

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-793

MEDICAL REVIEW(S)

# Medical Officer Review

## Division of Pulmonary Drug Products (HFD-570)

Application #:	20-793	Category of Drug:	Methylxanthine
Sponsor:	O.P.R. Development (Roxane)	Route of Administration:	iv
Proprietary Name:	CAFCIT	Medical Reviewer:	A. Trontell
USAN/Established Name:	Caffeine citrate	Review Date:	8/23/99

### Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
6/30/98	7/2/98		Partial response to approvable letter
10/26/98	10/27/98		Revised epidemiology protocol
3/22/99	3/24/99		Complete response to submission

**Overview of Application and Review:** NDA was approvable 2/24/98 with the major outstanding clinical issue being the further elucidation of the association of necrotizing enterocolitis with caffeine treatment of apnea of prematurity. The reviewed submissions contain a complete response to this issue, safety updates, and revised labeling.

**Outstanding Issues:** Labeling will need to be finalized in conjunction with the sponsor. Two Phase 4 commitments for PK studies (one to determine therapeutic plasma concentrations, the other to look at dosing in renal failure) should be a part of the action letter, and will require FDA guidance on their design.

### Recommended Regulatory Action

NDA/Supplements:      X   Approval  
                                        Approvable

Signature:   /S/  , Medical Reviewer    Date:   8/23/99  

Concurrence:   /S/   Team Leader    Date:   8/24/99  

cc: Div File NDA 20-793

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## EXECUTIVE SUMMARY

On February 25, 1998, CAF-CIT was found to be approvable with the primary clinical concern being the elevated incidence of necrotizing enterocolitis and associated mortality in the randomized clinical trial that formed the principal basis for approval.

In their submission of March 22, 1999, the sponsor addressed all the following clinical issues raised in the approvable letter:

- The ability to elucidate the potential association of caffeine citrate and enterocolitis by existing epidemiology databases
- The potential for withdrawal symptoms to occur in neonates upon cessation of caffeine therapy for apnea of prematurity
- Preliminary labeling comments from the FDA
- Development of a patient package insert

The sponsor has also provided safety updates based upon follow-up to the clinical trial and pertinent reports from the medical literature.

With respect to necrotizing enterocolitis, the sponsor has demonstrated that a retrospective epidemiologic study is not feasible because of database deficiencies. New literature and updates to the randomized clinical trial did not increase the level of suspicion for a relationship to caffeine therapy. Information provided by the sponsor further validated the known variability in the incidence of NEC between treatment centers and different years. As such, the occurrence of necrotizing enterocolitis during the clinical trial will be mentioned under the WARNINGS section of the product labeling, with appropriate wording to convey the uncertain clinical significance of this finding.

There is no documented evidence of caffeine withdrawal in infants treated for apnea of prematurity. Safety updates indicated no new safety concerns.

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## CHEMISTRY PERTINENT TO CLINICAL ISSUES

The dose of caffeine for the treatment of apnea of prematurity varies twofold depending upon whether the dose is expressed as caffeine base (10 mg/kg loading, 2.5 mg/kg maintenance) or caffeine citrate (20 mg/kg loading, 5 mg/kg maintenance). Two milligrams of caffeine citrate contain 1 mg of caffeine base.

Medical reviewer comment: *The revised product labeling submitted by the sponsor for CAFKIT is potentially confusing, since the product is caffeine citrate but all dosing is described solely in terms of caffeine base. Both the product labeling and the product label itself should make it extremely clear that each mL of CAFKIT supplies 10 mg of caffeine base as 20 mg of caffeine citrate. Otherwise, clinicians accustomed to dosing caffeine citrate at 20 mg/kg might confusedly double the dose of CAFKIT.*

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## RESPONSE TO FDA COMMUNICATIONS CONCERNING THE NUMERICAL INCREASE IN THE INCIDENCE OF NECROTIZING ENTEROCOLITIS AMONG CAFFEINE-TREATED PATIENTS IN OPR-001

In their submission of 3/22/99, the sponsor documented the inadequacies of available neonatal databases to determine whether or not caffeine citrate is associated with an increased incidence of necrotizing enterocolitis. In addition, the sponsor submitted data on the historical incidence of NEC from a variety of sources to support their contention that variability in the incidence of NEC is sufficient to discount the numerical increase seen with caffeine in trial OPR-001. These database issues and arguments about the incidence of necrotizing enterocolitis are discussed further below.

### **Inability of Neonatal Databases to Resolve the Potential Association of NEC with Caffeine citrate exposure**

A draft protocol for a case control study of the incidence of NEC in infants was submitted by the sponsor on May 18, 1998 and found to be inadequate by FDA on July 9, 1998. The sponsor responded to FDA concerns with a submission on October 26, 1998. After review of that submission, the FDA determined that the available epidemiological databases, including the one proposed for study by the sponsor, were inadequate to characterize the risk of NEC associated with caffeine or methylxanthine use. On February 8, 1999, the FDA asked the sponsor to address the deficiencies of existing databases as well as provide an argument for why the potential association of NEC with caffeine citrate was not of clinical concern.

The sponsor examined 5 potential databases of neonatal information, and dismissed 4 because of missing or inadequate data. The two research databases (NICU Network and Vermont-Oxford) did not contain sufficient information to characterize whether caffeine citrate had been used. Two other administrative databases (the Medical Data Systems NeoKnowledge Network and the HCIA database) contained data that were incomplete or of questionable validity/reliability. The sponsor proposed using The Pediatric Health Information System Database (PHIS) maintained by the Child Health Corporation of America (CHCA).

Although the PHIS database contains audited and quality-checked information about caffeine and other methylxanthine use, the database cannot determine the timing of caffeine administration or the time of onset of reported cases of NEC. The database could therefore not determine whether caffeine administration preceded the development of NEC. Medical record data were not available to validate the diagnosis of NEC across multiple sites or to determine the basis upon which NEC was diagnosed (clinical, radiological, surgical, or pathological). Two factors known to influence the incidence of NEC, concomitant drug use and hospital site, were not available for analysis. Missing information about hospital site would not allow adjustment of rates of NEC for site-specific treatment practices, NEC coding, and background incidence. In short, although the database contained quality-checked data and characterized

methylxanthine use, the degree of detail contained in the administrative files was still insufficient and could not be validated by medical records.

