis to the package insert of Ceftin

9. AMENDMENTS AND OTHER (REPORTS, etc.) DATES
SE1-014BC 7/21/99

10. PHARMACOLOGICAL CATEGORY
Anti-bacterial

11. HOW DISPENSED
X
Rx OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM(s)
Powder for Oral Suspension

14. POTENCY(ies)
125mg and 250mg per 5 mL

15. CHEMICAL NAME AND STRUCTURE

$C_{20}H_{22}N_4O_{10}S$ MW: 510.48

(RS)-1-Hydroxyethyl(6R,7R)-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7²-(Z)- (O-methyloxime),1-acetate 3-carbamate

16. RECORDS AND REPORTS

	Yes	No
CURRENT	X	
REVIEWED	X	

17. COMMENTS: EA categoric exclusion claimed.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend approval letter to issue for this supplement.

cc: Orig: NDA 50-672 HFD-520/Gavrilovich
HFD-520 HFD-520/Nambiar
HFD-520/Osterberg HFD-520/Duvall-Miller
HFD-520/Yu HFD-520/DKatague:R/D initialed DBK 8/2/99

NAME Andrew Yu, PhD

REVIEWER SIGNATURE /S/

DATE COMPLETED 30-JUL-1999

DISTRIBUTION ORIGINAL JACKET REVIEWER DIVISION FILE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50605/S-032

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 50672 & 50605 50-672/SE1-014; 50-605/SE1-032
PRODUCT: Ceftin® for Oral Suspension and Ceftin® Tablets (cefuroxime axetil)
SUBMISSION DATE: September 15, 1998
SPONSOR: GlaxoWellcome
TYPE OF SUBMISSION: Supplemental Application: Labeling for use in Pediatric Sinusitis
OCPB REVIEWER: Kathleen Uhl

BACKGROUND:

Ceftin® is a semi-synthetic, broad –spectrum cephalosporin antibiotic for oral use. Ceftin® for Oral Suspension (cefuroxime axetil) is currently indicated for the treatment of pediatric patients from 3 months to 12 yrs in pharyngitis/tonsillitis, acute bacterial otitis media, and impetigo. The indications for Ceftin® Tablets (cefuroxime axetil) are broader and include acute bacterial maxillary sinusitis in adults. The NDA studies with Ceftin® Tablets were conducted in both adults and pediatric patients. The sponsor is submitting this Supplemental Application to support the addition of pediatric sinusitis to the PRECAUTIONS: Pediatric Use section of the labeling for Ceftin for Oral Suspension and Ceftin Tablets.

COMMENTS:

The pharmacokinetics/dynamics information submitted represent two publications in the literature. Previous Clinical Pharmacology/Biopharmaceutics reviews of pediatric data concluded linear kinetics across doses 10, 15, and 20 mg/kg given as single doses. Patients had the following diagnoses: facial cellulitis, pneumonia, cervical adenitis, and otitis media. Pharmacokinetics were not subclassified by diagnosis, however, those cases with predominantly otitis media appear to fit to the same concentration-time curves. Of particular note, one child was 12 years old and 4 children were 3-6 years old; due to this small number conclusions about dosing in these age groups should be made with caution. In addition, the Biopharmaceutics reviewer noted that the analytical methods for determination of cefuroxime in plasma were not fully validated and the data were therefore unacceptable. Two points were used to determine ke and half-life and this was concluded to represent an unreliable method.

RECOMMENDATIONS:

There are no new clinical pharmacology data submitted for review. No further action is necessary at this time.

/S/ 11/3/98

Kathleen Uhl, MD
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III
November 3, 1998

RD/FT initiated by F. PELSOR, Pharm D, Team Leader /S/ 11/3/98

cc:
HFD-520 Holli Hamilton, MO
HFD-520 ~~Carmen DeBellas,~~ CSO/ B. Duvall-Miller
HFD-880 Division File
HFD-880 F. Pelsor, Team leader
HFD-880 K. Uhl, Reviewer
CDR (attn. B. Murphy)
HFD-520/ Division File

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-672 50-605 Supplement # S-014 S-032 Circle one: SE1 SE2 SE3 SE4 SE5 SE6 S

HFD-520 Trade and generic names/dosage form: Ceftin (cefuroxime axetil) Tablets & Oral Suspension Action: (AP) AE NA

Applicant Glaxo Wellcome, Inc. Therapeutic Class cephalosporin

Indication(s) previously approved pharyngitis/tonsilitis, AOM, sinusitis, AECB, USSSI, UUTI, uncomp. gonorrhea, early Lyme

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___

Indication in this application pediatric sinusitis (Pediatric USL Subsection) impetigo (For supplements answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Project Manager 7/12/99
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 50-605, 50-672
HFD-520/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

