CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 050667/S011 and 050668/S013

Trade Name LORABID

Generic Name Loracarbef

Sponsor Lilly Research Laboratories

50-667/S-011
50-668/S-013

Lilly Research Laboratories
Attention: Wayne Millar, Ph.D.
Senior Regulatory Scientist
Lilly Corporate Center
Indianapolis, Indiana 46285

97-03-19P04:22

Dear Dr. Millar:

Please refer to your November 8, 1995 supplemental new drug applications submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Lorabid® (Loracarbef) for Oral Suspension, NDA 50-667/S-011 and Lorabid® (loracarbef) Capsules, NDA 50-668/S-013.

We also reference your amendment dated November 8, 1996.

These supplemental applications provide for the addition of Pediatric Sinusitis to the **INDICATIONS AND USAGE** section of the labeling.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated November 8, 1995. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on November 8, 1995.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 50-667/S-011 and 50-668/S-013. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

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

NDA 50-667/S-011
NDA 50-668/S-013

If you have any questions, please contact:

Carmen DeBellas
Consumer Safety Officer
(301) 827-2125

Sincerely yours,

11.13.96

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-667
50-668
HFD-520/Div. files
HFD-520/CSO/C.DeBellas 11/12/96
HFD-520/SMO/Bonwit
HFD-104/D.Feigal
HFD-101/L.Carter
HFD-830/E.Sheinin
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

Concurrence:

HFD-520/SCSO/Bona
HFD-520/ACTDIVDIR/Feigal
HFD-520/SMO/Soreth

drafted: cld/November 5, 1996/50667.11
r/d Initials:
final: APPROVAL

NDA 50-667/S-011
NDA 50-668/S-013

REVIEW OF DRAFT FINAL PRINTED LABELING (FPL)

APPLICANT: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

DATE OF SUBMISSIONS: November 8, 1995

DATE OF REVIEW: November 6, 1996

NAME OF DRUG: NDA 50-667 Lorabid® (Loracarbef) for Oral Suspension
NDA 50-668 Lorabid® (Loracarbef) Capsules

GENERIC NAME: See above

Purpose of Submission:

To request approval of the following proposed revisions to the package insert for Lorabid®

DOSAGE AND ADMINISTRATION

INFANTS AND CHILDREN (6 months to 12 years)

Acute maxillary sinusitis 30 mg/kg/day in divided doses q12h

RECOMMENDATIONS:

The Medical Officer recommends approval of the requested labeling changes based on the use of the U.S. Code of federal Regulations 201.57(9)(iv) (Pediatric Rule) with the clinical and microbiologic data previously submitted to approve Lorabid Oral Suspension/Lorabid Capsules for the treatment of acute maxillary sinusitis in a adults and acute otitis media in children. The label should be amended as follows:

INDICATIONS AND USAGE

PRECAUTIONS

The Pediatric Use statement should read as follows:

DOSAGE AND ADMINISTRATION

Population/infection	Dosage (mg	Duration (days)
Acute maxillary sinusitis	30 mg/kg/day in divided doses q12h	10

Carmen DeBellas, R.Ph.

Andrew Bonwit, M.D.

Janice Soreth, M.D.

Orig NDA
50-667
50-668

HFD-520/Div. files
HFD-520/SMO/Soreth 11/8/96
HFD-520/CSO/C.DeBellas
HFD-520/MO/Bonwit
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling)
drafted: /11/7/96/
r/d Initials:CLD
final:

Concurrence:

HFD-520/SCSO/Bona
HFD-520/DivDir/Feigal 11/13/96

Wayne
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NOV 13 1996

MEDICAL OFFICER'S REVIEW OF SUPPLEMENT: SINUSITIS IN CHILDREN

NDA 50-668/SES-013
50-667/SES-011

SPONSOR: Eli Lilly and Company

Date of Supplement Submission:	8 Nov 1995
Date of Supplement Receipt:	14 Nov 1995
Date of Assignment to This Reviewer:	28 Feb 1995
Review Initiated:	26 Mar 1996
First Draft to Supervisory M.O.:	30 Aug 1996
Review Completed:	8 Nov 1996

NAME OF DRUG.