Medical reviewer comment: *The most appropriate database based on data elements and data quality, the PHIS database, is inadequate for either a case-control or cohort analysis of the incidence of NEC in relation to caffeine citrate use. Critical data are lacking about the timing of methylxanthine use in relationship to NEC, variability due to concomitant drugs and hospital site cannot be controlled, and medical records are not available for validation of diagnosis and other important information. These shortcomings were shared with Dr. David Graham of the CDER Office of Post-Marketing Drug Risk Assessment, and he concurred that the database was indeed inadequate to elucidate any relationship of caffeine citrate to NEC.*

### Incidence of NEC

The sponsor provided tabulations and summary data over 4 – 7 years from a variety of sources to document the incidence of NEC, and also provided information on whether caffeine and/or methylxanthine use occurred among identified cases of NEC. The sources of data included the following:

- Eight of the nine investigational sites for OPR-001
- Two additional investigators (Drs. Sola and Purohit) with a total of approximately 3000 births in infants weighing  $\leq 2000$ g
- 26 PHIS sites encompassing  $>23,000$  births  $\leq 2000$ g

For the 8 investigational sites for OPR-001, the annual incidence of NEC among infants  $<2000$  g BW ranged from 0 to 20.3%, with an averaged overall incidence of 6.7% for the entire group. All sites had annual incidences within the range reported in the literature of 2 to 13.5%, with the exception of the Medical College of Georgia site, where the annual incidence ranged from 13.7 – 20.3%. Excluding this site, the incidence among investigational sites ranged from 0 – 10%. For Drs. Sola and Purohit, the annual rates of NEC ranged from 2.2 to 7.0% with an averaged overall incidence of 4.5%. Among the 26 hospitals summarized from the PHIS database, the annual incidence of NEC ranged from 1.28 to 31.75%.

Medical reviewer comment: *The overall incidence of NEC shows variation from center-to-center, as well as within center from one year to the next. The incidence of NEC observed in OPR-001 (7.9% for caffeine exposed and 4.5% for placebo,  $p=1.0$ ) is within the range reported by multiple sites and by the literature. The rate of NEC seen in association with caffeine use in OPR-001 does not exceed historical ranges, and the observed variability between and within sites provides a potential explanation for the observed numeric difference from placebo treatment.*

For selected sites where data were provided/available, the sponsor tabulated information about exposure to caffeine, aminophylline, and theophylline among the

reported cases of NEC. Only one site provided information about how many children in each cohort were exposed to therapy. Matched control data were not provided for any site.

Medical reviewer comment: *Without data on overall exposure or exposure among matched unexposed controls, an estimate of association using either a cohort or case-control methods is impossible. Quantitative comparison of the rate of methylxanthine use among NEC cases is not meaningful; all that can be stated is that NEC occurred both with and without methylxanthine exposure. Examining the different categories of methylxanthine use among cases of NEC does not address whether methylxanthines may increase or promote the development of NEC in treated patients. These data were therefore not analyzed.*

For one investigational site under OPR-001 (Dr. Visser), incidence data for NEC were described according to methylxanthine use (see following table).

Incidence of NEC among Infants  $\leq 2000g$

Year	Total Births	Incidence of NEC among cases treated with methylxanthines	Incidence of NEC among cases not treated with methylxanthines
1994	367	8/151 (5.3%)	9/216 (4.2%)
1995	391	4/166 (2.4%)	14/225 (6.2%)
1996	394	11/169 (6.5%)	15/226 (6.6%)
1997	438	9/215 (4.2%)	5/223 (2.2%)

Medical officer comment: *These crude data show year-to-year variation in the incidence of NEC, with a greater incidence among patients treated with methylxanthines during 1994 and 1997. Conversely, the incidence of NEC was lower among methylxanthine-treated patients in 1995 and 1996. These data provide some gross reassurance that the rates of NEC seen among patients on methylxanthines range within historical limits described in the literature. However, since these data are not adjusted for differences in birth weight, other diagnoses (including apnea of prematurity), and numerous other factors, they cannot provide any conclusive evidence about the potential association of NEC with methylxanthine use.*

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## **Discussion and Conclusions about the Association of NEC with Caffeine Citrate**

*The observed numeric increase in NEC seen in caffeine-exposed infants with apnea of prematurity cannot be clarified by available epidemiological databases. The observed variability in the incidence of NEC, overall and in association with methylxanthine use, adds some credence to the sponsor's contention that the higher numerical incidence of NEC in OPR-001 seen with caffeine citrate may be a random finding. In light of the statistically insignificant findings in OPR-001, high background variability in the incidence of NEC, and continued uncertainty about the pathogenesis of NEC, the extensive use of pharmacy-formulated caffeine citrate for AOP and the weight of evidence for its efficacy argue for its approval with appropriate labeling about the occurrence of necrotizing enterocolitis.*

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## RESPONSE TO DETERMINE IF SIGNS OR SYMPTOMS OF WITHDRAWAL HAVE BEEN REPORTED IN NEONATES EXPOSED TO CAFFEINE

An extensive literature search on caffeine withdrawal in neonates identified no articles on withdrawal symptoms following discontinuation of caffeine therapy in preterm infants or neonates. A Medline literature search by the Medical reviewer confirmed the absence of literature on neonatal withdrawal from the therapeutic use of caffeine. In addition to the review that follows, the Division of Anesthetic, Critical Care, and Addiction Drug Products consulted on the sponsor's submission.

The literature search conducted by the sponsor did identify 4 articles describing withdrawal symptoms in neonates associated with caffeine exposure *in utero*. In these infants, maternal caffeine consumption prior to delivery ranged from 200 to 1800 mg daily. A total of 14 infants were described, with detailed case information provided for only 4 of the infants.

In the one preterm infant (31 weeks gestational age or GA) among the complete case descriptions, a serum caffeine concentration of 40.3 mg/L was found by Khanna et al. on day 4 of life prior to a loading dose of caffeine administered for apnea of prematurity. The extrapolated serum level at birth, assuming a half-life of 100 hours, was 80 mg/L. According to authors, no clinical evidence of caffeine toxicity was noted at any time during the hospital stay. Measured caffeine levels ranged from 51.1 mcg/ml at day 23 of life, to 0.7 mcg/mL on day 37 of life; therapeutic caffeine was administered on at least 2 occasions during the infant's hospital stay. The authors found the infant's manifestation of apnea in the presence of high serum concentrations of caffeine intriguing, and postulated that perhaps the apnea itself was a manifestation of methylxanthine withdrawal. No evidence to support or nullify this hypothesis was provided.

In the 3 remaining case reports with adequate detail, all infants were  $\geq 2300$ g and two were described as term infants. One infant had an episode of apnea; the other two did not. Symptoms attributed to withdrawal in these children included vomiting, tonic episodes, bradycardia and cyanosis, and a dilated bowel gas pattern on x-ray. For these 3 infants and an additional 5 described by McGowan et al., tremulousness/jitteriness was noted in 6, and nonbilious vomiting that required discontinuation of feeding was noted in 5. Two infants each were described as having bradycardia (with heart rates as low as 70bpm) and tachypnea (>60 breaths/minute). Vasomotor instability was observed in one infant.