HFD-520

DUVALL

MEMORANDUM OF TELECON

DATE: Tuesday, December 1, 1998

APPLICATION NUMBER: NDAs 50-605/SE1-032 and 50-672/SE1-014; Ceftin® (cefuroxime axetil) Tablets and Suspension

BETWEEN:

Name: Ms. Anne Stokley, Product Director, Regulatory Affairs
Mr. Bob Watson, Product Director, Regulatory Affairs
Ms. Melissa Beaman, Manager, Labeling Policy
Dr. Preston Holley, Clinical Program Head, Ceftin
Phone: (919) 483-0400
Representing: GlaxoWellcome

AND

Name: Ms. Beth Duvall-Miller, Project Manager
Dr. Holli Hamilton, Medical Officer
Dr. Kathleen Uhl, Biopharmaceutics Reviewer
Dr. Janice Soreth, Medical Team Leader
Dr. Gary Chikami, Division Director
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Pooling of existing data to support inclusion of beta-lactamase producing strains of *Haemophilus influenzae* in product labeling

GlaxoWellcome (GW) submitted supplemental applications 50-605/SE1-032 and 50-672/SE1-014 on September 14, 1998 for inclusion of pediatric use information for the treatment of sinusitis with Ceftin. Dr. Holli Hamilton noted in her preliminary review of these applications that the adult indication for sinusitis is written as follows: "**Acute Bacterial Maxillary Sinusitis** caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-beta-lactamase producing strains only)". On October 20, 1998 FDA and GW discussed the possibility of collating existing clinical trial data that demonstrate Ceftin's effectiveness towards both beta-lactamase producing strains of *H. influenzae* as well as *Moraxella catarrhalis* such that the labeling for the adult sinusitis indication can be updated to included these pathogens. This telecon was held as a follow-up to the October 20, 1998 telecon in order to determine what data, if any, both FDA and GW personnel were able to uncover in order to support such a labeling change. Prior to the telecon, FDA and GW exchanged facsimiles dated December 1, 1998 (attached) summarizing the microbiological and clinical data that were unearthed. These facsimiles served as the basis for discussion during this telecon.

GW referred FDA to Table 6 which summarized data from a comparative (versus Augmentin) Canadian clinical trial, 506/120, where samples for culture were obtained by endoscopy. This trial would add a total of 6 cures/8 isolates of beta-lactamase producing strains of *H. influenzae* treated with Ceftin for the treatment of sinusitis.

FDA asked GW what the response rates were in the subset of patients whose isolates were identified as 23% pencillinase-producing strains of *H. influenzae* and 95% penicillinase-producing strains of *M. catarrhalis* as described below Table III on page 110 of the literature article faxed by GW. GW responded that they are not sure whether they can get further data from that clinical trial to answer that question. FDA commented that the cure rates in those subsets would be helpful. GW noted that the literature article was submitted primarily to support a claim for *M. catarrhalis*. FDA also commented that it would be helpful to know what type of aspiration was done in that trial as well as obtaining Gram-stain data to corroborate the results from endoscopy.

GW noted that they cannot easily obtain data from Bayer's study of ciprofloxacin versus cefuroxime axetil in the treatment of sinusitis and therefore wondered if the two sources of data they have summarized in their facsimiles would be enough to support inclusion of labeling for both beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*. FDA responded that submission of Gram-stain data, the clinical and microbiological protocols including the entry criteria used in the trials, and the response rates of the subset of patients with the pathogens in question would make a strong package. GW noted that they can provide the protocols but are not sure if the Gram-stain data can be obtained. FDA noted that without Gram-stain data it would be difficult to validate endoscopic samples because such samples could be contaminated. Less than that, FDA commented that approval of updated labeling to include labeling for beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* would depend on the overall package submitted by GW. FDA acknowledged that while the numbers of isolates GW provided in their facsimiles looks strong, the data need to be validated for inclusion into product labeling. GW responded that they need to get a better feel for the strength of their package, in light of FDA's recommendations, before they proceed with the submission of an efficacy supplement to update the adult sinusitis indication.

GW agreed to look into obtaining primary data for both the Canadian study (506/120) and the sparfloxacin literature study although they noted that it may be difficult to obtain proprietary information (sparfloxacin study). FDA commented that it might also be helpful to look into both the Gatspar and CAE-T72 foreign studies that were part of GW's original application for the sinusitis indication. FDA commented again that Gram-stain data would be important to obtain, especially in cases of mixed infections. GW agreed to look at data from these studies.