Generic: Loracarbef
Trade: Lorabid(R) Oral suspension / Lorabid(R) Pulvules(R)
Class: Carbacephem

MATERIALS SUBMITTED TO THE FDA FOR THIS SUPPLEMENT:

1. Cover letter from Dr. T. R. Franson of Lilly Research Laboratories, describing the requested labeling change and the reasons to support it.
2. Executive Summary.
3. References from the medical literature.
4. "Integrated Efficacy Summary, Submitted to Loracarbef NDA on February 19, 1991."
5. "Multiple Dose Pharmacokinetics in Pediatric Patients, B9U-MC-AZAZ, Final Report, Submitted to Loracarbef NDA on August 27, 1990."
6. "Integrated Safety Summary, Submitted to Loracarbef NDA on February 19, 1991."
7. "Proposed Revised Loracarbef Label."
8. "Frequency of Treatment-Emergent Signs and Symptoms by Age Group."

RELATED MATERIAL:

Medical Officer's Review of NDAs 50-667 and 50-668, dated December 29, 1991.

PURPOSE OF SUBMISSION:

To request approval of the following *proposed revisions to the package insert for Loracarbef(R)*: in the section on DOSAGE AND ADMINISTRATION, to add:

CURRENT LABEL PERTAINING TO SINUSITIS:
ADULTS (13 years and older)

Upper Respiratory Tract		–
Pharyngitis/Tonsillitis	200 q12h	10[a]
Sinusitis	400 q12h	10

From CLINICAL STUDIES SECTION:

ACUTE MAXILLARY SINUSITIS

In a controlled clinical study of acute maxillary sinusitis performed in Europe, loracarbef was compared to doxycycline. In this study there were 210 sinus-puncture evaluable patients. As expected in a European population, this study population had a lower incidence of ß-lactamase-producing organisms than usually seen in U.S. trials. In this study, using very strict evaluability criteria and microbiologic and clinical response criteria at the 1- to 2-week post therapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (ie, clinical success) were obtained:

European Acute Maxillary Sinusitis Study
Loracarbef vs Doxycycline

Efficacy:

Pathogen	% of Cases With Pathogens (n=210)	Outcome
S. pneumoniae	47.6%	Loracarbef equivalent to doxycycline
H. influenzae	41.4%	Loracarbef equivalent to doxycycline
M. catarrhalis	11.0%	Loracarbef equivalent to doxycycline
Overall	100.0%	Loracarbef equivalent to doxycycline

BACKGROUND:

Loracarbef, a drug of the carbacephem class, is the carbacephem analogue of cefaclor. Drugs of this class differ from their cephalosporin analogues by the substitution of a carbon atom for the sulfur atom of the dihydrothiazine ring of the cephalosporin nucleus. The advantages conferred by this chemical change are: increased chemical stability in serum compared to other β-lactam antibiotics; longer serum half-life; and preserved spectrum of antimicrobial activity against a variety of community-acquired pathogens in respiratory, skin, and urinary tract infections.

This supplement review is organized in the following sections:

Introduction
Pathophysiology of Acute Sinusitis in Children
Clinical Studies of Loracarbef for Acute Maxillary Sinusitis in Adults
Microbiology from Clinical Studies of AMS in Adults
Comparative Pharmacokinetics of Loracarbef in Adults and Children
Integrated Safety Study

Introduction.

This supplement seeks to amend the existing label for Lorabid(R) by establishing the drug as safe and effective for the treatment of acute maxillary sinusitis in children. No results from new clinical trials specifically for this indication are supplied. Instead, the indication is sought based on previously-submitted data on Lorabid(R):

(1) clinical data from two previous studies in adults which demonstrated the efficacy and safety of Lorabid(R) in the treatment of acute bacterial or purulent maxillary sinusitis. B9U-MC-AZAD compared Lorabid(R) and Augmentin(R) in treatment of acute bacterial maxillary sinusitis, and B9U-EW-E003 compared Lorabid(R) and doxycycline in the treatment of acute purulent maxillary sinusitis.

(2) clinical data from B9U-MC-AZAZ, a previous study of multiple dose pharmacokinetics of Lorabid(R) in pediatric patients undergoing treatment for either otitis media or pharyngitis.

