

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20-793**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW****NDA: 20-793****Caffeine Citrate****(10 mg caffeine base equivalent/ml)****SUBMISSION DATE:**

11/12/97

12/12/97

02/04/98

**BRAND NAME: Cafcit Injection****SPONSOR: O.P.R. Development, L.P.****REVIEWER: Tien-Mien Chen, Ph.D.****TYPE OF SUBMISSION: Information Amendment**

Code: 2P

**TITLE: "Review of Information Amendment for Cafcit's NDA"****BACKGROUND:**

Previously on 08/22/97, O.P.R. Development, L.P., filed NDA 20-793 for Cafcit (caffeine citrate) Injection. It is to be indicated for apnea of prematurity in preterm neonates. Submitted under NDA 20-793 were one double-blind clinical trial OPR-001 in preterm neonates with apnea of prematurity and 90 literature articles. No formal pharmacokinetic (PK) studies were conducted in preterm neonates.

In study OPR-001, sparse (284) blood samples were also collected from 58 preterm neonates and samples were delivered to [redacted] for determination of caffeine plasma levels using a validated [redacted] method. Results of analysis of caffeine plasma levels for population PK using NONMEM were also provided to support human PK and bioavailability (Bio) in preterm neonates.

During the review, it was found that only 19 plasma levels were indicated as "concentration-time point reliable" (Volume 6, page 788) for the NONMEM analysis. Information request (IR) was conveyed to the sponsor through the CSO on 10/16/97 for 1) clarification on the reliability of these 19 samples and 2) missing caffeine plasma levels found in some patients. The NDA had been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) and found overall acceptable on 11/12/97. An Advisory Committee meeting was held on 12/15/97.

**SYNOPSIS:**

On 11/12/97, 12/12/97, and 02/04/98, the sponsor submitted their responses to the 10/16/97 IR and also to a previous telecon on the issues of drug-drug interactions and dose adjustments. The sponsor's responses are, therefore, reviewed.

Regarding Point 1 of 10/16/97 IR, it was realized that a mistake/typo occurred. It should have been reported as only 19 plasma levels were "concentration-time point NOT reliable". The sponsor submitted a new page to replace the old page for the above mistake/typo found in the original NDA.

Regarding Point 2 of 10/16/97 IR, the sponsor indicated that the missing caffeine plasma levels were all within the range of values observed for all other subjects in the NONMEM database. The sponsor feels that the absence of these data points from the NONMEM analysis for caffeine PK does not affect the validity of the original analyses.

Regarding the telecon (Nov./97) on the issues of drug-drug interactions and dose adjustments, the sponsor responded that 1) there were no studies conducted in preterm infants or adults for potential drug-drug interactions between erythromycin and caffeine, although erythromycin is known to inhibit cytochrome P-450 1A2 (CYP1A2) and caffeine is metabolized by CYP1A2, 2) since caffeine metabolism differs in preterm infants compared to adults, it is difficult to anticipate an adjustment of dosage to be given to preterm infants based on data obtained from the adult population, and 3) it is also difficult to adjust dosage for preterm infants with impaired hepatic or renal function.

#### RECOMMENDATION:

The information amendments that were submitted under NDA 20-793 for Cafcit (caffeine citrate) Injection by O.P.R. Development, L.P. on 11/26/97, 12/12/97, and 02/04/98 have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the sponsor's responses are overall acceptable. The following Comment Nos. 2 and 3 as appropriate need to be sent to the sponsor.