GW asked if they were unable to obtain the necessary supportive data to garner labeling for beta-lactamase-producing strains of *H. influenzae*, would the data they have collected be supportive of a claim for effectiveness against *M. catarrhalis*. FDA agreed that a reasonable argument could be made for *M. catarrhalis* based on the data discussed herein but would have to review the data to respond more definitively.

Action Items:

- GW to determine if primary data is available from studies 506/120, Gatspar, CAE-T72, and the sparfloxacin literature study to support labeling claims for effectiveness against both beta-lactamase producing strains of *H. influenzae* as well as *Moraxella catarrhalis*

in the treatment of sinusitis.

- GW to assess strength of data for future filing of efficacy supplement to support claims stated above.
- GW and FDA to coordinate logistics of filing abovestated supplement within framework of PDUFA timelines for 50-605/SE1-032 and 50-672/SE1-014 (PDUFA goal date: September 14, 1999; Action Performance Goal Date: July 14, 1999).

/S/

Beth Duvall-Miller
Project Manager

cc:
Original NDA 50-605/SE1-032
Original NDA 50-672/SE1-014
HFD-520/Div. Files
HFD-520/B. Duvall-Miller
HFD-520/MO/H. Hamilton
HFD-520/DivDir/G. Chikami

Concurrence only:
HFD-520/SCSO/J. Bona
HFD-520/MO/H. Hamilton 12/14/98
HFD-520/SMO/J. Soreth 12/15/98
HFD-520/DivDir/G. Chikami 12/14/98

drafted: bdm/December 8, 1998/M:\TELECON\N50605.032
r/d initials:
final: 12/14/98

TELECON

Journal of Antimicrobial Chemotherapy (1996) 37, *Suppl. A*, 105–114

Sparfloxacin versus cefuroxime axetil in the treatment of acute purulent sinusitis

P. Gehanno[a], P. Berche[b] and the Sinusitis Study Group*

[a]*Service d'Oto-rhino-laryngologie, Hôpital Bichat-Claude Bernard, Paris;*
[b]*Hôpital Necker-Enfants malades, Laboratoire de microbiologie, Paris, France*

In a double-blind, multicentre trial, 382 patients with a diagnosis of acute purulent sinusitis were randomised to receive sparfloxacin 200 mg once daily for 5 days following a loading dose of 400 mg on day 1 ($n = 193$) or cefuroxime axetil 250 mg twice daily for 8 days ($n = 189$). Patients were classified as success or failure according to clinical symptoms plus bacteriological and radiological data at the end of treatment and at a follow-up visit. In analyses of the intent-to-treat ($n = 374$) and evaluable populations ($n = 304$), the 5 day course of sparfloxacin was at least as effective and well tolerated as the 8 day course of cefuroxime axetil. The success rates at the end of treatment in the evaluable population were 82.6% and 83.2% in the sparfloxacin and cefuroxime axetil groups, respectively. The pathogens isolated most frequently were *Haemophilus influenzae* (33%) and *Streptococcus pneumoniae* (28%). Response rates according to the bacterial aetiology of the acute sinusitis were similar in the two treatment groups. Both drugs were well tolerated. The commonest adverse events were gastrointestinal and were reported in 2.6% and 3.8% of sparfloxacin- and cefuroxime axetil-treated patients, respectively.

Introduction

Acute bacterial sinusitis is a common infectious disease (Lowenstein & Parrino, 1987). The bacteria most frequently isolated are *Haemophilus influenzae* and *Streptococcus pneumoniae*. *Streptococcus pyogenes*, *Staphyloccocus aureus*, *Moraxella catarrhalis* and the Enterobacteriaecae are implicated less frequently (Ylikoski Savolainen & Jousimiès-Somer, 1989; Gehanno *et al.*, 1991). The number of strains resistant to antimicrobial therapies generally recommended for the treatment of acute sinusitis is increasing in France. According to the French Centre National de Référence of *H. influenzae*, in 1990 23% of isolates from the upper respiratory tract were β-lactamase producers and had reduced susceptibility to amoxycillin (Dabernat, 1991). The same year, the French Centre National de Référence of *S. pneumoniae* published that 12%

*Sinusitis Study Group: Dr Danon, Dr Darmon, Dr Car, Dr Amsellem, Dr Timsit, Dr Amsellem, Dr Nemi, Dr Tlili, Dr Trottin, Dr Cambriel, Dr Levy, Dr Meaux, Dr Lafosse, Dr Blassin, Dr Hamman, Dr Lefranc, Dr Marsac, Dr Reboul, Dr Donnadieu, Dr Lefebvre, Dr Aronio de Ron, Dr Deloix-Vericel, Dr Dubouz, Dr Flieder, Dr Rousselet, Dr Samson, Dr Vericel, Dr Tsigaridis, Dr Popot, Dr Jacquin, Dr Huart, Dr Ebbo, Dr Dufour, Dr Cornubert, Dr Baculard, Dr Meunier, Dr Lopez-Moya, Dr Vigneron, Dr Bonnard, Dr Isasa, Dr Bourrel, Dr Agustin, Dr Asseus, Dr Banal, Dr Barrier, Dr Betsch, Dr Bringart, Dr Cassat, Dr Chattey, Dr Chevet, Dr Gavilan, Dr Grison, Dr Guedon, Dr Guerin, Dr Janssen, Dr Kraimps, Dr Lelièvre, Dr Miller, Dr Pichelin, Dr Alvarez-Vincent and Dr Sabatier.