Five infants whose mothers reported substantial caffeine intake were reported by Thomas to manifest neonatal abstinence syndrome, with symptoms beginning at approximately 5 days of age; these included excessive crying, irritability, poor sleep patterns, and feeding difficulties with "possetting" and vomiting.

To summarize the literature survey, withdrawal symptoms have not been reported in neonates following discontinuation of caffeine treatment for apnea of prematurity.

Infants born to mothers who consumed large quantities of caffeine during pregnancy (200 to 1800 mg daily) have developed symptoms attributed to caffeine withdrawal, chiefly irritability and vomiting. Apnea has also been reported in these infants.

In Dr. Pina's review of the placebo-controlled trial conducted by the sponsor, she notes that the sponsor provided safety information on the patients for 4 days after caffeine was withdrawn. The CRFs did not show evidence of symptoms that could possibly be related to drug withdrawal, although the protocol was admittedly not focused on capturing such events.

Medical reviewer comment: *The placebo controlled trial had no voluntary reports of withdrawal symptoms in treated infants, and the medical literature does not describe neonatal withdrawal in response to caffeine administration. The data on infants exposed to high concentrations of caffeine in utero are suggestive but not conclusive that neonatal irritability and vomiting may be consequences of such exposures. The data appear to be largely derived from cases that occurred in term neonates, with a solitary case report in a premature infant with apneic episodes who showed no clinical signs of toxicity. The literature data are not of sufficient quality to mention in the product labeling.*

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## CAFFEINE SAFETY UPDATES

### Follow-Up to Clinical Trial OPR-001

The sponsor obtained follow-up information on 74 of the 85 infants who received study drug under OPR-001. Information was not obtainable on the remaining 11 patients.

The safety data provided for the 74 patients consisted solely of a table containing reports for 6 patients. From the table, 2 patients with no adverse events reported during the trial were subsequently suspected of having necrotizing enterocolitis. One infant (307) who received randomized and open label caffeine citrate ruled out for this diagnosis. The other patient (116) received placebo throughout the trial but subsequently received open-label caffeine at the time NEC was suspected.

*Medical officer comment: OPR-001 was not designed to provide long-term follow-up data on caffeine exposure. The information obtained by the sponsor about two additional cases of suspected necrotizing enterocolitis neither increases nor decreases the concerns raised about the potential association of NEC with caffeine exposure.*

### Literature reviews

A literature search by the sponsor of multiple databases from 1997 through May 1998 identified 24 articles. The literature search was not provided by the sponsor. Three articles were clinical studies reviewed in entirety by the sponsor for safety data. No safety data were found according to the sponsor; the primary articles were not provided with the submission. In addition, the sponsor reported on a case report of intentional poisoning of a 5 month old with caffeine. Signs and symptoms included tachycardia, tachypnea, elevated temperature, hepatomegaly, a cardiac murmur, agitation, crying and vigorous movement. The caffeine level was 117 mcg/mL and cardiac and liver enzymes were transiently elevated. Within 36 hours, irritability and tachycardia had resolved and within 48 hours the hepatomegaly had resolved.

Two updated literature searches were conducted by the sponsor for 1998 through February 15, 1999 on any safety issues potentially related to caffeine and other methylxanthines. These searches identified 137 articles; titles were provided for 120 of these articles. The sponsor selected 21 titles for full abstract. The sponsor did not consider any of these abstracts to present significant new safety data pertaining to caffeine citrate.

A literature search done 8/2/99 by the medical reviewer resulted in one relevant citation by Lane et al. about the effect of caffeine on neonatal splanchnic blood flow. A dose of 50 mg/kg of caffeine citrate was administered IV over 30 minutes to 12 infants with a mean gestational age of 31 weeks and postnatal age of 8 days. Using Doppler ultrasound, a significant reduction in peak systolic velocity in the superior mesenteric artery (SMA) and the coeliac axis (CA) was for 6 hours after caffeine infusion. The maximal decrease occurred at 176 minutes (SMA) and 133 minutes (CA). The authors indicated that the clinical significance of the observed decrement in blood flow was

unclear, and suggested further study, especially of the effects after the second and subsequent doses of caffeine.

Medical reviewer comment: *Lane et al. undertook this study because of the vasoactivity of caffeine and the anecdotal reports that have linked methylxanthines with NEC. Although the findings are provocative, this study should not be included in the labeling since it was uncontrolled and used an unusually high dose of IV caffeine.*

The sponsor also conducted a literature search for the years 1998 and 1999 (through March 8, 1999) on the topic of necrotizing enterocolitis. Of the 175 titles identified, 48 were chosen for full abstract but no abstract existed for 17 references. The rationale for the selection of abstracts from listed titles was not specified and was not clear to the medical reviewer from inspection of the titles. Four titles describing studies of mesenteric blood flow via Doppler in infants were not examined by the sponsor. Four complete references were retrieved with no rationale for their selection.

Of the four complete references, one (Al-Salem et al., 1998) on a series of 40 infants with GI perforations described one case of localized ileal perforation occurring in an infant on aminophylline therapy for apnea. This child (undescribed in terms of prematurity or other risk factors for NEC) had no evidence of antecedent disease of the bowel. The authors stated " We presume the cause of perforation was can be traced to aminophylline", but provided no further evidence in support of this hypothesis.

The medical reviewer conducted a Medline literature search of 1996 through August 10, 1999 and found no articles on necrotizing enterocolitis that also mentioned caffeine. One abstract (Zanardo et al., 1997, *Pediatr. Med. Chir.*) indicated that premature infants exposed to theophylline antenatally and postnatally had a significantly greater rate of gastric residuals than matched controls. The authors concluded that antenatal theophylline did not appear to increase the risk of NEC in premature infants; one case was seen among 59 exposed infants and none in control infants. In the opinion of the medical reviewer, this study is not relevant to the discussion of caffeine and NEC.

Medical reviewer comment: *The recent medical literature does not include any studies of sufficient quality or clinical relevance to prompt a reevaluation of the potential relationship of NEC to caffeine or other methylxanthine use in premature infants. There appears to be a number of recent investigations of splanchnic blood flow changes in association with NEC, but the evidence from such studies is preliminary and not suitable for regulatory use at this time.*

#### Discussion and Conclusions:

*The sponsor's search of the literature and supplemental literature searches of Medline by the medical reviewer suggest that there are no studies that add materially to the understanding of safety issues associated with caffeine citrate, including the potential association of NEC with caffeine citrate in OPR-001.*

**PATIENT PACKAGE INSERT**

The following section is a rewrite of the sponsor's submission, which needed reorganization and additional detail.