#### COMMENTS: (Nos. 2 and 3 need to be sent to the sponsor)

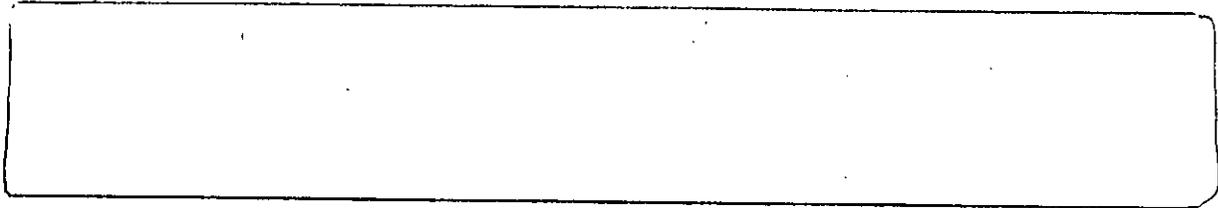
1. On 12/18/97, an internal meeting was held in HFD-570 after the Advisory Committee meeting. A modification of the duration of treatment for Cafcit in the PI from  days to "short term treatment" was proposed. In the labeling meetings held later, the Indication and Usage section of the PI was proposed by HFD-570 as follows:

CAFCIT™ is indicated for the short term treatment of apnea of prematurity in infants between 28 and <33 weeks of gestational age.

Since the duration of treatment employed in the clinical trial OPR-001 was 10 to 12 days only, a concern was raised by this reviewer, i.e., the term "short-term treatment" is loosely defined because it could mean 3 months or 6 months and there is no control of the use of Cafcit (by parents or caregivers) for those apnea outpatients after 10-12 days of hospitalization. Furthermore, it should be noted that the hepatic enzyme systems of those apnea outpatients could be developed

rapidly (and reached adult's metabolic function by the age of 9 months) and therefore, drug-drug interaction could be an additional concern.

2. The firm is encouraged to collect and analyze plasma data of caffeine for the preterm neonates with renal impairment in Phase IV studies to address the concerns raised by the advisory committee members on the dose adjustment of caffeine in this population.
3. Under Drug/Laboratory Test Interactions subsection of Cafcit labeling, it is currently stated



The article to support the above statement, however, was not submitted (McEvoy GK, Welsh OH, eds. AHFS 95 Drug information. Bethesda, MD: American Society of Health-System Pharmacists; 1995). Therefore, it is recommended that article be submitted for review and the above statement is acceptable provided that article is reviewed and found acceptable by the Agency.

APPEARS THIS WAY  
ON ORIGINAL

/S/

02/04/98

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD/FT initialed by Mei-Ling Chen, Ph.D.

/S/ 2/13/98

cc: NDA 20-793, HFD-570 (Pina, Cobbs), HFD-870 (M.L. Chen, T.M. Chen), CDR (B. Murphy).

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
DIVISION OF PHARMACEUTICAL EVALUATION II

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**Date:** September 18, 1997

**To:** Director, Mei-Ling Chen, Ph.D. (HFD-870)

**Through:** Team Leader, Dale Conner, Pharm.D. (HFD-870) /S/ 9/19/97

**From:** Tien-Mien Chen, Ph.D. (HFD-870) /S/ 09/18/97

**RE:** Filing Meeting for Caffeine Citrate Injection (NDA 20-793) Code: 1P

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**SUMMARY:**

On 8/22/97, the sponsor, O.P.R. Development, L.P., submitted Cafcit (caffeine citrate injection) for review that was filed under NDA 20-793. Caffeine citrate has never been approved in the US or any other countries, therefore, it is considered as an NME. It has been designated as an orphan drug for treating apnea of prematurity and it has an expedited review time of 6 months (1P drug). Each  ml single-dose vial contains 10 mg caffeine base equivalent per ml. The recommended dose is a loading dose of 10 mg (base)/kg given by intravenous (IV) route over 30 min followed by maintenance doses of 2.5 mg (base)/kg by IV (over 10 min) or oral route every 24 hr. Please see the package insert in Attachment 1 for details.

For this NDA, one clinical trial was conducted, but there were no human pharmacokinetic (PK) studies. Included in Human Pharmacokinetics and Bioavailability (PK/Bio) section of this NDA were 1) summary of PK information (including information on infants) that was obtained from 19 published articles, 2) information on drug-drug interaction that was summarized from 71 published articles, and 3) population PK analysis using NONMEM for plasma caffeine levels that were obtained from 58 children who participated in the clinical trial (284 blood samples). Human PK/Bio section and raw data used for the above NONMEM analysis were provided on diskettes.