(3) the integrated safety summary for adult and pediatric patients, submitted to the Lorabid(R) NDA on February 19, 1991.

Pathophysiology.

To extrapolate from adult sinusitis efficacy data to the efficacy of treatment in children, one must prove that the disease in adults and children is essentially the same. The etiology and pathophysiology must be demonstrably similar. Any differences between adults and children in sinus anatomy, physiology, and microbiology must be shown to be so small as to be insignificant in their effects on treating the disease. The sponsor must then show that the pharmacokinetics of the drug in children do not differ significantly from those in adults.

The natural history, treatment, and cure of acute maxillary sinusitis are influenced by:
(1) developmental anatomy of the paranasal sinuses;
(2) anatomic relationships in adults' and children's sinuses;
(3) mucociliary clearance and drainage characteristics in adults and children;
(4) the pathogens which cause AMS in adults and in children;
(5) the pharmacokinetics of a particular antimicrobial drug in adults and in children;
(6) the MICs of pathogens isolated from adults and children with AMS.

In the adult, the dimensions of the maxillary sinus are 31-32 mm by 18-20 mm by 19-20 mm, with a volume of about 15 mL. At birth, the maxillary sinuses are 7-8 mm by 4-6 mm, and usually, they are not well-enough pneumatized to be demonstrated on plain radiographs until 4 to 5 months of age. The periods of significant growth are during the first three years of life and

again from about the age of seven to 18 years. Normal secretions of the paranasal sinuses serve to moisten the mucosa and to trap airborne particulate matter, including microbes. In the healthy state, the mucociliary apparatus of the mucosa produces a steady flow of secretions, with trapped particulate matter, to the ostium of the sinus. From there, secretions move to the posterior nasal area, and thence into the pharynx and the alimentary tract, where microbes are neutralized or excreted.

This normal process of clearance depends, among other things, on the patency of the maxillary sinus ostium. The obstruction of the ostium is the necessary intermediate step in the development of acute maxillary sinusitis. Most workers in the field accept a sequence of events, centered around this step, which leads to acute maxillary sinusitis in adults and in children. Viral infection or allergic inflammation of the upper respiratory tract causes edema of the nasal mucosa. The ostium of the maxillary sinus, which in adults averages only 2.5 mm in diameter and 6 mm in length, may be obstructed as the mucosa on opposing sides of this small passage become inflamed and edematous. Drainage of the sinus stops and sinus secretions collect within the cavity. Less often, the ostium may be obstructed by nasal polyps, benign or malignant neoplasms, a deviated nasal septum, trauma to the nose or sinuses, or clotted blood.

Although the contents of the paranasal sinuses are normally kept sterile by the action of the mucociliary clearance system, these spaces can be contaminated by the flora of the posterior nasal passages when the obstructed ostium is transiently forced open by sneezing, nose-blowing, or sniffing. Even if the obstructed ostium opens spontaneously, contaminated nasal secretions may be drawn into the sinus cavity, because during the period of obstruction, the oxygen tension in the sinus will decrease, and the sinus will develop negative pressure with respect to the atmosphere.

The collected and stagnant secretions provide a good medium for microbial growth. Invasion of the mucosa (tissue infection) may follow, with greater inflammation, which further obstructs the ostium, preventing normal drainage. The production of pus ensues, which also inhibits normal drainage and impairs ciliary function.

The table below shows the distribution of pathogens responsible for acute bacterial sinusitis. The two leading etiologies, *Streptococcus pneumoniae* and *Haemophilus influenzae*, are the same in adults and children, and even occur with nearly the same frequency. In adults, there is no predominance of an organism among the remaining cases of AMS. In children, however, *Moraxella catarrhalis* is clearly the third major pathogen causing AMS, following closely in frequency behind *H. Influenzae*.

Pathogen	Percentage Incidence in Sinusitis Patients	
	Adults	Children
Streptococcus pneumoniae	31 (20-35)	36
Haemophilus influenzae (unencapsulated)	21 (6-26)	23
S. pneumoniae and *H. influenzae*	5 (1-9)	—
Mixed anaerobes	6 (0-10)	—
Staphylococcus aureus	4 (0-8)	—
Streptococcus pyogenes	2 (1-3)	2
Moraxella catarrhalis	2	19
Other gram-negative organisms	9 (0-24)	2

(From Gwaltney, JM, "Sinusitis," in **Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases**, 4th Ed.)