0305–7453/96/37A105 + 10 $12.00/0

of strains were less susceptible or resistant to penicillin and approximately 20% were resistant to macrolides (Geslin *et al.*, 1992). In this context, it could be useful to propose an alternative antimicrobial therapy for the treatment of acute purulent sinusitis.

Sparfloxacin is a new aminofluoroquinolone which is more active against *S. pneumoniae* than the currently available quinolones, irrespective of the susceptibility profile to penicillin and macrolides (MIC_{90} 0.25 mg/L). It is also active against *M. catarrhalis* and *H. influenzae*, including β-lactamase producers (MIC_{90} < 0.03 mg/L) (Cooper *et al.*, 1990). In addition, sparfloxacin is active against other Gram-positive cocci, including staphylococci, Enterobacteriaceae and intracellular pathogens (Cooper *et al.*, 1990; Rolston *et al.*, 1990; Barry & Fuchs 1991; Chin *et al.*, 1991; Visser *et al.*, 1991).

Sparfloxacin diffuses rapidly into the upper respiratory tract (Honeybourne *et al.* 1994). It attains concentrations in sinus mucosa (5.8 mg/kg) five to ten times greater than those in plasma after a single oral 400 mg dose (Massias *et al.* 1993). Sparfloxacin has a long terminal plasma elimination half-life (20 h) and is widely distributed into most body fluids and tissues (Shimada, Nogita & Ishibushi, 1993). These pharmacokinetic characteristics, combined with its prolonged post-antibiotic effect (Patron *et al.*, 1991), suggest that sparfloxacin administered once daily for 5 days should be a valuable treatment for acute purulent sinusitis.

Cefuroxime axetil, a broad-spectrum oral cephalosporin, is an established treatment for acute purulent sinusitis (Camacho *et al.*, 1992). The aim of this study was to compare the efficacy and safety of sparfloxacin with that of cefuroxime axetil in the treatment of acute purulent sinusitis in adults.

Materials and methods

Study design

This randomised, double-blind, comparative multicentre study was conducted between October 1990 and November 1991. The study was approved by the local Ethics Committees and the investigators adhered to the terms of the declaration of Helsinki. All patients had to give their written consent to participate in the study.

Patients

Out-patients ≥ 18 years of age were enrolled in the study if they had acute onset sinusitis (<3 weeks' duration) which was diagnosed according to the following criteria: pus on the middle meatus and/or purulent rhinorrhoea and pain or tenderness over the affected sinuses. A sample of sinus discharge was taken by aspirate from the middle meatus for microbiological culture and sensitivity tests. Patients with any of the following conditions were excluded: other pathology causing nasal airway obstruction; a history of chronic sinusitis, chronic liver disease, renal failure (serum creatinine > 170 μmol/L); and any condition, including a significant underlying disease or concomitant infection, which might have obscured the evaluation of the clinical response. Administration of other antibacterial agents within 48 h before inclusion in the study, systemic or local corticosteroid therapy within 7 days of inclusion and the use of non-steroidal anti-inflammatory drugs was not allowed. Patients with a history of hypersensitivity to

quinolones or β-lactams and women who were pregnant or breastfeeding were excluded from the study.

Treatment

Patients were assigned randomly to receive either sparfloxacin (400 mg on day 1, 200 mg on days 2–5, and placebo on days 6–8) or cefuroxime axetil (250 mg twice daily on days 1 to 8) (Glaxo Laboratories, Paris, France). Blinding was prepared by the Rhône Poulenc Rorer CMP/IBP Department and maintained throughout the study.