**RECOMMENDATION:**

Cafcit (caffeine citrate injection) that was submitted under NDA 20-793 on 08/22/97 by O.P.R. Development, L.P., has been briefly reviewed by Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that it will not oppose the filing of this NDA, although no formal human PK studies were conducted in infants.

**APPEARS THIS WAY  
ON ORIGINAL**

cc: NDA 20-793, HFD-570 (Pina, Cobbs), HFD-870 (M.L. Chen, D. Conner, T.M. Chen)  
CDR (B. Murphy).

NDA 20-793 for Cafcit (Caffeine Citrate Injection; 10  
mg caffeine base equivalent/ml)

Attachment 1

APPEARS THIS WAY  
ON ORIGINAL

Proposed package insert

14 Page(s) Redacted

DRAFT

Labeling

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 20-793

Caffeine Citrate  
(10 mg caffeine base equivalent/ml)

SUBMISSION DATE:

06/06/96 (IND [redacted]) Serial No. 035)  
08/22/97

BRAND NAME: Cafcit Injection

SPONSOR: O.P.R. Development, L.P.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original NDA

Code: 2P

TITLE: "Review of Human Pharmacokinetics and Bioavailability of Caffeine In Preterm Infants"

SYNOPSIS:

On 08/22/97, O.P.R. Development, L.P., filed NDA 20-793 for Cafcit (caffeine citrate) injection. It is to be indicated for apnea of prematurity in preterm neonates. There are currently no approved drug products available for the treatment of apnea of prematurity in the US and in other countries. Extemporaneous formulations of caffeine citrate are prepared by hospital pharmacists to meet the demand for treatment of apnea of prematurity.

Submitted under NDA 20-793 were one double-blind clinical trial OPR-001 in preterm neonates with apnea of prematurity (gestational/postconceptual age 25-32 weeks) and 90 literature articles. No formal pharmacokinetic (PK) studies were conducted in preterm neonates. Sparse blood samples were collected from those preterm neonates who participated in the clinical trial and samples were delivered to [redacted] for determination of caffeine plasma levels using a validated [redacted] method. Results of analysis of caffeine plasma levels for population PK using NONMEM were also provided to support human PK and bioavailability (PK/Bio) in preterm neonates.

For this NDA, the recommended dosing regimen is one loading dose by intravenous (IV) infusion over 30 min (10 mg caffeine base/kg) and then the maintenance dose (2.5 mg caffeine base/kg) by IV (over 10 min) or oral administration every 24 hr. Please see the package insert (PI) in Appendix 1 for details. The to-be-marketed formulation and the recommended dosing regimen had been employed in the clinical trial.

Literature information on caffeine PK in adult and young infants supports that for preterm neonates, **1)** caffeine is well and completely absorbed, although absolute bioavailability ( $F_{abs}$ ) was not fully investigated in this population, **2)** doses need to be adjusted individually since clearance ( $CL$ ) of caffeine is related to



## I. BACKGROUND:

Since the early 70s, the primary pharmacologic agents for apnea of prematurity are caffeine and theophylline. The sponsor indicated that as compared to theophylline, caffeine is the drug of choice because caffeine has 1) larger therapeutic index, 2) smaller fluctuation, 3) a longer half-life ( $T_{1/2}$ ), 4) less frequent administration (e.g., QD), 5) better penetration into cerebrospinal fluid, 6) more potent central respirogenic effect, and 7) fewer peripheral adverse effects.

Caffeine citrate was designated orphan drug status on 09/20/88 and the development of caffeine citrate injection for this indication was initiated under IND [ ] in Sept. 89. Summary of literature articles had been previously submitted on 06/06/96 under IND [ ] and it is also reviewed with this NDA submission.