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## Important Information for Patients Using CAFKIT (Caffeine citrate) Injection

Please read the following information before you start giving your baby CAFKIT. Make sure you have also carefully discussed CAFKIT with your baby's doctor, and that you continue to discuss it and any questions that you might have at your baby's checkups.

### What is CAFKIT?

- CAFKIT is a clear and colorless liquid that comes in small glass containers (vials).
- CAFKIT is used to treat apnea of prematurity, a condition which may occur in preterm infants whose breathing centers are not fully developed. Apneas are long pauses (usually 20 seconds or longer) when the baby stops breathing.
- The active ingredient in CAFKIT is caffeine.
- Each milliliter (mL) of CAFKIT (caffeine citrate) Injection contains 10 mg of the active ingredient caffeine. The entire vial contains 3 mL, or 30 mg of active caffeine (also called caffeine base).
- CAFKIT contains no preservatives, so each vial can be used only one time. Medication that is leftover after using a vial must be thrown away.

### How do I give CAFKIT to my baby?

- When given in the home setting, CAFKIT is usually given orally (swallowed by mouth or through a feeding tube). Your baby's health care provider should instruct you about how to give CAFKIT to your child.
- Your doctor will tell you how much CAFKIT to give to your baby. The amount varies from baby to baby depending on age, weight, and how they have reacted to CAFKIT previously. It is very important to follow your doctor's directions exactly. CAFKIT is usually given once a day.
- NEVER change your baby's dose of CAFKIT unless your doctor instructs you to do so. If your baby has periods of apnea while taking CAFKIT, contact your doctor immediately.
- CAFKIT is very concentrated, so it is very important that the dose be measured accurately. You will need to use a small syringe (1cc or smaller) and needle to measure the exact amount that your doctor has prescribed.
  1. First remove the aluminum top from the vial using a tweezers or other small tool.
  2. Remove the plastic disk without touching the rubber cap. If you touch the cap by accident, wipe it off with rubbing alcohol.
  3. Take the syringe with the needle attached and insert the needle through the rubber stopper. Withdraw slightly more than the amount that you need into the syringe, and then remove the needle and syringe from the stopper.
  4. Hold the syringe upright and squeeze out any extra to get the exact number of milliliters (1cc=1mL) that your doctor has prescribed.
  5. Remove the needle from the syringe and discard it safely. Administer CAFKIT to your baby as instructed by your doctor.
  6. Discard the opened vial and any medication that is still inside it.

- CAFGIT should be clear and colorless. Before you take CAFGIT out of the vial, look to see if it shows any small particles, cloudiness, or discoloration. If any of these are seen, do not use that vial of CAFGIT
- Remember that a CAFGIT vial can be used only once. Because there are no preservatives in CAFGIT, do not open the vial until just before you are going to use it. After you have given your baby a dose of CAFGIT, the opened vial and any medicine that is left in it should be thrown away.

#### **What are the possible side effects of CAFGIT?**

Like all medications, CAFGIT may cause side effects in some individuals. The most common side effects are listed below. If your baby has one or more of these symptoms, you should call your doctor.

- Being irritable or fussy
- Restlessness
- Jitteriness or shakiness
- Faster heart rate
- Upset stomach
- Increased wetting of diapers

**If your baby starts to show signs of a stomach problem in one or more of the following ways, call your doctor immediately since these may indicate a serious problem.**

- Bloated or distended stomach
- Vomiting
- Bloody stools
- Acting sluggish or lethargic

This is not a complete list of side effects reported with CAFGIT. If you have a concern about your baby's health or behavior, or wish more information about CAFGIT, you should talk to your doctor.

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## CLINICAL COMMENTS ON REVISED PHYSICIAN LABELING

The following marked-up copy of the sponsor's revisions reflects editorial concerns as well as the decision to eliminate discussion of efficacy endpoints based upon questionable statistical principles. These include failure to adjust for multiple comparisons and the likelihood of some association of the multiple endpoints.

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21 Page(s) Redacted

Draft

Labeling

# MEDICAL OFFICER REVIEW

## Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: 20-793

APPLICATION TYPE: NDA

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

PRODUCT/ Caffeine citrate

PROPRIETARY NAME:

USAN / Established Name: Cafcit Injection

CATEGORY OF DRUG: methylxanthine

ROUTE OF ADMINISTRATION: Intravenous

MEDICAL REVIEWER: L. Miriam Pina, M.D.

REVIEW DATE: January 27, 1998

### SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
08/22/97	08/25/97	New NDA	For the treatment of apnea of prematurity

#### Overview of Application/Review:

Cafcit is proposed for the treatment of apnea of prematurity. The NDA was supported by a single adequate and well controlled clinical trial and a comprehensive review of the published literature. The available data supported the conclusion that Cafcit is safe and effective for the treatment of apnea of prematurity. However, due to an important and unresolved question raised in the published literature regarding the association of caffeine use and the incidence of necrotizing enterocolitis, and the numerical, though not statistically significant, increase in cases of necrotizing enterocolitis found in the caffeine-treated group, the sponsor is being asked to evaluate other available sources of neonatal data that could help elucidate this question before the approval of this application.

Recommended Regulatory Action:

N drive location:

New Clinical Studies: \_\_\_\_\_ Clinical Hold \_\_\_\_\_ Study May Proceed

NDA:  Approvable

Efficacy / Label Supp.: \_\_\_\_\_ Approvable \_\_\_\_\_ Not Approvable

Signed: Medical Reviewer: \_\_\_\_\_

Date: 1/28/98

Medical Team Leader: \_\_\_\_\_

Date: 1/28/98

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## I. General Information

### A. Material reviewed

The sponsor submitted one pivotal study, Protocol No. O.P.R-001, to support the efficacy and safety of caffeine citrate and to characterize its pharmacokinetics as administered during the clinical trial. Because of the extensive experience and body of information already available in the published literature regarding the use of caffeine in the target population, a summary of a comprehensive search of the literature was considered by the sponsor an acceptable complement to support this NDA. The sponsor reviewed, submitted, and discussed 27 publications to support efficacy and 41 to support its safety.

Other submissions reviewed in this NDA are as follows, in the order they were submitted:

07-03-97, 08-22-97, 08-26-97, 09-12-97, 09-25-97, 09-26-97, 10-20-97, 10-23-97, 11-07-97, 11-12-97, 11-20-97, 12-12-97.

### B. Related IND

IND  The pivotal study submitted to the NDA was conducted under this IND.

### C. Proposed Indication

The sponsor, O.P.R. Development, L.P. is seeking approval of caffeine citrate for the treatment of apnea of prematurity.