Assessment criteria

Patients were assessed by the investigators at study entry (inclusion visit), after 4 days of treatment if necessary, at the end of treatment (on day 11 ± 1) and at follow-up (on day 20 ± 1). The patients were telephoned by the investigators on days 4 and 20 to determine whether a visit was necessary. At each evaluation, patients were assessed for clinical symptoms such as purulent rhinorrhoea, pus on the middle meatus or posterior pharyngeal wall and the severity of pain and tenderness over affected sinuses. Patients were given a diary card on which they recorded their temperature, pain and nasal discharge once daily for the duration of the study. Sinus X-rays were taken within 24 h of starting treatment and either at the end of treatment or at follow-up. All inclusion and post-treatment sinus X-rays were assessed blind by the co-ordinator of the study. Bacteriological culture of the middle meatus aspirate was performed at inclusion and repeated at the end of treatment and follow-up in case of treatment failure. All bacteriological procedures were performed at a central reference laboratory (Prof. P. Berche, Hôpital Necker-Enfants malades, Laboratoire de microbiologie). MICs of isolates were determined in the reference laboratory using preprepared microtitre trays with prediluted antibiotics (Flow Laboratories) to sparfloxacin, penicillin, amoxycillin/clavulanic acid and erythromycin.

Efficacy was assessed according to a combination of clinical, bacteriological and radiological variables, both at the end-of-treatment and the follow-up visit. Patients were considered as overall success when (i) the clinical symptoms (e.g. purulent rhinorrhoea, pus on the middle meatus and pus on the posterior pharyngeal wall) resolved, (ii) the follow up X-ray taken after day 20 was normal and (iii) the bacteria isolated at inclusion were eradicated or presumed to be eradicated. Because there is usually a delay before the X-ray normalises, a patient who was clinically cured but in whom an early follow-up X-ray (before day 21) was not normalised was still considered a success. Patients who were clinically and radiologically cured but did not have a repeat culture and those with sterile culture at inclusion and at the endpoint were classified as success. All other patients were automatically classified as non-success and ambiguous cases were reviewed in blinded fashion by an external steering committee. Patients who were classified as non-success at the end of treatment and were evaluable at follow-up were automatically classified as non-success.

Safety

All patients who received at least one dose of the study medication were included in the safety analysis. The primary safety variables were adverse events, changes in physical

findings and clinically significant adverse events. Adverse events (volunteered or elicited by non-specific questioning) were recorded at each visit after admission and were classified by the investigator as to severity and relationship to study medication.

Statistical analysis

The intent-to-treat population included all patients who received at least one dose of the study medication. The evaluable population included all patients with clinical symptoms of acute sinusitis and abnormal X-ray and/or positive culture results. Efficacy was assessed in both the evaluable and intent-to-treat populations. An equivalence approach was used and based on a two-sided 90% confidence interval (90% CI) of the difference between success rates of cefuroxime axetil and sparfloxacin. The objective was to demonstrate that the cefuroxime axetil success rate was not more than 10% above the sparfloxacin success rate. Therefore, only the upper limit of the 90% CI of the difference was considered for the statistical interpretation of the results. The 90% CI indicated that there was a 90% probability that the true difference between the treatments was within the interval and, more specifically, that the probability of a true difference greater than the upper limit in favour of cefuroxime axetil was only 5%. All statistical analyses were carried out with SAS software package (SAS Institute, Cary, North Carolina, USA).

Results

Patients

A total of 382 patients were randomised in the study. The intention-to-treat population consisted of 374 patients because three patients in each treatment group withdrew their consent before taking any dose of the study drug. Two additional patients in the cefuroxime axetil group were excluded by decision of the Steering Committee, one because he began treatment 1 month after the inclusion visit and the other because he had no sign of purulent sinusitis. Thirty-five patients in each treatment group were excluded from the evaluable population. The main reason for exclusion from the evaluable population was a normal sinus X-ray plus a negative bacteriological sample at inclusion (28 sparfloxacin-treated patients and 29 cefuroxime axetil-treated patients). Other reasons for non-evaluation were: discontinuation because of an adverse event (6); unwarranted broken codes (3); missing efficacy data (2) and ingestion of prohibited medications during the study period (2). The reasons for exclusion were evenly distributed between the two treatment groups. A total of 304 patients were evaluable at the end-of-tretment visit, 155 in the sparfloxacin group, and 149 patients in the cefuroxime axetil group.

The demographic, clinical and radiological characteristics of the treated population are shown in Table I. The first clinical signs or symptoms of sinusitis appeared within 3 days before starting the treatment in 32.6% of patients, within 4–7 days in 33.7% and >7 days (but <3 weeks) in 33.9%. This distribution did not differ in the treatment groups.