Clinical Studies of Loracarbef for Acute Maxillary Sinusitis in Adults.

The following table briefly describes the pivotal adult clinical studies:

Table 1. Study Description
Studies B9U-MC-AZAD and B9U-EW-E003
Indication: Acute Maxillary Sinusitis in Adults
Therapy: Loracarbef vs. Comparator

Protocol	Design	Number of Patients	Comparator
B9U-MC-AZAD	single-blind (investigator)	113 (48 clinically and bacteriologically evaluable)	amoxicillin/ clavulanate
B9U-EW-E003	double-blind	662 (332 clinically and bacteriologically evaluable)	doxycycline

Studies B9U-MC-AZAZ and B9U-EW-E003 compared loracarbef to standard comparator drugs by pathogen. In both studies, sinusitis caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and polymicrobial infections were compared by treatment group. In these studies, loracarbef demonstrated comparable clinical efficacy (as measured by favorable clinical outcome) to amoxicillin-clavulanate and to doxycycline in treatment of acute bacterial maxillary sinusitis.

The combined data from studies B9U-MC-AZAD and B9U-EW-E003 demonstrate that

the clinical effectiveness of loracarbef in the treatment of AMS in adults, with culture-proven etiologies of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and polymicrobial infection, is comparable to that of amoxicillin-clavulanate or of doxycycline (see Table, below).

Table 2. Favorable Clinical Response by Pathogen
Studies B9U-MC-AZAD and B9U-EW-E003
Indication: Acute Maxillary Sinusitis
Therapy: Loracarbef vs. Comparator

Pathogen	Loracarbef		Amoxicillin/ Clavulanate		Doxycycline	
	n	%	n	%	n	%
S. pneumoniae	72/73	98.6%	9/9	100%	54/59	91.5%
H. influenzae	60/60	100%	3/4	75.0%	51/52	98.1%
H. influenzae (+)[a]	7/7	100%	1/1	100%	1/1	100%
M. catarrhalis	15/16	93.8%	2/2	100%	11/11	100%
M. catarrhalis (+)[a]	6/6	100%	2/2	100%	6/6	100%
S. pyogenes	9/10	90.0%	0/0	–	4/5	80.0%

a = Beta-lactamase producing

The sponsor has studied the treatment of bacterial upper respiratory infections, in children, caused by the three leading pathogens of childhood AMS. Studies AZAB 1 and AZAB 2, conducted in the United States; study E008, conducted in Scandinavia; study AZAN, conducted in South Africa; and study E007, conducted in Europe, all evaluated loracarbef for safety and efficacy in the treatment of otitis media with effusion (OME). The indication sought with these studies was for OME caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), *S. pyogenes* (group A β-hemolytic streptococci), and *Staphylococcus* spp. In these studies, treatment with loracarbef of acute otitis media caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. pyogenes* in a combined total of 372 evaluable patients showed efficacy and safety comparable to treatment with comparator in 368 evaluable patients (233 treated with amoxicillin-clavulanate and 135 treated with amoxicillin). The combined results of these studies yielded an overall clinical success rate of 64.3%. Loracarbef was approved for treatment of acute otitis media caused by the pathogens requested, except *Staphylococcus* spp. The dose approved was 30 mg/kg/day, divided q 12 hours.

Microbiology from Clinical Studies of AMS in Adults.

The MIC 90s of loracarbef for the pertinent organisms in AMS were measured in the original submission of NDAs 50-667/50-668.

Streptococcus pneumoniae:

- twelve (12) isolates; MIC_{90} from ≤ 0.05 to 2.0 mcg/mL.
- two (2) penicillin-resistant isolates; $MIC_{90} \leq 8$ mcg/mL.

Haemophilus influenzae:

- seven (7) β-lactamase-producing strains; MIC_{90} from ≤ 0.5 to 8 mcg/mL.
- eight (8) β-lactamase-negative strains; MIC_{90} from ≤ 0.5 to 4 mcg/mL.