The definition of apnea of prematurity, suggested by a National Institutes of Health consensus development panel, is periodic breathing with pathologic apnea in a premature infant. Pathologic apnea is a respiratory pause  $\geq 20$  seconds with or without bradycardia, pallor or cyanosis. For purposes of the clinical trial conducted by the sponsor, apnea was defined as cessation of breathing for  $\geq 20$  seconds. For infants  $\leq 1,000$  g at birth the incidence of apnea of prematurity is in the range of 84%.

Although the cause of this condition has not been defined, it is probably related to the overall neurologic immaturity of preterm infants, and is most likely central in origin. It has been associated with irreversible neurological damage secondary to hypoxia and acidosis, which, if untreated, may apparently lead to death.

### D. Proposed Directions for Use

Loading dose.	The sponsor recommends that caffeine citrate be given 10 mg/Kg intravenously over 30 minutes as a loading dose.
Maintenance doses	2.5 mg/Kg intravenously over 10 minutes, or orally, every 24 hours, beginning 24 hours after the loading dose.

**E. Foreign Marketing**

Caffeine citrate injection for the treatment of apnea of prematurity has not been marketed or its approval has not been pursued by the sponsor, O.P.R. Development, L.P., in any foreign country.

There is a product monograph for a parenteral solution of caffeine citrate prepared in a French hospital pharmacy for hospital use only.

[redacted] manufactures an injectable form of caffeine citrate for the treatment of apnea of prematurity in Australia. This product is not registered for general distribution and is manufactured as a "Special Therapeutic". No further information on the product is available.

**F. Composition**

Caffeine is a white crystalline powder or granule, practically odorless with a bitter taste. The product is supplied as a clear, colorless, sterile, non-pyrogenic, preservative-free, aqueous solution.

Each ml of Cafcit contains:

10 mg of caffeine USP anhydrous  
[redacted] mg citric acid, USP, monohydrate  
[redacted] mg sodium citrate, USP, dihydrate  
Water for injection, USP

**II. Clinical Study**

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

**A. Objective**

1. To determine the efficacy of caffeine citrate solution in the treatment of apnea of prematurity by comparing the rate of apnea episodes in patients treated with caffeine citrate solution or placebo.
2. To determine the safety of caffeine citrate solution compared to placebo in patients with apnea of prematurity.
3. To obtain the plasma concentration of caffeine citrate in premature infants treated for up to 12 days.

**B. Design**

This was a multicenter (9 centers), randomized, double-blind, placebo-controlled, parallel study with an open label rescue phase provided.

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C. Protocol

1. Population

a) Inclusion Criteria

1. Post conceptual age of 28 weeks to  $\leq 32$  weeks, 6 days.
2.  $>24$  hours after birth.
3. With at least 6 apnea episodes ( $\geq 20$  seconds) in a 24-hour period or less.

Reviewer's note: No upper bound limits were provided for chronological age.

b) Exclusion Criteria

1. Patients with identifiable causes of apnea (CNS disorders, primary lung disease, generalized, metabolic, and cardiovascular disturbances, abnormal temperature, obstructive apnea).
2. BUN  $>20$  mg/dl, serum creatinine  $>1.5$  mg/dl and after the first 48 hours of life, urine output  $<1$  mL/kg/hr.
3. Serum AST and ALT  $>3$  time upper limit of normal.
4. Requiring mechanical ventilation.
5. Previous treatment with xanthine or  $H_2$  antagonists within 7 days prior to study enrollment.
6. Receiving CNS-active medication.
7. Informed consent.

2. Procedures

a) Specific formulations.

Caffeine citrate sterile solution in 5 and 3 ml glass vials: 10 mg/mL of caffeine, 5 mg/mL of citric acid, and 8.3 mg/mL of sodium citrate. Diluted with water for injection (WFI).

Placebo: sterilized solution in 5 and 3 ml glass vials: 5 mg/mL of citric acid and 8.3 mg/mL of sodium citrate, diluted with WFI.

b) Randomization and blinding.

Patients were randomized to caffeine citrate or placebo in blocks of 6.

To maintain the blinding, a contract laboratory assessed the caffeine blood levels but the results were not made available to the investigator.

c) **Dosage schedule, duration. Route.**

**Double-blind treatment (days 1 - 12).**

Loading dose: 10 mg/Kg (1 ml/Kg) intravenously over 30 minutes.  
Maintenance dose: 2.5 mg/Kg, daily (given orally or IV), beginning 24 hours after the loading dose. Previous versions of the protocol specified that the dose be given daily for up to 10 days as long as the patient had less than 50% of the baseline number of apnea events, or in the investigator's opinion, continued double-blind treatment did not place the patient at risk. The duration of double blind treatment was extended to 12 days in the last amendment (amendment #5).

**Open-label Rescue**

A patient could be rescued with open label caffeine citrate if 24 hours after the loading dose and before day 8, the number of apnea events did not remain <50% of baseline apnea events, and continued double-blind treatment placed the patient at an unacceptable risk.

Loading dose: 10 mg/Kg IV

Maintenance dose: 3.0 mg/Kg/day PO or IV.

The duration of treatment of open-label caffeine was to total 12 days, including the days the patient was in double-blind treatment.

d) **Plasma caffeine concentration**

Blood samples for caffeine levels were obtained at:

1. One hour prior to and 1 hour after the loading dose of double-blind study medication;
2. Prior to the dose of study medication on Days 2 to 12;
3. On days 5 and 8 at a time left to the discretion of the investigator
4. one hour prior to and 1 hour after the loading dose of open-label caffeine, if necessary;
5. At the time any patient was withdrawn from the study due to nonresponsiveness or recurrence of apnea episodes;
6. At the time of adverse events associated with administration of the study medication.

e) **Follow up**

Patients were to be followed for 4 days after cessation of treatment, if no alternative treatment was initiated.

3. **Endpoints**

a) **Primary efficacy variable.**

The rate of apnea episodes during hours 24 - 48 after the double-blind loading dose.

Apnea was defined as cessation of breathing for  $\geq 20$  seconds. All apnea episodes had to be clinically observed and recorded in the CRF. The number and duration of each episode, the lowest  $O_2$  desaturation value and pulse rate associated with each episode,

and the intervention required to reverse each episode were to be recorded as well. Each patient used a standard cardiorespiratory monitor. The lower alarm limit for apnea was set at 20 seconds.

**Reviewer's note:** Note that the above primary endpoint as presented in the last version of the protocol was modified in amendment #5 (March 1995). The previous primary endpoint was the success rate. Success being defined as having  $\geq 50\%$  reduction of the baseline number of episodes of apnea per day during hours 24 to 48 after the double-blind loading dose. Thus, the primary endpoint was changed from the difference in the number of apnea episodes between treatment and baseline to the rate of apneas between the caffeine citrate and placebo treatment groups.