Of 304 patients evaluable for efficacy, 237 (78.0%) had an abnormal sinus X-ray at inclusion. The sinus X-ray revealed maxillary sinusitis in 92.9% of cases, half of which were bilateral. Six per cent of patients had a pansinusitis. Opacity of the affected sinus

Table I. Patient demographic, clinical and radiological characteristics

	Sparfloxacin (n = 190)	Cefuroxime axetil (n = 186)
Mean age (±S.E.M.) (y)	41 ± 1	42 ± 1
Male/female	74/116	86/100
Purulent rhinorrhoea (%)	98.4	96.8
Pus on middle meatus (%)	94.7	94.6
Pain (moderate or severe) (%)	72.6	72.4
Tenderness (moderate or severe)	69.0	66.4
Mean temperature ±S.E.M. °C	37.9 ± 0.07	37.9 ± 0.06
Abnormal sinus X-ray (%)	127 (66.8%)	111 (59.7%)
opacity	99 (78.0%)	91 (82.0%)
air-fluid level	15 (11.8%)	11 (9.9%)
mucosal swelling	12 (9.4%)	9 (8.1%)
other	1	—

was the main abnormality observed (79.1%), followed by an air-fluid level (11.2%) and mucosal swelling (8.6%). More patients in the sparfloxacin group had an abnormal sinus X-ray at inclusion (81.9% *vs* 73.8% in the cefuroxime axetil group). Moreover, the follow-up X-ray was performed after day 21 in 19 patients (12.3%) in the sparfloxacin group and in only nine patients (6.0%) in the cefuroxime axetil group.

Two hundred and thirty-two patients (76.3%) had a positive bacteriological culture at inclusion: 117 in the sparfloxacin group (75.5%) and 115 in the cefuroxime axetil group (77.2%). *H. influenzae* and *S. pneumoniae* were the most frequently isolated pathogens (Table II). *Corynebacterium* spp. and *Staphylococcus epidermidis*, which were not classified as pathogens, were seldom isolated and accounted for 1.8 and 1.5% of the isolated strains, respectively. There was no difference in the distribution of pathogens between patients who had an abnormal X-ray plus positive bacteriological culture and those who only had a bacterial documentation of the acute sinusitis; *H. influenzae* 33 and 36%, *S. pneumoniae* 32 and 25%, *M. catarrhalis* 7.5 and 17% and *S. aureus* 13 and 11% in these subgroups, respectively. The MIC_{90}s of sparfloxacin, penicillin, amoxycillin/clavulanic acid and erythromycin for the three main pathogens isolated are presented in Table III. Penicillin resistance (MIC ≥ 0.1 mg/L) was detected in 10.6% of *S. pneumoniae* strains and erythromycin resistance (MIC ≥ 1 mg/L) was

Table II. Distribution of pathogens isolated in 232 patients evaluable for primary efficacy. (Percentages were calculated on the total number of isolated pathogens)

	Sparfloxacin	Cefuroxime	Total
H. influenzae	53	39	92 (32.4%)
S. pneumoniae	38	41	79 (27.8%)
M. catarrhalis	17	13	30 (10.6%)
S. aureus	15	18	33 (11.6%)
Enterobacteriaceae	14	14	28 (9.9%)
Pseudomonas aeruginosa	2	3	5 (1.8%)
β-Haemolytic streptococci	3	0	3 (1.1%)
Other	7	7	14 (4.9%)
Total	149	135	284

Table III. Susceptibility profile of the main isolated pathogens. The percentages of *H. influenzae* and *M. catarrhalis* penicillinase producing-strains were 23% and 95% respectively. The resistance rate of *S. pneumoniae* to penicillin was 11% (MIC ≥ 0.1 mg/L), 15% to erythromycin (MIC ≥ 1 mg/L). The resistance rate of *H. influenzae* to erythromycin was 31% (MIC ≥ 2 mg/L)

	MIC_{90} mg/L(range)		
	S. pneumoniae ($n = 63$)	*H. influenzae* ($n = 88$)	*M. catarrhalis* ($n = 27$)
Sparfloxacin	0.25 (0.03–1.0)	0.008 (0.008–0.015)	0.015 (0.008–0.015)
Cefuroxime axetil	0.125 (<0.015–4.0)	1.0 (<0.015–4.0)	1.0 (0.125–2.0)
Penicillin	0.06 (0.03–1.0)	—	—
Amoxycillin-clavulanate	—	0.125 (<0.06–8.0)	0.125 (<0.06–0.25)
Erthromycin	>8 (<0.015–32)	2.0 (0.25–8.0)	0.125 (0.03–0.125)

detected in 15.3% of *S. pneumoniae* strains. The MIC of erythromycin against 30.7% of the strains of *H. influenzae* was ≥2 mg/L. Of the *H. influenzae* and *M. catarrhalis* strains isolated, 23 and 95%, respectively, were penicillinase-producers.

One hundred and fifty-three evaluable patients out of the 374 had both an abnormal X-ray and a positive culture at inclusion, 82 (43.2%) and 71 (38.6%) in the sparfloxacin and cefuroxime axetil treatment groups, respectively.