## II. SUMMARY OF LITERATURE INFORMATION:

### 1. PHARMACOKINETICS:

It has been reported in the Goodman and Gilman's "The Pharmacological Basis of Therapeutics" 9th edi. that in adults, 1) the orally administered caffeine solution is completely absorbed ( $\approx 100\%$ ) with a mean  $T_{max}$  about 1 hr, 2) the mean ( $\pm$  standard deviation; SD) clearance of caffeine is  $98 \pm 35$  ml/min (for a 70-kg man) with a mean apparent terminal  $T_{1/2}$  of  $4.9 \pm 1.8$  hr, 3) its mean volume of distribution ( $V_d$ ) is  $0.61 \pm 0.02$  liter/kg with a mean in vitro plasma protein binding ( $f_b$ ) of  $36 \pm 7\%$ , 4) caffeine is extensively metabolized in the liver, and 5) only  $1.1 \pm 0.5\%$  of dose was excreted unchanged in urine.

It is also reported that 1) caffeine crosses placenta and passes into breast milk and 2) for caffeine, neonates (from birth to 1 month) and infants (1 month to 2 years old), may have a larger mean  $V_d$  (0.8-0.9 liter/kg) and a smaller  $f_b$  value. However, the  $F_{abs}$  of orally administered caffeine was not fully examined nor were formal or specific PK/Bio studies conducted in preterm neonates.

The summary of the literature review showed that in preterm neonates, 1) after oral absorption of 10 mg caffeine base/kg, the  $T_{max}$  was about 30 min to 2 hr, 2) the extent of absorption (in terms of  $C_{max}$  and  $AUC_{0-12}$ ) was not affected by formula feeding with a slightly longer mean  $T_{max}$  in the formula feeding group as compared to the fasting group, 3) mean caffeine levels in cerebral spinal fluid approximate their corresponding plasma levels

(mean ratios being 0.9-1.0), and 4) the multiple-dose PK of caffeine support its recommended dosing regimen and the proposed target therapeutic range of 8-20 mg/L in preterm neonates.

During the double-blind clinical trial OPR-001, sparse blood samples were collected from 9 study centers and delivered to [REDACTED]. Caffeine plasma levels were measured using a [REDACTED] method. A total of 284 caffeine plasma levels obtained from 58 infants were used in the NONMEM analysis of population PK. The above NONMEM analysis was also reviewed by Dr. Raymond Miller of the Division of Pharmacometrics (HFD-851).

The results of NONMEM analysis support the weight adjusted dosing (both loading and maintenance doses) of caffeine to those young infants since both Vd and CL of caffeine are found to increase with body weight. However, the PK/PD relationship between caffeine plasma levels and frequency of apnea/day was not investigated.

## 2. METABOLISM:

In adults, caffeine is metabolized almost entirely in the liver via oxidation, demethylation, and acetylation. Cytochrome P450 1A2 isozyme (CYP 1A2) is known to be involved in the above biotransformation. The elimination of caffeine in neonates and infants, however, is markedly reduced primarily due to immature hepatic enzyme systems and/or renal function. The mean fraction of unchanged caffeine excreted in urine (Ae) and the mean  $T_{1/2}$  are reported to be inversely related to gestational/postconceptual age.

It was reported in one article that 1) mean Ae was around 86% (within 6 days) in 0-1 month neonates with very small fractions of metabolites found in urine and 2) mean Ae decreased gradually to adult value (around 1%) by the age of 7-9 months. In another article,  $T_{1/2}$  of caffeine was studied in premature infants longitudinally for several months and the results showed that the mean ( $\pm$  SD)  $T_{1/2}$  values in neonates and infants were 97.6 ( $\pm$  32.7) hr at 0-1 month, 75.2 ( $\pm$  28.8) hr at 1.25-2 months and 71.1 ( $\pm$  32.3) hr at 2.25-3 months, 42.8 ( $\pm$  25.2) hr at 3.25-4 months, 28.8 ( $\pm$  20.9) hr at 4.25-5 months, 11.7 ( $\pm$  9.9) hr at 5.25-6 months, 12.2 ( $\pm$  9.9) hr at 6.25-7 months, and 5.2 ( $\pm$  5) hr at greater than 7 months.