Moraxella catarrhalis:

- seven (7) β-lactamase-producing strains; MIC_{90} from ≤ 0.12 to 2 mcg/mL.
- eight (8) β-lactamase-negative strains; MIC_{90} from ≤ 0.5 to 4 mcg/mL.

Streptococcus pyogenes:

- nine (9) isolates; MIC_{90} from ≤ 0.06 to 0.25 mcg/mL.

This information should be considered in light of expected concentrations of loracarbef in the sinus secretions of children with acute maxillary sinusitis. As noted above, the clinical studies of loracarbef for acute maxillary sinusitis in adults demonstrated overall clinical success rates greater than 90% for all major pathogens.

Comparative Pharmacokinetics of Loracarbef in Adults and Children.

Study B9U-MC-AZAT, the results of which are quoted in the submission, examined concentrations of loracarbef in the fluid of the infected middle ear of children after administration of a single dose of loracarbef. About two hours after a dose of 7.5 mg/kg, concentration of loracarbef in the middle ear fluid was 42% of the plasma concentration. About two hours after a dose of 15 mg/kg, concentration of loracarbef in the middle ear fluid was 48% of the plasma concentration. Since the mean plasma concentrations of loracarbef ranged from 4.2 mg/L to 9.4 mg/L, the middle ear concentrations following the higher dose were sufficient to have in-vitro activity against all of the major pathogens of acute maxillary sinusitis in children.

Study B9U-MC-AZAZ evaluated pharmacokinetics of loracarbef in children with active infectious disease (in this case, otitis media and streptococcal tonsillitis/pharyngitis). The subjects of this study were children aged 6 months to 16 years, with 90.5% of the subjects being younger than 12 years. The results "were consistent with findings in pediatric patients given single doses of loracarbef and healthy adult volunteers given either single or multiple doses of loracarbef."

Table 3. Age Ranges
Study B9U-MC-AZAZ
Indications: Otitis Media and Pharyngitis
Therapy: Loracarbef

Age Ranges	Total
6 months - < 1 yr.	4 (19.0%)
1 - < 3	1 (4.8%)
3 - < 12	14 (66.7%)
12 - 16	2 (9.5%)

The bioequivalence of the suspension and capsule forms of loracarbef was evaluated in the original NDA. The suspensions, or granules for reconstitution, ranged from 100 mg/5 mL to 200 mg/5 mL. The biopharmaceutics reviewer reported:

> The clinical trial capsule formulation was found to be bioequivalent to the market capsule formulation. The various suspension formulations were bioequivalent to the market capsule formulation as far as AUC was concerned. In general, the suspensions gave a higher CMAX occurring at a much earlier time.

The current label for loracarbef summarizes the pharmacokinetic comparability of the dosing schedule for sinusitis in children, as proposed, to the schedule already approved for the treatment of AMS in adults.

Dosage (mg)	Mean Plasma Loracarbef Concentrations (μg/mL) Peak Cmax	Time to Peak Tmax
Capsule (single dose)		
200 mg	8	1.2 h
400 mg	14	1.2 h
Suspension (single dose)		
400 mg (adult)	17	0.8 h
7.5 mg/kg (pediatric)	13	0.8 h
15 mg/kg (pediatric)	19	0.8 h

The adult dosage for AMS, already approved, is 400 mg q 12 hours. The proposed dose for children with sinusitis is 15 mg/kg per dose, to be given q 12 hours. The Cmax and the time-to-peak is very close in the two dosing schedules.

None of the studies available specifically examined the concentration of loracarbef in the sinuses. There has been, however, a study of loracarbef

concentration in middle ear fluid of children, study B9U-MC-AZAT. This study measured loracarbef concentration in the middle ear after single doses of loracarbef, at either 7.5 mg/kg or 15 mg/kg. As this study evaluated a closed structure connected with the upper respiratory tract, it gives a useful indication that we may expect similar results when loracarbef concentrations in sinus secretions are studied. The study tested middle ear concentrations of loracarbef about 2 hours after administering a single dose. The results of the study are summarized in the table below:

	Single Dose 7.5 mg/kg	Single Dose 15 mg/kg
Mean Plasma Concentration (mg/L)	4.2	9.4
Mean Middle Ear Concentration (mg/L)	2	3.9

These results give us reason to believe that effective inhibitory concentrations of loracarbef in sinus fluid are probably attained in patients on appropriate doses of the drug. This question is still not definitively answered, however, and this merits the rigorous measurement of concentrations of loracarbef in the sinuses of selected pediatric patients with sinusitis (see MEDICAL OFFICER'S CONCLUSIONS below).