Overall efficacy

The 5 day course of sparfloxacin proved to be at least equivalent in efficacy to the 8 day course of cefuroxime axetil, both in the intention-to-treat and evaluable population analyses (Table IV).

The efficacy in patients with both an abnormal sinus X-ray and a control X-ray performed plus a positive bacteriological sample at inclusion was slightly lower in the sparfloxacin group than in the cefuroxime axetil group (80.3% *vs* 82.4%). The efficacy in bacteriologically evaluable patients was similar in the two treatment groups (84.3% in sparfloxacin-treated patients *vs* 84.4% in cefuroxime axetil-treated patients). The efficacy in patients with an abnormal X-ray at inclusion was 79.8% (83/104) in the cefuroxime axetil group and 76.7% (92/120) in the sparfloxacin group. Efficacy results according to bacterial aetiology are shown in Table V. The numbers of each organism isolated were too small to allow statistical comparisons between the two treatment groups.

Clinical efficacy

Most of the patients were not examined clinically at the follow-up visit because this visit was not mandatory and could be limited to a telephone call. Therefore, for clinical efficacy, results at the end of treatment appear the most relevant.

The clinical efficacy (based on the resolution of all signs and symptoms) of sparfloxacin was 87.6%, similar to that for cefuroxime axetil (87.2%) and 4–5% higher than that of overall efficacy which took into account clinical, radiological and bacteriological efficacy.

Table IV. Overall efficacy and clinical efficacy

	Sparfloxacin	Cefuroxime axetil	Statistical results (90% CI)
Overall Efficacy			
intent-to-treat analysis, follow-up	150/190 (79.0%)	145/184 (78.8%)	[−7.1; 6.8%]
evaluable population, end of treatment	128/155 (82.6%)	124/149 (83.2%)	[−6.5; 7.7%]
evaluable population, follow-up	122/152 (80.3%)	119/145 (82.1%)	[−5.6; 9.3%]
Clinical Efficacy			
evaluable population, end-of-treatment	134/153 (87.6%)	130/149 (87.2%)	

Bacteriological efficacy

Purulent rhinorrhoea or the presence of pus on the middle meatus had disappeared at the end of treatment visit in the majority of cases. This explains why the number of bacteriological samples at the end-of-treatment visit was very low (11/220 patients). In this context, bacterial eradication was presumed in patients who were clinically cured. Presumed or definite bacterial eradication was achieved in 93.6% and 89.2% of patients in the sparfloxacin and cefuroxime axetil treatment groups, respectively. There were no cases of persistant pathogens in the sparfloxacin treatment group and three cases in the cefuroxime axetil group (one *M. catarrhalis* and two *S. aureus*). Two cases of superinfection occurred in both treatment groups: one case of *H. influenzae* and one of *S. aureus* in the cefuroxime axetil treatment group and one case of *S. pneumoniae* (considered to be a new pathogen, as the MICs differed from those of the original isolate for at least three drugs) and one case of *S. aureus* in the sparfloxacin group.

Analysis of failures

According to the rules of the protocol, 56 evaluable patients were classified as treatment failures at follow-up: 30 in the sparfloxacin group and 26 in the cefuroxime axetil group. The rate of persisting pus was similar in both groups (77% of patients classified as non-success, 23 and 20 patients in the sparfloxacin and cefuroxime axetil treatment groups, respectively) but the rate of persisting abnormal X-rays was slightly higher in the sparfloxacin group (24/30, 80%) than in the cefuroxime axetil group (14/26, 54%).

Table V. Overall efficacy according to the bacterial actiology in the evaluable population at follow-up

	Sparfloxacin	Cefuroxime axetil
H. influenzae	43/51 (84.3%)	32/38 (84.2%)
S. pneumoniae	34/38 (89.5%)	36/39 (92.3%)
M. catarrhalis	16/17 (94%)	11/13 (85%)
S. aureus	14/14 (100%)	14/18 (78 %)
Enterobacteriaceae	13/14 (93%)	14/14 (100%)
P. aeruginosa	1/2	2/3
β-haemolytic streptococci	1/3	—

Twenty-two of fifty-six patients (39%) received a second-line antibiotic therapy: nine patients in the sparfloxacin group (30% of all patients classified as non-success) and 13 of those treated with cefuroxime axetil (50%).

Safety

Both study medications were well tolerated. Nineteen patients (10%) in the sparfloxacin group and 15 (8.1%) in the cefuroxime axetil group experienced adverse events. The most commonly reported adverse events were gastrointestinal in nature: five in the sparfloxacin group (14% of reported adverse events) and seven in the cefuroxime axetil group (24% of reported adverse events). Definite or presumed phototoxicity was experienced by six patients who were treated with sparfloxacin (3.0%) and rash occurred in five patients in the cefuroxime axetil group (2.7%). Treatment was discontinued as a result of an adverse event in seven patients (3.7%) in the sparfloxacin group and five patients (2.7%) who received cefuroxime axetil.

