CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-793

CHEMISTRY REVIEW(S)

Division of Pulmonary Drug Products

Chemist NDA Review

Review of Chemistry Manufacturing & Controls

JUL 15 1999

NDA #: N 20793 **CHEM. REVIEW: 4** **REVIEW COMPLETION DATE:** July 14, 1999

REVIEW CHEMIST: Vibhakar Shah, Ph.D.

SUBMISSION TYPE		DOC. DATE	CDER DATE	RECEIPT DATE	REMARKS
Amendment*	BC	20-MAY-1999	21-MAY-1999	25-May-1999 ✓	
Amendment*	BC	28-APR-1999	29-APR-1999	10-MAY-1999 ✓	
Amendment*	BC	26-APR-1999	27-APR-1999	10-MAY-1999 ✓	
Amendment*	BZ	23-DEC-1998	28-DEC-1998	06-JAN-1999 ✓	Subjects of this
Amendment*	BC	10-DEC-1998	11-DEC-1998	17-DEC-1998 ✓	Review*
Amendment*	BZ	30-JUN-1998	02-JUL-1998	09-JUL-1998 ✓	
Amendment*	BC	14-MAY-1998	15-MAY-1998	18-MAY-1998 ✓	
Amendment*	BC	13-APR-1998	16-APR-1998	27-APR-1998 ✓	
Amendment	BC	05-MAR-1998	06-MAR-1998	11-MAR-1998	Chem. Rev. 3
Amendment	BC	18-NOV-1997	19-NOV-1997	25-NOV-1997	Chem. Rev. 2.1
Original NDA (v2.03)		22-AUG-1997	25-AUG-1997	28-AUG-1997	Chem. Rev. 1-2

NAME & ADDRESS OF APPLICANT:

Applicant:
O. P. R. Development, L.P.
1501 Wakarusa Drive
Lawrence, Kansas 66047
Tel No. (913) 749-0034

U.S. Agent:
Roxane Laboratories, Inc.
1809 Wilson Road
Columbus Ohio 43228
Tel No. (614) 276-4000

DRUG PRODUCT NAME:

Proprietary:	CAFCIT™ (caffeine citrate) Injection, 3 mL/Vial
Nonproprietary/USAN:	Caffeine Citrate Injection
Code Name:	Not applicable
Chemical Type/Therapeutic Class:	2P

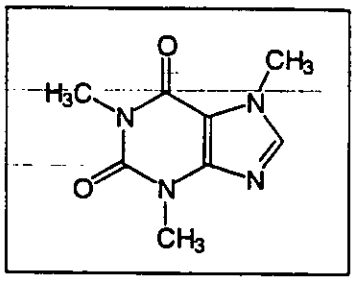
PHARMACOLOGICAL CATEGORY:

Indication:	Apnea of permaturity
Dosage Form:	Parenteral Injection (Intravenous)
Strengths:	10 mg/mL, 30mg/Vial
Loading Dose:	10 mg/kg (1 mL/kg)/over 30 min
Maintenance Dose:	2.5 mg/kg (0.25 mL/kg)/over 10 min/ every 24 hrs
Route of Administration:	Intravenous (IV), Oral
Dispensed:	**Rx** ☒ **OTC** ☐
Special Products:	**Yes** ☐ **No** ☒ (If yes, fill out the form for **special products** and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:
3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; **or**
1,3,7-trimethylxanthine or 1,3,7-trimethyl-2,6-dioxopurine

Molecular Formula: $C_8H_{10}N_4O_2$
Molecular Wt: 194.19
CAS Reg. No.: [58-08-2] anhydrous



Caffeine, USP (USP 23, p 241)

SUPPORTING DOCUMENTS:

A. DMFs:

DMF/ Type	DMF Holder	Subject	LOA Date	Status	Chemist DMF Review Reference
Type II		Manufacturing of Caffeine	11-15-1996	Adequate	Dr. Brown, R./HFD-625/ 01-14-1997. Dr. Bennett, M./HFD-647/ 07-20-1995.
Type II		Manufacturing of Caffeine anhydrous	11-18-1996	Adequate	Dr. Langowski, A./HFD-645/ 05-09-1995.
Type III		Manufacturing of molded glass containers;	12-13-1995	Adequate	Dr. Liu, S. H./HFD-625/ 02-04-1994
Type III		Manufacturing of rubber stoppers (for Glass Vials) Formula:	12-19-1995	Adequate	formula: Dr. Venkataram, U.V. /HFD-647/ 03-12- 1996 Formula: Dr. Bertha, C.M. /HFD-570/ Review-3/ 04-23-1997.