Integrated Safety Studies.

The sponsor has submitted an Integrated Safety Summary to evaluate, in combination, all treatment-emergent signs and symptoms (TESS) appearing in all patients treated with loracarbef during any of the completed clinical trials. In the aggregate, this comprises 4506 patients, of whom 965 (21.4%) were under 12 years of age and were considered pediatric patients. Those patients 12 years of age and older were considered as adults for the purposes dosing and of safety evaluation, and included 3541 patients (94.9% of those in the clinical trials). All of this safety information was available in previous reviews and is offered here for information and reference only.

The integrated safety summary reported no deaths in these studies. None of the events were described as being of "high severity." Only rash or "allergic reaction" caused early discontinuation of the study drug, and these affected only six (0.6%) of the pediatric patients 23 (0.6%) adult patients treated with

loracarbef. In the groups of patients treated with comparator drugs, these combined hypersensitivity events (rash or allergic reaction) occurred in 1.6% of pediatric patients and 0.8% of adult patients. There were no reports of erythema multiforme or serum sickness-related signs or symptoms among the loracarbef-treated patients.

The most commonly involved organ system was the digestive system, with an overall TESS incidence of 9.3%. The next most commonly involved organ systems were "body as a whole," 8.7% overall TESS rate, and respiratory system, 7.1% overall TESS rate.

Table 4. Overview of All Reported Treatment-Emergent Signs and Symptoms (TESS) by Body System: Loracarbef-Treated Patients by Age Group.
(All Events Reported from Completed Controlled Clinical Trials.)

	Loracarbef						Comparators		
Body System	Pediatric N = 965 n	(%)	Adults N = 3541 n	(%)	Total N = 4506 n	(%)	Total N = 4518 n	(%)	p-Value*
Patients with one or more events	294	(30.5%)	878	(24.8%)	1172	(26.0%)	1291	(28.6%)	0.0004
Patients with no events	671	(69.5%)	2663	(75.2%)	3334	(74.0%)	3227	71.4%	0.0004
Body as a Whole	59	(6.1%)	310	(8.8%)	369	(8.2%)	392	(8.7%)	0.041
Cardiovascular	2	(0.2%)	44	(1.2%)	46	(1.0%)	33	(0.7%)	0.005
Digestive	114	(11.8%)	304	(8.6%)	418	(9.3%)	532	(11.8%)	0.002
Endocrine	0		3	(0.1%)	3	(0.07%)	2	(0.04%)	0.366
Hemic and Lymphatic	3	(0.3%)	9	(0.3%)	12	(0.3%)	6	(0.1%)	0.762
Metabolic and Nutritional	1	(0.1%)	12	(0.3%)	13	(0.3%)	15	(0.3%)	0.227
Musculoskeletal	3	(0.3%)	15	(0.4%)	18	(0.4%)	14	(0.3%)	0.623
Nervous	35	(3.6%)	79	(2.2%)	114	(2.5%)	105	(2.3%)	0.014
Respiratory	104	(10.8%)	252	(7.1%)	356	(7.9%)	322	(7.1%)	0.0002
Skin and Appendages	49	(5.1%)	64	(1.8%)	113	(2.5%)	171	(3.8%)	<0.0001
Special Senses	48	(5.0%)	31	(0.9%)	79	(1.8%)	80	(1.8%)	<0.0001
Urogenital	3	(0.3%)	109	(3.1%)	112	(2.5%)	125	(2.8%)	<0.0001

*p-Values calculated from comparison of loracarbef age groups.

Most of the excess digestive system TESS rate in children was related to diarrhea or vomiting. As is pointed out in the sponsor's submission, these excess pediatric rates probably reflect (1) part of the disease process being treated (vomiting occurring in ear infection), or (2) an excess rate of diarrhea caused by a

dose-per-kg-body-weight used in the treatment of otitis media or pharyngitis in children which was larger than the dose-per-kg-body-weight used in any adult infections. This higher dose, and the associated increase in diarrhea in children, is postulated to be the cause also of a higher rate of diaper rashes and moniliasis in children. This excess rate of diarrhea was also seen in children in the comparator antibiotic arms of these clinical trials, and at a higher rate than in the loracarbef group.