The scheme of caffeine metabolic pathways proposed for adults is shown below:

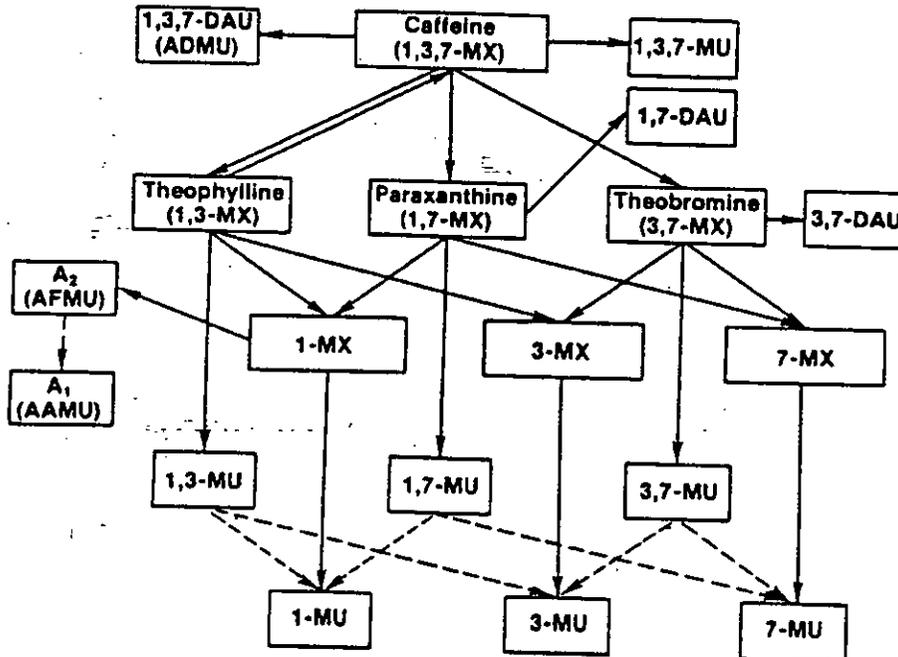


Figure 1 Metabolic pathways for caffeine in man based upon urinary excretion data. Dashed lines indicate unestablished pathways. Recent reports (Birkett *et al.*, 1983; Arnaud, 1984) indicate that the dimethyluric acids are not demethylated to produce monomethylurates. 1,3,7-DAU(ADMU) = 6-amino-5-[*N*-formylmethylamino]-1,3-dimethyluracil; 3,7-DAU = 6-amino-5-[*N*-formylmethylamino]-1-methyluracil; 1,7-DAU = 6-amino-5-[*N*-formylmethylamino]-3-methyluracil.

Although it was not reported in adults, the interconversion between caffeine and theophylline was indeed reported in neonates and infants, i.e., urinary or plasma caffeine levels were approximately 25% of theophylline content after theophylline administration and around 3-8% of caffeine administered was converted to theophylline. The former may be of clinical concern for those who received theophylline previously.

### 3. DRUG-DRUG INTERACTION:

Potential drug-drug (D-D) interaction studies that were reported in the literature for caffeine were mainly conducted in adult volunteers and/or patients and they were reviewed. Those agents prescribed in preterm infants are high-lighted (in bold). The results of literature review are summarized below:

A. **Drugs Decrease Caffeine Elimination:**

Several drugs were found to decrease elimination of caffeine in adults. They are mexiletine, ketoconazole, terbinafine, disulfuram, fluvoxamine, cimetidine, methoxsalen, quinolone antibiotics (enoxacin > ciprofloxacin = norfloxacin > ofloxacin = lomefloxacin), lidocaine, clozapine, oral contraceptives, and omeprazole.

The effects of cimetidine, mexiletine, or terbinafine on caffeine PK in adults were concluded to be statistically significant by the sponsor. Other drugs, e.g., ketoconazole, lidocaine were shown to have marginally significant effects or little to no effects on caffeine PK. The effects of erythromycin on caffeine, however, were not provided in the literature review.

B. **Drugs Increase Caffeine Elimination:**

Coadministration of several drugs caused an increase in clearance of caffeine in adults, e.g., anticonvulsants (**phenobarbital** and **phenytoin**). Two cases in infants who coadministered caffeine and **phenobarbital** were reported and as a result, a higher dose of caffeine was recommended. Other agents reported, e.g., carbamazepine, valproic acid, however, did not show similar effects on caffeine clearance.