The cardiorespiratory monitors had the drawback that they did not have recording capabilities. The recording of the events depended on the direct observation of the event by the attending personnel in a timely manner.

**b) Secondary endpoints.**

1. Duration of apnea events.
2. Average lowest oxygen saturation for apnea.
3. Proportion of apnea episodes associated with oxygen saturation  $< 85\%$ .
4. Average lowest heart rate for apnea episodes.
5. Proportion of apnea episodes associated with heart rate of  $< 80$  beats per minute.

**c) Safety endpoints.**

1. Vital signs
2. Laboratory values
3. Adverse reactions

**4. Statistical considerations.**

**a) Sample size.**

A total of 78 patients were chosen on the assumption that success (defined as a  $\geq 50\%$  reduction of apnea events during hours 24-48 after the double-blind loading dose) among caffeine citrate-treated patients would be 70% or more and only 20% or less in the placebo-treated group. To have a 5% significance level and a power of 95% required a total of 46 patients.

**Reviewer's note:** The sample size was not calculated based on the final, protocol-specified primary efficacy endpoint, but on the previous primary endpoint, i.e., 50% reduction of the number of baseline apnea events during hours 24 to 48 after the initial loading dose.

b) **Analysis of the primary efficacy variable.**

**Rate of apnea episodes during hours 24 - 48 after the double-blind loading dose.** The number of apneas recorded during day 2 was the numerator and the number of hours spent in the double blinded phase during hours 24 to 48 after the double-blind loading dose was to be considered the denominator. This analysis was to be done with the evaluable population, using an analysis of covariance model (baseline apnea rate and duration of baseline in hours were the covariates).

Reviewer's note: The study report stated that the data were adjusted for the length of the baseline period, and for the length of study days, by scaling all data to 24 hours (the baseline or the study days were not always of 24 hours duration). Hence, 10 apnea events in 12 hours was considered equivalent to 20 events in 24 hours. For missing data the last-value-carried-forward method was used.

The sponsor modified in its study report the protocol-specified definition of the primary endpoint, i.e., the apnea rate during hours 24 to 48 after the double-blind loading dose. In the study report, the sponsor used the original protocol-defined primary endpoint: the percentage of patients with at least a 50% reduction of the number of baseline apnea events during hours 24 to 48 after the initial loading dose, using a chi-squared test. This endpoint was modified to the above definition in the latest amendment the sponsor made to the protocol.

c) **Secondary efficacy variables.**

1. **Duration of apnea episodes.** The episodes were scored from 1 to 3, where 1 was 1 - 10 seconds duration, 2 was 10 - 30 seconds and 3 was more than 30 seconds beyond the apnea alarm. Average duration was defined as the average score for episodes recorded during hours 24 to 48 after the double-blind loading dose.

Reviewer's note: A flaw in the definition of the scoring system allowed overlapping of the categories, e.g., an apnea of 10 seconds of duration could have been scored as 1 or 2. The recording of the duration of the apnea event depended on the clinical observation of the event and how soon the caregiver arrived to the bed side. These issues, in part, made these results difficult to interpret.

2. **For the oxygen saturation response at 24 to 48 hours of treatment, two different analysis were made:**
  - the average lowest oxygen saturation observed for apnea episodes;
  - the proportion of apnea events associated with an oxygen saturation <85%.

Both analysis used analysis of variance models.

3. For the lowest heart rate observed during hours 24 to 48 of treatment, two different analysis were made:
  - the average lowest heart rate observed for apnea episodes;
  - the proportion of apnea events associated with heart rate of < 80 bpm.

Both analysis used analysis of variance models.

d) **Safety variables.**

The data were to be presented in summary tables and listings.

**D. Results**

A total of 87 patients were enrolled (46 randomized to caffeine and 41 to placebo) at 9 participating centers. Five patients were excluded from the efficacy analysis: three patients (1 patient in the caffeine and 2 in the placebo group) were excluded from the efficacy analysis (but were included in the safety analysis) because they had <6 baseline apnea events and were withdrawn early from the study; 2 placebo patients were never treated (See Table 1).

**Table 1 Patients excluded from efficacy analysis**

Patient TAN	Treatment assigned/ # of doses received	Reason for exclusion	Outcome
305	Placebo/ 1 dose	< 6 baseline apneas	No apneas or AEs reported
701	Caffeine/ 3 doses	< 6 baseline apneas	Continued w/apneas. No AEs reported.
702	Placebo/ 4 doses of DB and 1 dose of open-label caffeine	< 6 baseline apneas	Continued w/apneas even after open label dose. Was started on CPAP. No AEs reported.
314	Placebo/ 0 dose	was not given study drug	Was on NCPAP & reintubated
319	Placebo/ 0 dose	was not given study drug	Was on NCPAP & reintubated

A total of 82 patients (45 were assigned to caffeine and 37 to placebo) were included in the efficacy analysis and 85 in the safety analysis.

1. **Neonatal Characteristics.**

Among the 82 patients included in the efficacy analysis, no statistically significant differences were observed between the caffeine and placebo groups for the parameters evaluated (gestational age at birth and at entry, number of baseline apnea attacks, weight at study entry, sex, and race).

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Table 2 Neonatal characteristics

Parameter	Caffeine Group (N= 45)	Placebo group (N= 37)	p-value
Mean Gestational age at birth (weeks)	29.8	29.9	0.77
Mean Gestational age at entry (weeks)	30.6	30.6	0.99
Mean # baseline apnea attacks Minimum Maximum	9.6	9.8	0.84
Weight at entry (grams)	1247.6	1203.4	0.48
Sex (% males)	55.6	70.3	0.17
Race (% Caucasian)	35.6	54.1	0.09

Reviewer's note: The chronological age of the patients at study entry was not captured in the CRF as such. Age at entry was calculated from the date of birth and the date of first dose administered, the mean age at study entry is presented in the following table by treatment. There was no significant difference in age at entry or mean APGAR score at 5 minutes between the treatment groups.

Table 3 Other neonatal characteristics.

Parameter	Caffeine group	Placebo group	p-value
Age at entry (days)	7.3	6.6	0.68
APGAR at 5 min.	7.3	7.5	0.62

**2. Maternal Characteristics.**

Reviewer's note: Data regarding maternal characteristics e.g., problems suffered and medications taken during pregnancy, number of days with rupture of membranes, type of delivery, etc. were not submitted by the sponsor.

**3. Patient Disposition**

Patients who had an apnea rate >50% the baseline rate on day 1 or after day 8 could be withdrawn from the study.

Patients who had an apnea rate >50% the baseline rate on days 2 to 7 were allowed to receive open label caffeine.