Table 5. Frequency of Treatment-Emergent Signs and Symptoms (TESS), All Events Reported from Completed Controlled Clinical Trials.

Event Classification Term	Loracarbef N = 4506		Comparators N = 4518		p-Value
	n	(%)	n	(%)	
Patients with one or more events	1172	(26.0%)	1291	(28.6%)	0.006
Patients with no events	3334	(74.0%)	3227	(71.4%)	0.006
Diarrhea	185	(4.1%)	314	(6.9%)	<0.0001
Headache	132	(2.9%)	106	(2.3%)	0.084
Rhinitis	117	(2.6%)	96	(2.1%)	0.140
Nausea	87	(1.9%)	80	(1.8%)	0.573
Abdominal Pain	64	(1.4%)	76	(1.7%)	0.314
Vaginitis[a]	31	(1.3%)	42	(1.8%)	0.241
Rash	54	(1.2%)	90	(2.0%)	0.003
Lung Disorder	53	(1.2%)	40	(0.9%)	0.171
Vaginal Moniliasis[a]	26	(1.1%)	28	(1.2%)	0.868
Vomiting	48	(1.1%)	73	(1.6%)	0.023
Nausea and Vomiting	14	(0.3%)	17	(0.4%)	0.594
Pharyngitis	45	(1.0%)	32	(0.7%)	0.134
Cough Increased	40	(0.9%)	47	(1.0%)	0.458
Fever	40	(0.9%)	35	(0.8%)	0.554
Asthma	39	(0.9%)	39	(0.9%)	0.991
Pain	38	(0.8%)	33	(0.7%)	0.544
Somnolence	34	(0.8%)	35	(0.8%)	0.913
Anorexia	31	(0.7%)	32	(0.7%)	0.908
Dyspnea	30	(0.7%)	32	(0.7%)	0.807
Ear Disorder	28	(0.6%)	28	(0.6%)	0.992
Dizziness	25	(0.6%)	18	(0.4%)	0.281
Hyperventilation	23	(0.5%)	26	(0.6%)	0.380
Asthenia	22	(0.5%)	27	(0.6%)	0.480

[a]Denominators used for calculation of percentages were for female patients only: N = 2328 for loracarbef, N = 2401 for comparator drugs

Table 6. Frequency of Treatment-Emergent Signs and Symptoms (TESS) Loracarbef-Treated Patients by Age Group.

(All Events Reported from Completed Controlled Clinical Trials.)