C. **Others:**

Literature information on several agents that were reported to be the substrate of CYP 1A2, e.g., acetaminophen, clozapine, theophylline, were reviewed. It has been reported that the analgesic effects of acetaminophen had been potentiated by caffeine. For theophylline, please see interconversion between theophylline and caffeine in the Metabolism section of this review for details.

Other drugs, e.g., ketoprofen, lithium, MAO inhibitors, aspirin, sympathomimetics, etc. have been reviewed from literature information. Some of them did show interaction with caffeine, e.g., antiinflammatory effects of aspirin has been potentiated by caffeine.

**Note:** Several drugs which have potential to interact with caffeine were also allowed as concomitant medication and investigated in clinical trial OPR-001. They were acetaminophen, lorazepam, iron, ranitidine, theophylline, indomethacin, etc.

In conclusion, the literature review for potential D-D interactions of caffeine and certain drugs in patients provided very limited information on the clinical relevance of potential D-D interactions in preterm infants. Therefore, specific recommendations on caffeine dose adjustments could not be made when caffeine is coadministered with drugs that are prescribed to preterm infants.

4. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

The composition of Cafcit [ ] injection is 10 mg caffeine base, USP, anhydrous, [ ] mg citric acid, USP, monohydrate, [ ] mg sodium citrate, USP, dihydrate, and water for injection, USP. It is a clear, colorless, sterile, non-pyrogenic, preservative-free aqueous solution (pH 4.2 to 5.2). Each single-dose vial contains [ ] ml of Cafcit [ ] Injection. The to-be-marketed formulation and the recommended dosing regimen had been employed in the clinical trial.

It should be noted that 1) Cafcit was not and will not be used as an immediate rescue agent when apnea occurs and 2) during the clinical trial, plasma levels of caffeine were not analyzed on spot (in the hospital), therefore, they were not used as the basis for fine-tuning the dose either higher or lower in order to achieve the proposed therapeutic concentrations, 8-20 mg/L by the sponsor.

5. ASSAY:

Sparse blood samples were obtained from clinical trial No. OPR-001 and caffeine plasma levels were determined by [ ] using an [ ] method and [ ] as an internal standard. The assay validation report was reviewed and was found acceptable. The results are summarized below:

**Validation of assay method**

Standard curves: 0.5, 1.0, 2.5, 5.0, 7.5, 10.0, 25, and 50 mg/L  
Limit of Quantitation (LOQ): [ ] (based on [ ] plasma sample)

Quality Assurance (QA):

Recovery: 99% at 1.25 mg/L, 85% at 7.5 mg/L, and 100% at 50.0 mg/L (n=12)

Interday

Precision (CV): 7.0% at 1.25 mg/L, 7.5% at 7.5 mg/L, and 8.8% at 20.0 mg/L (n=38)

Accuracy: 96% at 1.25 mg/L, 92% at 7.5 mg/L, and 102% at 20.0 mg/L (n=38)

Intraday

Precision (CV): 5.9% at 1.25 mg/L, 4.4% at 7.5 mg/L, and 6.2% at 20.0 mg/L (n=6)

Accuracy: 101% at 1.25 mg/L, 97% at 7.5 mg/L, and 102% at 20.0 mg/L (n=6)

For this clinical trial, the QA for assay performance was also found acceptable:

Standard curves: 0.5, 1.0, 2.5, 5.0, 7.5, 10.0, 25, and 50 mg/L

Limit of Quantitation (LOQ): [redacted] (based on [redacted] plasma sample)

Precision (CV): 2% to 7.4% (n=16-17)

Accuracy: 95%-108% (n=16-17)

QA:

Interday

Precision (CV): 9.5% at 1.25 mg/L (n=30), 11.6% at 7.5 mg/L (n=33), and 5.7% at 35.0 mg/L (n=34)

Accuracy: 101% at 1.25 mg/L (n=30), 97% at 7.5 mg/L (n=33), and 107% at 30.0 mg/L (n=34)

III. GENERAL COMMENT:

According to protocol, a 2nd IV loading was allowed in the clinical trial for open-label treatment. Eleven preterm neonates received a 2nd IV loading dose and their caffeine plasma levels were, therefore, elevated throughout the treatment phase. OCPB wishes to bring to the reviewing medical officer's attention that 20 caffeine plasma levels from those who received a 2nd IV loading dose were higher [redacted] mg/L) than the reported desirable therapeutic range. The safety of these preterm infants may need to be examined more closely.