There were no statistically significant differences in the number of patients who received open-label caffeine or were prematurely discontinued between the caffeine and the placebo group.

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Table 4 Patients disposition

	Caffeine Group (N= 45)	Placebo Group (N= 37)
Completed 10 days of DB therapy (%)	20 (44)	11 (30)
Received open label caffeine	14 (31)	16 (43)
Withdrawn prior to day 10	10 (22)	9 (24)
Adverse events	2	1
Recurrence of apnea	5	6
Investigator discretion	2	2
Transferred to referring hospital	1	0
Other*	1 (2)	1 (3)

\* Patient said to have discontinued treatment per hospital protocol (not for "treatment failure").

Reviewer's note: Some patients were transferred to open label caffeine and others were discontinued permanently from the trial at different treatment days. In addition, the sponsor stated that 2 patients (1 in each treatment group) did not complete 10 days of double-blind treatment but were not considered withdrawals because they were discontinued per "hospital protocol", not as a result of treatment failure. However, when the CRFs of these patients were reviewed, the patient with TAN 304, in the placebo group, had actually been withdrawn from the trial after receiving 7 doses of DB treatment because of recurrence of apnea. The patient with TAN 523, in the caffeine group, did have 7 days without apnea and following the center's policy the treatment was discontinued.

Seventy-one patients were enrolled under a protocol that provided 10 days of double-blind treatment and 12 days of open-label caffeine. By means of the amendment #5, the duration of double-blind treatment was extended to 12 days. Only 16 patients were enrolled under this new provision, of them, only 5 completed 12 days of treatment.

The number of patients in the trial by day and by allocated treatment is shown in the following table (Table 5).

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Table 5 Number (%) of patients by treatment and study day.

Study Day	Caffeine group (N= 45)			Placebo group (N=37)		
	Double-blind N (%)	Transfer to Open label	Discontinued	Double-blind N (%)	Transfer to Open label	Discontinued
Baseline	45 (100)	-	-	37 (100)	-	-
1	41 (91)	2	2	32 (86)	5	-
2	28 (62)	11	2	19 (51)	9	4
3	26 (57)	1	1	18 (48)	-	1
4	24 (53)	-	2	16 (43)	-	2
5	23 (51)	-	1	15 (41)	1	-
6	22 (48)	-	1	14 (38)	1	-
7	21 (47)	-	1	12 (32) *	-	1
8	20 (44) *	-	-	11 (30)	-	1
9	20 (44)	-	-	11 (30)	-	-
10	20 (44)	-	-	11 (30)	-	-

\*1 patient was said to have discontinued treatment per hospital protocol (not for "treatment failure").  
N= number of patients who completed that study day.

#### 4. Primary Efficacy Endpoint.

According to amendment 5 of the protocol, the primary efficacy endpoint was the rate of apnea episodes during hours 24 to 48 (Day 2) of the double-blind study medication compared to baseline using a covariance model.

Reviewer's note: The sponsor did not submit the analysis of this endpoint as planned in the protocol, claiming that it did not anticipate the high drop-out rate.

The statistical reviewer analyzed the data for the primary endpoint as specified in the protocol. Scaling of duration of baseline and study days to 24 hours and the last-value-carried-over methods were used for the analyses. No statistically significant difference in the apnea rate during hours 24 to 48 after the double-blind loading dose between the caffeine and the placebo groups were found. Similar results were obtained whether baseline apnea rate and duration of baseline or baseline rate only were included as covariates. See Table 6 below.

The difference in the apnea rates compared to baseline between the caffeine and the placebo groups was not statistically significant for any of the treatment days.

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Table 6 Apnea rate during hours 24 to 48 after starting double-blind treatment

Analysis	Caffeine Group*	Placebo Group*	Difference	p-value
Covariance with baseline and duration	4.96	7.21	2.25	.1343
Covariance with baseline only	4.80	7.41	2.61	.0790
Differences from baseline	-8.29	-5.50	2.79	.1614

\* Means or adjusted means

## 5. Secondary Efficacy Endpoints.

### a) Reduction In Apnea Episodes By At Least 50%.

The percentage of patients with at least a 50% reduction in apnea events in the caffeine and placebo groups, as compared to baseline, was evaluated for each of the 10 treatment days. Scaling to 24 hours and last-observation-carried-over methods were used.

The difference in the number of patients with at least a 50% reduction in apnea events was statistically significant in favor of the caffeine group on days 4, 5, 7, 8, 9, and 10. The difference was not statistically significant on days 1, 2, 3 and 6.

The mean number of days with  $\geq 50\%$  reduction in apnea events when compared to baseline for the caffeine and the placebo group was 6.8 and 4.6 days, respectively (p-value = 0.025).

Table 7 Percent of patients with  $\geq 50\%$  reduction in apnea events by Day (scaled to 24 hours and last-observation-carried-forward).

Study Day	Caffeine Group (N=45)	Placebo Group (N=37)	p-value
1	62	49	0.21
2	76	57	0.07
3	67	49	0.09
4	67	43	0.03
5	67	43	0.03
6	69	49	0.06
7	69	46	0.03
8	69	41	0.01
9	67	41	0.01
10	69	43	0.01

Reference: NDA Table 5.1

Reviewer's note: The sponsor had considered this endpoint as the primary efficacy endpoint in the original protocol, but it was subsequently changed to the apnea rate during the second day of treatment in the latest amendment submitted to the agency. This analysis carries forward the apnea rate of the last day of double-blind treatment for those patients who were transferred to open label caffeine or were discontinued from the trial.

It is worth noting that, of the 60 patients (36 in the caffeine group and 24 in the placebo group) who had the apnea rate reduced by  $\geq 50\%$  of the baseline period at least once during the trial period, 20 patients in the caffeine group (55%) and 7 in the placebo group (29%) maintained that effect until the end of the study period.

There were several patients who were transferred to open-label caffeine or were permanently discontinued from the trial, (10 patients in the caffeine group [28%] and 6 patients in the placebo group [25%]) and had a reduction of  $\geq 50\%$  in their apnea rate the day they were transferred or discontinued from the trial; this value was carried over until the end of the study. Some of these patients, however, were transferred to open-label caffeine because of frequent bradycardic events without apneas, persistent apnea events even though the rate was  $\leq 50\%$  of the baseline period, or were transferred to another hospital. See Table 8.

In addition, a higher, statistically significant, percentage of patients in the caffeine group (32/45 [69%]) had 8 or more days with a  $\geq 50\%$  reduction in apnea events than in the placebo group (16/37 [43%]) (p-value=0.018).

