CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-793

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 20793/000**
Stamp: **25-AUG-1997** Regulatory Due: **24-SEP-1999**
Applicant: **OPR**
1501 WAKARUSA DR
LAWRENCE, KS 66047

Priority: **2P** Org Code: **570**
Action Goal: District Goal: **20-FEB-1998**
Brand Name: **CAFFEINE CITRATE SOLUTION 10MG PER ML**
Established Name:
Generic Name: **CAFFEINE CITRATE SOLUTION 10MG PER ML**
Dosage Form: **INJ (INJECTION)**
Strength: **10 MG/ML**

FDA Contacts:

J. COBBS	**(HFD-570)**	**301-827-1050**	**, Project Manager**
V. SHAH	**(HFD-570)**	**301-827-1050**	**, Review Chemist**
G. POOCHIKIAN	**(HFD-570)**	**301-827-1050**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 28-JUL-1999 by S. ADAMS (HFD-320) 301-594-0095
ACCEPTABLE on 17-NOV-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1519257**
BEN VENUE LABORATORIES INC
270 & 300 NORTHFIELD RD
BEDFORD, OH 441460568
DMF No:
AADA No:

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **28-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**
FINISHED DOSAGE OTHER TESTER

Establishment: **1510690**
ROXANE LABORATORIES INC
1809 WILSON RD
COLUMBUS, OH 43228

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
FINISHED DOSAGE RELEASE TESTER

APPEARS THIS WAY
ON ORIGINAL

CDER Establishment Evaluation Report for January 09, 1998

Application: NDA 20793/000
Stamp: 25-AUG-1997 Regulatory Due: 25-FEB-1998
Applicant: OPR
1501 WAKARUSA DR
LAWRENCE, KS 66047

Priority: 2P Org Code: 570
Action Goal: District Goal: 21-DEC-1997
Brand Name: CAFFEINE CITRATE SOLUTION 10MG PER ML
Established Name:
Generic Name: CAFFEINE CITRATE SOLUTION 10MG PER ML
Dosage Form: INJ (INJECTION)
Strength: 10 MG/ML

FDA Contacts:			
	J. COBBS	(HFD-570)	301-827-1050 , Project Manager
	V. SHAH	(HFD-570)	301-827-1050 , Review Chemist
	G. POOCHIKIAN	(HFD-570)	301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 17-NOV-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: 1519257
BEN VENUE LABORATORIES INC
300 NORTHFIELD RD
BEDFORD, OH 441460568

DMF No:
AADA No:

Profile: SVT OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 14-NOV-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Responsibilities: FINISHED DOSAGE OTHER TESTER

Milestone Date 24-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: CSN   OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL   OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Establishment: 1510690
ROXANE LABORATORIES INC
1809 WILSON RD
COLUMBUS, OH 43228

DMF No:
AADA No:

Profile: CTL   OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 26-SEP-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

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cc:
Orig NDA 20-793
HFD-570 /Div.
HFD-570 /Shah/ Cobbs

14.0 Patent Certification

Reference is made to the subject NDA for caffeine citrate in the treatment of apnea of prematurity and the requirements of 505(b)(2)(a) of the Federal Food, Drug and Cosmetic Act as amended.

O.P.R. Development L.P. offers the following Patent Certification with respect to the drug which is the subject of this submission.

Based on searches conducted in the Dialog Patents database and the U.S. Patent Office database system, no U.S. patent contains a claim which includes caffeine citrate. Therefore, to the best of our knowledge at the time of this filing, no patent exists for caffeine citrate.

Patent Certification

In the opinion and to the best knowledge of O.P.R. Development, L.P., there are no patents that claim the drug (caffeine citrate) on which investigations that are relied upon in this application were conducted or that claim a use of such drug.

William P. Duncan, Ph.D.
President
O.P.R. Development, L.P.

28 December 1996
Date

APPEARS THIS WAY
ON ORIGINAL

(913) 749-4166
Madeline Lane • Lawrence, Kansas 66049

EXCLUSIVITY SUMMARY FOR NDA # ___20-793___ SUPPL #_N/A__

Trade Name ___CAFCIT INJECTION_____ Generic Name _caffeine citrate_____

Applicant Name ___OPR DEVELOPMENT_____ HFD # ___570_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____N/A_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 years (Orphan Status)

e) Has pediatric exclusivity been granted for this Active Moiety?

No.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

See Attachment.

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /X/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

"Clinical Evaluation of Sterile Caffeine Citrate Solution in the Treatment of Apnea of Prematurity", Protocol OPR-001, amendment 5-March 31, 1995.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon: **N/A**

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on: **N/A**

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

"Clinical Evaluation of Sterile Caffeine Citrate Solution in the Treatment of Apnea of Prematurity", Protocol OPR-001, amendment 5-March 31, 1995.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND #_____ YES /X/ ! NO /___/ Explain: _____

!

! _____

Investigation #2 N/A!

!

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

!

!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

/S/ 9-17-99

Signature Date

Title: Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/21/99

Signature of Office/ Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20793	**Trade Name:**	Cafcit
Supplement Number:		**Generic Name:**	CAFFEINE CITRATE SOLUTION 10MG PER ML
Supplement Type:		**Dosage Form:**	Injectable; Injection
Regulatory Action:	AP	**Proposed Indication:**	The short term treatment of apnea of prematurity in infants between 28 and <33 weeks gestational age.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

X NeoNates (0-30 Days) ____Children (25 Months-12 years)

X Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Protocols are submitted and under review

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LINDSAY COBBS

/S/

Signature

9-20-99

Date

16.0 Debarment Certification

A Debarment Certification as specified by the Generic Drug Enforcement Act of 1992 is provided.

APPEARS THIS WAY
ON ORIGINAL

O.P.R. Development, L.P.

Certification of Compliance with the Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, O.P.R. Development hereby certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)] in connection with this application.

William P. Duncan, Ph.D.
President
O.P.R. Development, L.P.

28 December 1996
Date

APPEARS THIS WAY
ON ORIGINAL

(913) 749-4166
Madeline Lane • Lawrence, Kansas 66049