IV. LABELING COMMENT: (Needs to be sent to the sponsor)

The sponsor's proposed package insert needs to be revised and the following is the Agency's version for the revision of the pharmacokinetic subsection.

**Pharmacokinetics:** Compared to theophylline, caffeine has a larger therapeutic index and smaller fluctuation in plasma levels. The therapeutic plasma concentrations for caffeine were reported to be in a range of 8 to 20 mg/L. No formal or specific pharmacokinetic studies, however, were conducted in preterm neonates.

**Absorption:**

After oral administration of 10 mg caffeine base/kg to preterm neonates the

**Distribution:** Caffeine is rapidly distributed into brain. Caffeine levels in the cerebrospinal fluid of preterm neonates approximate their plasma levels. The mean volume of distribution of caffeine in infants (0.8-0.9 L/kg) is slightly higher than that in adults (0.6 L/kg).

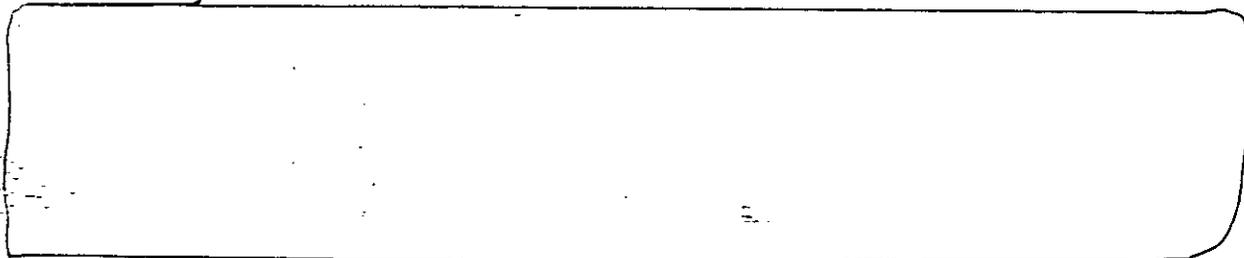
**Metabolism:** Hepatic cytochrome P450 1A2 (CYP 1A2) is involved in caffeine biotransformation.

Caffeine metabolism in preterm neonates is limited due to their immature hepatic enzyme systems.

Interconversion between caffeine and theophylline has been reported in preterm neonates, caffeine levels were approximately 25% of theophylline content after theophylline administration and around 3-8% of caffeine administered was converted to theophylline.

**Elimination:** In young infants, the elimination of caffeine is much slower than that in adults due to immature hepatic and/or renal function. Mean half-life ( $T_{1/2}$ ) and fraction excreted unchanged ( $A_e$ ) of caffeine in infants have been shown to be inversely related to gestational/postconceptual age. In neonates, the  $T_{1/2}$  and  $A_e$  were around 3-4 days and 86% (within 6 days), respectively, and by 9 months of age, the metabolism of caffeine approximates the adult values (5 hr and 1%, respectively).

*Special Population:* [redacted] Calcit should be administered with caution in preterm neonates with impaired renal or hepatic function.



**APPEARS THIS WAY  
ON ORIGINAL**

**NDA 20-793 for Cafcit (caffeine citrate) 1% Injection**

**Appendix 1:**

**APPEARS THIS WAY  
ON ORIGINAL**

**Proposed Package Insert (08/22/97 Version)**

**APPEARS THIS WAY  
ON ORIGINAL**

14 Page(s) Redacted

Draft

Labeling