

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-793

MICROBIOLOGY REVIEW(S)

REVIEW FOR DIVISION OF PULMONARY DRUG PRODUCTS, HFD-570  
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805  
MICROBIOLOGIST'S REVIEW No. 1  
December 19, 1997

MICROBIOLOGY REVIEWER: Carol K. Vincent

A. 1. NDA No.: 20-793

DRUG PRODUCT NAME: Cafcit [Caffeine citrate injection]

<u>APPLICANT:</u>	<u>U.S. Agent for Applicant:</u>	<u>Manufacturer:</u>
O.P.R. Development, L.P. Madeline Lane Lawrence, Kansas 66049 913-749-4166	Roxane Laboratories, Inc. P. O. Box 16532 Columbus, Ohio 43216 614-276-4000 fax: 614-276-8061	Ben Venue Laboratories, Inc 300 Northfield Road P. O. Box 46568 Bedford, Ohio 44146-0568 216-232-3320

2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:  
Sterile solution for intravenous and oral administration.

3. METHOD(S) OF STERILIZATION:

[redacted] preceded by [redacted]  
manufacturing process.

4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:  
The drug product is intended for prevention and treatment of apnea of prematurity in neonates.

5. DRUG PRIORITY CLASSIFICATION: 2 P, designated Orphan drug 09-20-88.

B. 1. DOCUMENT DATE: August 22, 1997  
2. DOCUMENT RECEIVED FOR REVIEW: September 12, 1997

C. REMARKS: Apnea of prematurity, cessation of breathing for 10 to 30 second periods, occurs in 25% of neonates with birth weight less than 2500 grams and in 84% of neonates with birth weights below 1000 grams. Commercially available sterile sodium caffeine benzoate is not suitable for treatment of infant apnea due to the concentration and presence of benzyl alcohol. Some hospital pharmacies prepare caffeine citrate for treatment of apnea of prematurity, but formulation errors have occurred. The introductory remarks in the NDA state (p 2-3) that the FDA contracted with the [redacted] in 1985 to survey and review the literature and provide

"a summary of published data concerning the use of selected marketed drugs in new born infants". Caffeine was one of the selected drugs for review. The completed report entitled "Literature Review for Unlabeled Use of a Marketed Drug", FDA Contract [redacted] was submitted to the Agency in April 1986. . . . and concluded that the literature provided persuasive evidence of caffeine's effectiveness . . . as drug of choice for apnea of prematurity in preterm infants on the basis of caffeine's larger therapeutic index, once daily administration, smaller fluctuations in plasma concentrations due to a longer half-life, penetration into the cerebrospinal fluid, more potent central respirogenic effect, and fewer peripheral adverse effects. The FDA Contract Report concluded that it would be in the interest of public health to encourage a New Drug Application (NDA) for caffeine for the indication of apnea of prematurity. . . . caffeine was designated as a Orphan Drug . . . and the development of Caffeine Citrate Injection was initiated under IND No. [redacted] for this indication."

D. **CONCLUSION:** We recommend NDA 20-793 for approval from the microbiology perspective on the basis of sterilization process validation information.

cc:  
Orig. NDA 20-793  
HFD-160/Consult/CKVincent [HFD-805]  
HFD-570/Himmel/Pina/VShah/Cobbs  
Drafted by: CKVincent/11-10-97/  
Revised by: CKVincent/12-19-97  
Concur: PHCooney/ 12-19-97

Filename:NDA20793

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12-19-97

Carol K. Vincent  
Review Microbiologist [HFD-805]

/S/

12/24/97

APPEARS THIS WAY  
ON ORIGINAL