Discussion

In most cases, antibacterial treatment for community-acquired acute sinusitis is empirical and must be effective against the most likely potential pathogens including *S. pneumoniae*, *H. influenzae* and, less frequently, *M. catarrhalis*.

β-Lactam antibiotics and macrolides are widely used for the treatment of upper respiratory tract infections. Until recently, the fluoroquinolones available were not indicated in the treatment of acute purulent sinusitis because they lack sufficient activity againt *S. pneumoniae* (Canton *et al.*, 1992; Körner, Reeves & MacGowan, 1994). Sparfloxacin is a new aminofluoroquinolone which has good antibacterial activity *in vitro* against the commonest pathogens responsible for acute sinusitis, particularly *S. pneumoniae*, irrespective of the susceptibility profile to penicillin and macrolides. Moreover, sparfloxacin can be administered once daily for five days, a shorter regimen than the 7- to 14-day course generally necessary for other antimicrobial agents used to treat this infection.

The clinical characteristics of the present study population corresponded well with the usual clinical features of the disease; purulent rhinorrhoea and pain and/or tenderness in the face were the most common signs and symptoms. Radiological evidence of sinusitis was observed in only 63.4% of patients and this could appear as a low rate. This was probably because the sinus X-rays were interpreted centrally by one person and the criteria for classifying an X-ray as abnormal were very stringent. In previous clinical trials, sinus X-rays have generally been interpreted by the various practitioners involved, resulting in a 100% of patients having radiological documention of sinusitis in these studies (Gehanno *et al.*, 1990). It is therefore difficult to compare the results of the present clinical trial with those of others. However, the method for bacteriological sampling, which was not invasive in contrast to the reference method of sinus puncture, resulted in a bacterial epidemiology similar to that reported in the literature (Jousmies-Somer, Savolainen & Yliroski, 1988; Camacho *et al.*, 1992).

H. influenzae and *S. pneumoniae* were the commonest pathogens isolated. The rate of isolation of *S. aureus* (11.8%) could appear high, suggesting the presence of skin colonising strains. However, *Corynebacterium* spp. and *S. epidermidis* accounted for a very low rate of isolates and similar rates of acute sinusitis caused by *S. aureus* have

been published in the literature (Gehanno *et al.*, 1990; Camacho *et al.*, 1992). The rate of β-lactamase-producing strains of *H. influenzae* was in the same range as data collected in France. In contrast, the percentage of *S. pneumoniae* strains found to be less susceptible or resistant to penicillin was less than some reported French data (Geslin, Fremaux & Sizsia, 1992). However, at the time this study was conducted, the rate of *S. pneumoniae* resistance to penicillin was not as high in acute sinusitis in adults as it is at present.

The statistical analysis used for this clinical trial was based on an equivalence approach. This was justified because the success rate of antibiotic treatment in this disease is usually 85% or greater. In this context, it is difficult to prove that a new antibacterial agent is superior to standard therapy by 5–10%. From the overall efficacy results and according to the statistical analysis, sparfloxacin 200 mg once daily for 4 days following a loading dose of 400 mg was as effective as an 8 day course of cefuroxime axetil 250 mg twice daily. However, the global 83% success rate observed in the evaluable population in this trial was nearly 10% lower than those found in similar studies in acute sinusitis (Gehanno *et al.*, 1990; Scandinavian Study Group, 1993). This can be explained by the more stringent inclusion and assessment criteria in the present study. That is also true considering the intent-to-treat analysis where, in order to avoid any bias, all the patients classified as unevaluable or those with missing data were automatically classified as non-success. In the sparfloxacin group, the rate of abnormal X-ray at inclusion was higher and follow-up X-rays were more frequently performed later than in the comparator group. This may have placed the sparfloxacin group at a slight disadvantage since some patients were classified as non-success because their sinus X-ray was not yet resolved or had chronic abnormalities although all signs and symptoms had disappeared. This is supported by the similar clinical success rates and by the fact that a lower proportion of patients classified as non-success received a second-line antibiotic therapy in the sparfloxacin group compared to the cefuroxime axetil group. This indicates that a non-success was not necessarily considered as treatment failure by the physicians.

In conclusion, this study demonstrated in a well-defined population of out-patients suffering with acute purulent sinusitis that sparfloxacin 200 mg for five days could be a suitable empirical antibiotic treatment. It may be a particularly appropriate choice in countries where there is a high incidence of β-lactamase-producing strains of *H. influenzae* or *S. pneumoniae* strains that are not fully susceptible to penicillin.

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