	Loracarbef						Comparators		
	Pediatric N = 965		Adults N = 3541		Total N = 4506		Total N = 4518		
Adverse Event	n	(%)	n	(%)	n	(%)	n	(%)	p-Value[b]
Patients with one or more events	294	(30.5%)	878	(24.8%)	1172	(26.0%)	1291	(28.6%)	0.004
Patients with no events	671	(69.5%)	2663	(75.2%)	3334	(74.0%)	3227	(71.4%)	0.004
Diarrhea	56	(5.8%)	129	(3.6%)	185	(4.1%)	314	(6.9%)	0.003
Headache	9	(0.9%)	123	(3.2%)	132	(2.9%)	106	(2.3%)	<0.0001
Rhinitis	61	(6.3%)	56	(1.6%)	117	(2.6%)	96	(2.1%)	<0.0001
Nausea	0		87	(2.5%)	87	(1.9%)	80	(1.8%)	<0.0001
Abdominal Pain	11	(1.1%)	53	(1.5%)	64	(1.4%)	76	(1.7%)	0.406
Vaginitis[a]	0		31	(1.6%)	31	(1.3%)	42	(1.8%)	0.006
Rash	28	(2.9%)	26	(0.7%)	54	(1.2%)	90	(2.0%)	<0.0001
Lung Disorder	2	(0.2%)	51	(1.4%)	53	(1.2%)	40	(0.9%)	0.002
Vaginal Moniliasis[a]	1	(0.2%)	25	(1.3%)	26	(1.1%)	28	(1.2%)	0.046
Vomiting	32	(3.3%)	16	(0.5%)	48	(1.1%)	73	(1.6%)	<0.0001
Nausea and Vomiting	1	(0.1%)	13	(0.4%)	14	(0.3%)	17	(0.4%)	0.192
Pharyngitis	14	(1.5%)	31	(0.9%)	45	(1.0%)	32	(0.7%)	0.111
Cough Increased	24	(2.5%)	16	(0.5%)	40	(0.9%)	47	(1.0%)	<0.0001
Fever	24	(2.5%)	16	(0.5%)	40	(0.9%)	35	(0.8%)	<0.0001
Asthma	8	(0.8%)	31	(0.9%)	39	(0.9%)	39	(0.9%)	0.890
Pain	0		38	(1.1%)	38	(0.8%)	33	(0.7%)	0.001
Somnolence	20	(2.1%)	14	(0.4%)	34	(0.8%)	35	(0.8%)	<0.0001
Anorexia	22	(2.3%)	9	(0.3%)	31	(0.7%)	32	(0.7%)	<0.0001
Dyspnea	0		30	(0.8%)	30	(0.7%)	32	(0.7%)	0.004
Ear Disorder	25	(2.6%)	3	(0.1%)	28	(0.6%)	28	(0.6%)	<0.0001
Dizziness	1	(0.1%)	24	(0.7%)	25	(0.6%)	18	(0.4%)	0.033
Hyperventilation	0		23	(0.5%)	23	(0.5%)	26	(0.6%)	0.012
Asthenia	1	(0.1%)	21	(0.6%)	22	(0.5%)	27	(0.6%)	0.053

[a] Denominators used for calculation of percentages were for female patients only: N=446 for loracarbef pediatric, N=1882 for loracarbef adults, N=2328 for total loracarbef group, and N=2401 for total comparator group.

[b] p-values calculated from comparison of loracarbef age groups.

MEDICAL OFFICER'S CONCLUSIONS AND RECOMMENDATIONS

1. The medical officer recommends the approval of loracarbef for the treatment of acute maxillary sinusitis in infants and children aged 6 months to 12 years, at a dose of 30 mg/kg per day, divided into two equal doses given every 12 hours, for ten days. This recommendation is made under the Pediatric Rule of the Code of Federal Regulations, 201.57(9) (iv), based on two adequate and well-controlled studies of acute maxillary sinusitis in adults, and supported by studies of pharmacokinetics in children, *in vitro* studies of antimicrobial effect on pathogens involved in pediatric sinusitis, and the integrated safety studies of loracarbef use in children.

2. The medical officer recommends that Eli Lilly and Company conduct a Phase 4 clinical trial of loracarbef in children with demonstrated acute maxillary sinusitis. For this study, loracarbef therapy should be evaluated alongside of a standard, FDA-licensed treatment for acute maxillary sinusitis in children.

3. The medical officer recommends that Eli Lilly and Company attempt to study the concentrations of loracarbef attained in infected sinuses. The M.O. is not recommending that such a study be required; however, because this product is being recommended for approval without microbiological studies, a study to measure levels of loracarbef achieved in infected sinuses could be helpful in understanding the capabilities of this drug. The M.O. suggests a single-dose pharmacokinetics study in patients who will require sinus drainage or debridement, with administration of loracarbef before the procedure, and measurement of the concentration of loracarbef in sinus secretions obtained at drainage. The M.O. recognizes the obstacles to such a study: there are varied empiric therapies available to treat sinusitis in children; it is no longer standard practice to perform antral puncture in the evaluation and treatment of this condition; only a small selection of children with sinusitis, who have failed empirical antimicrobial therapy (often serial courses of therapy, using different antimicrobials) will undergo sinus puncture or debridement as part of their evaluation and treatment.

Andrew M. Bonwit, M.D.
Medical Officer

cc: NDA 50-668
HFD-340
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/MO/Bonwit
HFD-520/Micro/Dionne
HFD-520/Chem/Roy
HFD-520/PMS/Debellas

Concurrence Only:
HFD-520/DivDir/Feigal 10-13-96
HFD-520/SMO/Soreth 11/12/96

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