CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 12/15/97

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AGENDA

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING
December 15, 1997
Food and Drug Administration
Center for Drug Evaluation and Research

Ramada Inn, Embassy Ballroom, 8400 Wisconsin Avenue,
Bethesda, Maryland

Monday, December 15, 1997

Morning Session:

8:00-8:05 Welcome - James T.C. Li, M.D., Chairman PADAC

Meeting Announcements - John K. Jenkins, M.D., Director, Division of Pulmonary Drug Products, Center for Drug Evaluation and Research, CDER, FDA

Conflict of Interest Statement -- Leander B. Madoo, Health Science Administrator, CDER, FDA

8:05 a.m. **Open Public Hearing**

(Open for public hearing. One hour is allocated. Next agenda item will begin immediately if less than one hour is needed)

Issue: The committee will discuss the safety and efficacy of new drug application (NDA) 20-793, Cafcit (caffine citrate injection, 10 milligram/milliliter) for intravennous or oral use in the treatment of apnea of prematurity. The sponsor is Roxane Laboratories, Inc.

8:30-9:45 Sponsor Presentation: Roxane Laboratories, Inc.

- Introduction - Sean Alan Reade, M.A., Director, Regulatory Affairs Roxane Laboratories
- History of Caffeine Development - Kirk V. Shepard, M.D. Sr. V.P., Marketing/Medical Affairs and Product Development Roxane Laboratories
- Apnea of Prematurity - Allen Erenberg, M.D., Medical Director Kern Medical Center Bakersfield, CA

- Literature Overview: Pharmacokinetics - Richard D. Leff, Pharm.D., V.P., Clinical Services Child Health Corporation of America and Professor of Pediatrics, University of Kansas Medical Center

- Literature Overview: Efficacy/Safety - Kristen Mosdell, Pharm.D., Consultant, Roxane Laboratories, Inc.

- Clinical Data Presentation - Beverly A. Wynne, Ph.D., Medical Director, Medical Affairs, Roxane Laboratories

- Dennis G. Haack, Ph.D., Consultant Biostatistian, International Pharmaceutical Industry, Lexington, KY

9:45-10:15 Committee Questions on Sponsor's Presentation

10:15-10:30 **BREAK**

10:30-11:15 FDA Presentation NDA 20-793, Caffine Citrate

Safety and Efficacy of the NDA by
Liza Miriam Pina, M.D., FDA Medical Reviewer

11:15-11:45 Committee Questions on FDA's Presentation

11:45-12:30 **Lunch**

OPEN COMMITTEE DISCUSSION Cafcit (Caffeine Citrate Injection)

12:30-1:30 Comments by PADAC Primary Reviewers:

- Peter Rothstein, M.D., PADAC Consultant

- Vernon Chinchilli, Ph.D., PADAC Member

- Stanley Szefler, M.D., PADAC Member

1:30-5:00 Committee consideration of Agency Proposed Questions

5:00 **Adjourn**

Pulmonary-Allergy Drugs Advisory Committee Meeting
December 15, 1997

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QUESTIONS

QUESTIONS FOR THE PULMONARY AND ALLERGY DRUGS ADVISORY COMMITTEE

Caffeine Citrate For The Treatment Of Apnea Of Prematurity

EFFICACY

The sponsor submitted study OPR- 001 as the pivotal study and a comprehensive review of the literature to support the efficacy of caffeine citrate injectable, in patients with apnea of prematurity. Study OPR- 001 was randomized, double-blind, placebo-controlled, with a 10-12 day treatment period. In this study the primary efficacy endpoint, the apnea rate during hours 24 - 48 after the double-blind loading dose in a covariance model, did not reach statistical significance in favor of caffeine citrate. However, the study showed superiority of caffeine citrate over placebo in other clinically relevant endpoints: mean number of days with ≥ 50% reduction in apnea events when compared to baseline (p-value=0.025) and mean number of days with 100% reduction in apnea events (p-value=0.005). Twenty two percent of the patients in the caffeine group had 100% reduction in apnea events for 8 or more days versus 0% in the placebo group.

Twenty seven published studies were submitted to support the efficacy of caffeine citrate in patients with apnea of prematurity. All controlled trials identified by the sponsor used untreated or historical controls or compared theophylline to caffeine. The majority of these trials showed that the patients improved after the treatment with caffeine was initiated or that the effect of caffeine was clinically comparable to that of theophylline.

1. Do the effects shown in study OPR-001 and the published literature constitute sufficient evidence of the efficacy of caffeine citrate for the treatment of apnea of prematurity?

SAFETY

In study OPR-001, 46 premature neonates were treated with caffeine citrate for a period no longer than 12 days. The adverse event profile of caffeine citrate was generally similar to that of placebo. For many years, however, a question has been raised by many authors regarding the association of methylxanthines (theophylline in most cases) with an increase incidence of necrotic enterocolitis (NEC) in premature patients at higher risk (i.e., lower gestational age, lower birth weight). In study OPR-001, there were 6 confirmed cases of NEC, 4 cases in the caffeine group and 2 in the placebo group. One of the 2 patients in the placebo group, by protocol, received open-label caffeine for 8 days. Three of the 6 patients died. None of the deaths were clearly drug related but each of the three patients who died had been exposed to caffeine. The literature does not report any death or NEC in direct association with caffeine citrate. Only one article studied the association of NEC with the use of caffeine citrate in particular.

2. Does the NDA database together with the data available from published literature and the spontaneous reporting system experience demonstrate the safety of the short term use of caffeine citrate in patients with apnea of prematurity?

APPROVABILITY

3. Taking into consideration the overall benefits and risks of using caffeine citrate for the treatment of apnea of prematurity, do you recommend that this drug be approved for marketing?
4. If you do not recommend approval for marketing, what additional studies should be done to support approval?
5. If caffeine citrate were to be approved for the treatment of apnea of prematurity, in the labeling:
   a. would you recommend that the dosing period be restricted to 10-12 days?
   b. would you recommend a warning regarding the concern of necrotic enterocolitis and caffeine?
6. If caffeine citrate were to be approved for this indication, what, if any, post-marketing studies would you recommend be completed by the sponsor?