B. INDs/NDAs:
Following **IND** has been specified by the applicant in support of this application. Caffeine Citrate for Apnea of prematurity

IND

RELATED DOCUMENTS (if applicable): None

CONSULTS:

CONSULT	Forward Date	Status	Comments
1. Establishment Evaluation (EER)	07-07-1999	Pending	Awaiting acceptance recommendation from the Office of Compliance.
2. Microbiology	09-29-1997	Acceptable	Microbiology consult recommendation. Refer to Microbiologist's review dated December 24, 1997.
3. Pharmacology	-	-	Not needed

CONSULT	Forward Date	Status	Comments
4. Biometrics	-		Not needed
5. Methods Validation		Pending	To be Initiated on approval of the NDA .
6. Labeling & Nomenclature	09-18-1997 05-21-1999	Pending	L & C consult was reinitiated. Awaiting final acceptance of the Regd. Trade name, Cafcit from the Labeling & Nomenclature Review committee.
7. Environmental Assessment	-	Acceptable	A categorical exclusion has been claimed in AMD dated September 26, 1997.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

From CMC perspective this NDA application may be **approved** contingent upon an acceptable EER and acceptable recommendation for the registered trade mark, CAFCIT®. **This approval is for CAFCIT® (Caffeine Citrate) Injection, 10 mg/mL (caffeine base equivalent), 3 mL/Vial product only**. It should be noted that marketing of CAFCIT® (Caffeine Citrate) Injection, 10 mg/mL (caffeine base equivalent), [redacted] has been withdrawn by the applicant.

[redacted]

Vibhakar J. Shah, Ph.D. 07/14/1999
Review Chemist for DPDP (HFD-570)
DNDC-II (HFD-820), Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Org. NDA 20793
HFD-570/Division File
HFD-570/Chemist/Vshah
HFD-570/CSO/LCobbs
HFD-570/TL/GPoochikian 7/15/99

R/D Init by: GPoochikian

Document: N20793Rev4.doc
File Location:

APPROVED

Chemist NDA Review
Review of Chemistry Manufacturing & Controls

NDA #: N 20793 **CHEM. REVIEW:** 2.1 **REVIEW COMPLETION DATE:** January 23, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	REMARKS
Amendment (BC)*	November 18, 1997	November 19, 1997	November 25, 1997	*Subject of the Review
Original NDA (v2.03)	August 22, 1997	August 25, 1997	August 28, 1997	

NAME & ADDRESS OF APPLICANT:

Applicant:
O. P. R. Development, L.P.
1501 Wakarusa Drive
Lawrence, Kansas 66047
Tel No. (913) 749-0034

U.S. Agent:
Roxane Laboratories, Inc.
1809 Wilson Road
Columbus Ohio 43228
Tel No. (614) 276-4000

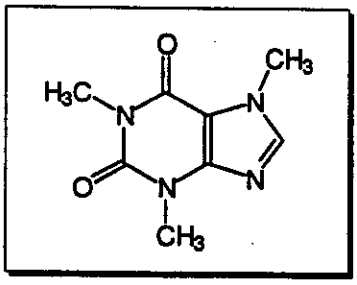
DRUG PRODUCT NAME:

Proprietary:	CAFCIT™ (caffeine citrate) Injection
Nonproprietary/USAN:	Caffeine Citrate Injection
Code Name/#:	Not applicable
Chemical Type/Therapeutic Class:	2P

PHARMACOLOGICAL CATEGORY:

INDICATION:	Apnea of permaturity
DOSAGE FORM:	Parenteral Injection (Intravenous)
STRENGTHS:	10 mg/mL
Loading Dose:	10 mg/kg (1 mL/kg)/over 30 min
Maintenance Dose::	2.5 mg/kg (0.25 mL/kg)/over 10 min/ every 24 hrs
ROUTE OF ADMINISTRATION:	Intravenous (IV), Oral
DISPENSED:	**Rx** ☒

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Caffeine, USP (USP 23, p 241)
3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; **or**
1,3,7-trimethylxanthine or 1,3,7-trimethyl-2,6-dioxopurine

Molecular Formula: $C_8H_{10}N_4O_2$ **Molecular Wt:** 194.19 **CAS Reg No:** [58-08-2] anhydrous

SUPPORTING DOCUMENTS:

A. DMFs:

DMF/ Type	DMF Holder	Subject	LOA Date	Status	Chemist DMF Review Reference
Type II		Manufacturing of Caffeine	11-15-1996	Adequate	Dr. Brown, R./HFD-625/ 01-14-1997. Dr. Bennett, M./HFD-647/ 07-20-1995.
Type II		Manufacturing of Caffeine anhydrous	11-18-1996	Adequate	Dr. Langowski, A./HFD-645/ 05-09-1995.
Type III		Manufacturing of molded glass containers: (USP type I)	12-13-1995	Adequate	Dr. Liu, S. H./HFD-625/ 02-04-1994
Type III		Manufacturing of rubber stoppers (for Glass Vials) Formula:	12-19-1995	Adequate	formula: Dr. Venkataram, U.V. /HFD-647/ 03-12- 1996 Formula: Dr. Bertha, C.M. /HFD-570/ Review #3/ 04-23-1997.

B. INDs/NDAs:
Following **IND** has been specified by the applicant in support of this application. Caffeine Citrate for Apnea of prematurity

IND

RELATED DOCUMENTS (if applicable): None

CONSULTS:

CONSULT	Forward Date	Status	Comments
1. Establishment Evaluation (EER)	10-23-1997	Acceptable	Office of Compliance recommendation dated Nov. 17, 1997
2. Microbiology	09-29-1997	Acceptable	Microbiology consult recommendation. Refer to Microbiologist's review dated December 24, 1997.
3. Pharmacology	-	-	Not needed
4. Biometrics	-		Not needed
5. Methods Validation		Pending	To be forwarded to FDA Labs on satisfactory resolution of all the pending CMC issues.
6. Labeling & Nomenclature	09-18-1997	Pending	Request for trademark review has been submitted to Labeling & Nomenclature committee.
7. Environmental Assessment	-	Acceptable	Applicant has filed for categorical exclusion in AMD dated September 26, 1997.

REMARKS/COMMENTS:

This is an addendum to the **Chemist Review-2** dated November 21, 1997.

CONCLUSIONS & RECOMMENDATIONS:

The CMC deficiencies identified in a IR letter dated December 02, 1997 have not been addressed by the applicant as of the date of this review. Consequently this NDA application remains **approvable** from CMC perspective.

However the CMC deficiencies, identified in the IR letter dated December 02, 1997, should be restated in an **approvable** letter along with the CMC comments contained in this review, pertaining to the package insert and draft labeling for vial, carton and the shelf carton. The CSO should draft the action letter and forward it to the NDA applicant.

/S/

Vibhakar J. Shah, Ph.D. 02/03/98
Review Chemist, DNDCII (HFD-820)

cc:
Org. NDA 20793
HFD-570/Division File
HFD-570/Chemist/Vshah/ /S/
HFD-570/CSO/LCobbs
HFD-570/TL/GPoochikian

R/D Init by: GPoochikian /S/ 2/3/98

Document: n20793rvu2.1.doc

APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

Division of New Drug Chemistry II
Office of New Drug Chemistry

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Chemist NDA Review

Review of Chemistry Manufacturing & Controls

NDA #: N 20793 **CHEM. REVIEW: 2** **REVIEW COMPLETION DATE:** November 21, 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	REMARKS
Amendment (AC)	October 03, 1997	October 06, 1997	October 07, 1997	Subject of the Review
Amendment (BC)	September 26, 1997	September 29, 1997	October 03, 1997	Subject of the Review
Original NDA	August 22, 1997	August 25, 1997	August 28, 1997	Subject of the Review
Presubmission	December 28, 1996	January 07, 1997	January 20, 1997	Chemist Review 1

NAME & ADDRESS OF APPLICANT:

Applicant:	**U.S. Agent:**
O. P. R. Development, L.P.	Roxane Laboratories, Inc.
1501 Wakarusa Drive	1809 Wilson Road
Lawrence, Kansas 66047	Columbus Ohio 43228
Tel No. (913) 749-0034	Tel No. (614) 276-4000

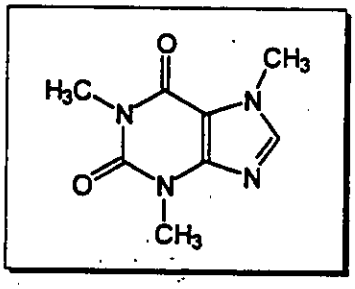
DRUG PRODUCT NAME:

Proprietary:	CAFCIT™ Injection
Nonproprietary/USAN:	Caffeine Citrate Injection
Code Name/#:	Not applicable
Chemical Type/Therapeutic Class:	2P

PHARMACOLOGICAL CATEGORY:

INDICATION:	Apnea of permaturity
DOSAGE FORM:	Parenteral Injection (Intravenous)
STRENGTHS:	10 mg/mL
Loading Dose:	10 mg/kg (1 mL/kg)/over 30 min
Maintenance Dose::	2.5 mg/kg (0.25 mL/kg)/over 10 min/ every 24 hrs
ROUTE OF ADMINISTRATION:	Intravenous (IV), Oral
DISPENSED:	**Rx** ☒

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Caffeine, USP (USP 23, p 241)
3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; or
1,3,7-trimethylxanthine or 1,3,7-trimethyl-2,6-dioxopurine

Molecular Formula: $C_8H_{10}N_4O_2$ **Molecular Wt:** 194.19 **CAS Reg No:** [58-08-2] anhydrous

SUPPORTING DOCUMENTS:

A. DMFs:

DMF/ Type	DMF Holder	Subject	LOA Date	Status	Chemist DMF Review Reference
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Type III		Manufacturing of molded glass containers: (USP type I)	12-13-1995	Adequate	Dr. Liu, S. H./HFD-625/ 02-04-1994
Type III		Manufacturing of rubber stoppers (for Glass Vials) Formula:	12-19-1995	Adequate	formula: Dr. Venkataram, U.V. /HFD-647/ 03-12- 1996 Formula: Dr. Bertha, C.M. /HFD-570/ Review #3/ 04-23-1997.

B. INDs/NDAs:
Following IND has been specified by the applicant in support of this application. Caffeine Citrate for Apnea of prematurity

IND

RELATED DOCUMENTS (if applicable): None

CONSULTS:
This being a presubmission, the appropriate consults will be initiated only after the filling of the NDA.

CONSULT	Forward Date	Status	Comments
1. Establishment Evaluation (EER)	10-23-1997	pending	Awaiting acceptable recommendation from office of Compliance.
2. Microbiology	09-29-1997	pending	See pages 7-8 of this review.
3. Pharmacology	-	-	Not needed
4. Biometrics	-		Not needed
5. Methods Validation		Pending	
6. Labeling & Nomenclature	09-18-1997	Pending	Request for trademark review has been submitted to HFD-530.
7. Environmental Assessment	-	-	Applicant has filed for categorical exclusion. Amendment dated September 26, 1997.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

Several CMC deficiencies have been identified in this 2nd review cycle with reference to the amendment dated October 03, 1997, which is submitted to NDA 20793 in response to the agency's deficiency letter dated July 03, 1997. The CMC comments should be drafted in a IR letter and forwarded to the NDA applicant by the CSO. The applicant should be encouraged to resolve these issues as soon as possible (e.g., within 30 days).

/S/

Vibhakar J. Shah, Ph.D.
Review Chemist, DNDCII (HFD-820)

cc:
Org. NDA 20793
HFD-570/Division File
HFD-570/Chemist/Vshah /S/ 11-21-1997
HFD-570/CSO/LCobbs
HFD-570/TL/GPoochikian

R/D Init by: GPoochikian 11/21/97

Document: n20793rvu2.doc

NOT APPROVED

APPEARS THIS WAY
ON ORIGINAL

JUN 20 1997

Division of Pulmonary Drug Products
Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Chemist Review of Chemistry Manufacturing & Controls of NDA

NDA #: N 20793 **CHEM. REVIEW:** # 1 **REVIEW COMPLETION DATE:** June 18, 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Presubmission	December 28, 1996	January 07, 1997	January 20, 1997

NAME & ADDRESS OF APPLICANT:

Applicant:
O. P. R. Development, L.P.
1501 Wakarusa Drive
Lawrence, Kansas 66047
Tel No. (913) 749-0034

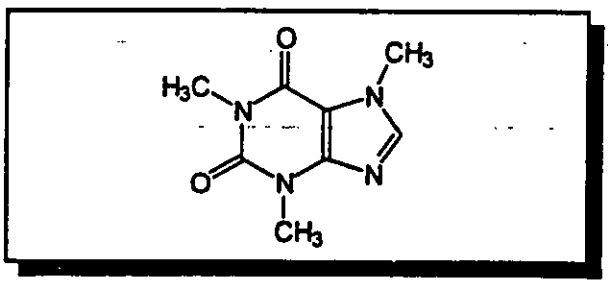
U.S. Agent:
Roxane Laboratories, Inc.
1809 Wilson Road
Columbus Ohio 43228
Tel No. (614) 276-4000

DRUG PRODUCT NAME:

Proprietary:	CAFCIT™ Injection
Nonproprietary/USAN:	Caffeine Citrate Injection
Code Name/#:	Not applicable
Chemical Type/Therapeutic Class:	2P

PHARMACOLOGICAL CATEGORY:
INDICATION: Apnea of prematurity
DOSAGE FORM: Parenteral Injection
STRENGTHS: 10 mg/ml (maximum dose/day: not provided yet)
ROUTE OF ADMINISTRATION: Parenteral
DISPENSED: Rx ☒ OTC ☐

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Caffeine, USP (USP 23, p 241)
3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; or
1,3,7-trimethylxanthine or 1,3,7-trimethyl-2,6-dioxopurine

Molecular Formula: $C_8H_{10}N_4O_2$ **Molecular Wt:** 194.19 **CAS Reg No:** [58-08-2] anhydrous

SUPPORTING DOCUMENTS:

A. DMFs:

DMF/ Type	DMF Holder	Subject	LOA Date	Status	Chemist DMF Review Reference
Type II		Manufacturing of Caffeine	11-15-1996	Adequate	Dr. Brown, R./HFD-625/ 01-14-1997. Dr. Bennett, M./HFD-647/07-20-1995.
Type II		Manufacturing of Caffeine anhydrous	11-18-1996	Adequate	Dr. Langowski, A./HFD-645/ 05-09-1995.
Type III		Manufacturing of molded glass containers (USP type I)	12-13-1995	Adequate	Dr. Liu, S. H./HFD-625/ 02-04-1994
Type III		Manufacturing of rubber stoppers (for Glass Vials) Formula:	12-19-1995	Adequate	formula: Dr. Venkataram, U.V. /HFD-647/ 03-12- 1996 Formula: Dr. Bertha, C.M. /HFD-570/ Review #3/ 04-23-1997.

B. INDs/NDAs:
Following IND has been specified by the applicant in support of this application.

IND Caffeine Citrate Injection for Apnea of prematurity.

RELATED DOCUMENTS (if applicable): See the above list of the DMFs

CONSULTS:
This being a presubmission, the appropriate consults will be initiated only after the filling of the NDA.

CONSULT	Forward Date	Status	Comments
1. Establishment Evaluation	-	-	Will be initiated on filling of the NDA.
2. Microbiology	-	-	Will be initiated on filling of the NDA.
3. Pharmacology	-	-	May be initiated depending upon responses to the comments regarding impurities contained in this review and after the submission of complete NDA.
4. Biometrics	-	-	Will be initiated upon receipt of the updated stability data
5. Methods Validation		Pending	Will be acted upon filing of the NDA
6. Labeling & Nomenclature		Pending	Will be acted upon filing of the NDA
7. Environmental Assessment		Pending	Will be initiated on filing of the NDA

REMARKS/COMMENTS:

- This review covers the evaluation of presubmitted CMC section of NDA 20793 in support of the drug product, caffeine Citrate Injection (60 mg/ml).

- The applicant, O.P.R. Development, L.P. has authorized Roxane Labortories, Inc. as their U.S. agent for any communications/correspondence related to regulatory affairs with the agency (FDA). It should be noted that the regulatory specifications for the drug substance (caffeine anhydrous) and the drug product (Caffeine Citrate Injection) are provided under Roxane Labortories, Incoporation's business letter head in support of this application. In addition, it is noted that the letters of authorization from the DMF holders and other contract manufacturing and testing facilities which are referenced in this NDA are also addressed to Roxane Laboratories, Inc.

- The applicant has proposed a expiration period of (months for caffeine Citrate Injection, 10 mg/ml, however this proposed expiration dating period of month will be reevaluated when appropriate and updated full term stability data are submitted at the time of NDA submission

CONCLUSIONS & RECOMMENDATIONS:

Several CMC deficiencies have been found in the presubmitted CMC section of NDA 20793 . Consequently NDA 20793 submitted by O.P.R. Development, L.P. in support of Caffeine Citrate Injection™ can not be approved until all the CMC issues contained in the draft letter of this review are completely resolved.

/S/ 06/20/'97
Vibhakar J. Shah, Ph.D.
Review Chemist, DNDC II

cc:
Org. NDA 20793
HFD-570/Division File
HFD-570/Chemist/VShah /S/ 06/20/'97
HFD-570/CSO/BKuzmik
HFD-570/TL/GPoochikian

R/D Init by: (S) 6/20/97

Document: N20793RV.V01

NOT APPROVED

APPEARS THIS WAY
ON ORIGINAL