Table 8 Patients with at least one day with apnea rate reduced  $\geq 50\%$  of baseline

	Caffeine group (n=36)	Placebo group (n=24)	p-value
Once reduction of apnea rate $\geq 50\%$ was achieved, it was maintained *	20 (55%)	7 (29%)	0.037**
Reduction $\geq 50\%$ was not maintained once achieved.	6 (17%)	11 (46%)	
Patients with a reduction in apnea rate $\geq 50\%$ carried forward after transferred to open-label caffeine or early withdrawal.	10 (28%)	6 (25%)	

\* Patients who completed double-blind treatment only.

\*\* Chi square test, using both groups as 3 categories.

A secondary analysis of the percentage of patients with  $\geq 50\%$  reduction in apnea events in the caffeine and placebo groups, as compared to baseline, according to the number of patients with data in the double blind group available at each treatment day showed a statistically significant difference in favor of the caffeine group on day 8 only (see table below). The failure to reach statistical significance could be due in part to the sample size in the double-blind treated groups that decreased considerably after the second treatment day.

Table 9 Percent of patients with  $\geq 50\%$  reduction in apnea events by Day. Double-blind phase.

Day	Caffeine Group			Placebo Group			p-value <sup>c</sup>
	N <sup>a</sup>	n <sup>b</sup>	%	N <sup>a</sup>	n <sup>b</sup>	%	
1	45	28	62.2	37	18	48.6	0.266
2	41	33	80.5	32	21	65.6	0.184
3	28	23	82.1	19	14	73.7	0.496
4	26	23	88.5	18	12	66.7	0.128
5	24	22	91.7	16	12	75.0	0.195
6	23	22	95.7	15	14	93.3	1.000
7	22	22	100	14	12	85.7	0.144
8	21	21	100	12	9	75.0	0.040
9	20	19	95	11	9	81.8	0.281
10	20	20	100	11	10	90.9	0.355
11	3	3	100	1	1	100	-
12	3	3	100	1	1	100	-

<sup>a</sup>N = Number of patients in the double-blind group who had an observation that day.

<sup>b</sup>n = Number of patients with  $\geq 50\%$  reduction of apnea events

<sup>c</sup> Fishers exact test

Reference: NDA table 5.3 modified

For the patients who were transferred to open-label caffeine, the following table (Table 10) shows the number of patients available (N) and the number of patients who had  $\geq 50\%$  reduction in apnea events (n) by days of exposure to open-label caffeine. Overall, more patients who were originally in the placebo group, when switched to open-label caffeine, had  $\geq 50\%$  reduction in apnea events from baseline when compared to patients originally assigned to the caffeine group. Of note is that the patients in the caffeine group who received open-label caffeine were those who had already failed treatment with caffeine.

Table 10 Number of patients with  $\geq 50\%$  reduction of apnea events by days of exposure. Open-label

Days of exposure	Caffeine Group (N=14)			Placebo Group (N=16)			
	N <sup>a</sup>	n <sup>b</sup>	%	Days of exposure <sup>c</sup>	N <sup>a</sup>	n <sup>b</sup>	%
1	14	9	64	1	16	13	81.3
2	14	5	36	2	15	9	60.0
3	12	6	50	3	15	10	66.7
4	12	5	42	4	12	8	66.7
5	8	4	50	5	12	8	66.7
6	6	1	17	6	10	8	80.0
7	3	0	0	7	7	6	85.7
8	2	1	50	8	6	5	83.3
9	2 <sup>d</sup>	-	-	9	6	5	83.3
10	2 <sup>d</sup>	-	-	10	5	3	60.0

<sup>a</sup> Days of exposure to caffeine during the open label phase.

<sup>b</sup>N = total number of patients transferred to open-label

<sup>c</sup>n = Number of patients with data available, with  $\geq 50\%$  reduction in apnea events from baseline

<sup>d</sup> Apnea events data not available for this day for both patients.

Reference: NDA table 5.3 modified

**b) Elimination Of Apnea Episodes:**

The percentage of patients who had zero apnea events in the caffeine and placebo groups was evaluated for each of the first 10 treatment days. Scaling to 24 hours and last-observation-carried-over methods were used. Success was defined as elimination of apnea events. In addition, failures occurred when an infant was withdrawn from double-blind medication or transferred to open label caffeine.

Table 11 shows the percentage of patients with elimination of apnea events at each treatment day. The difference in elimination of apnea events was statistically significant in favor of the caffeine group on days 2, 4, 7, 8, and 9.

Table 12 shows the number of patients by total number of days with zero apnea events by treatment group. The mean number of days with zero apnea events in the caffeine and the placebo groups were 3.0 and 1.2, respectively (p value = 0.005).

**Table 11** Percent of patients with elimination of apnea events by treatment Day.

Study Day	Caffeine Group (N=45)	Placebo Group (N=37)	p-value
1	20.0	10.8	0.256
2	26.7	8.1	0.030
3	31.1	13.5	0.060
4	31.1	5.4	0.003
5	31.1	16.2	0.118
6	28.9	13.5	0.094
7	33.3	10.8	0.016
8	33.3	10.8	0.016
9	33.3	10.8	0.016
10	31.1	16.2	0.118

Reference: NDA table 6.1 modified

**Table 12** Number of patients by total # of days with zero apnea events. Double-blind phase.

# of Days with 0 apneas	Caffeine Group (N=45)	Placebo Group (N=37)	p-value
Mean	3.0	1.2	0.005*
0	21	24	
1	2	1	
2	4	4	
3	5	3	
4	0	2	
5	0	1	
6	2	2	
7	0	0	
8	4	0	
9	4	0	
10	3	0	

\* Student's t-test

Reference: NDA table 6.2 modified

Reviewer's note: The p-values above are not adjusted for multiple comparisons. Table 12 shows that 11 patients had 8 or more days without apnea events, however, the review of the CRFs showed that 1 patient (TAN 205) was

withdrawn on day 5 due to transfer to the referring hospital, thus, only 10 patients can be considered in this subset. Nevertheless, it is still remarkable that 10 patients in the caffeine group (22%) had zero apnea events for 8 days or more, versus 0 patients in the placebo group. Six of the 10 patients (60%) remained apnea-free through out the study period from the first day they had zero apnea events/day.

A secondary analysis of the percentage of patients with zero apnea events, between the caffeine and the placebo treated groups, according to the number of patients with data in the double blind group available at each treatment day, was statistically significant in favor of the caffeine group on days 2 and 4 (See Table 13).

Table 13 Percent of patients with elimination of apnea events by treatment Day. Double-blind phase

Study Day	Caffeine Group (N=45)			Placebo Group (N=37)			p-value <sup>c</sup>
	N <sup>a</sup>	n <sup>b</sup>	%	N <sup>a</sup>	n <sup>b</sup>	%	
1	45	09	20.0	37	4	10.8	0.365
2	41	12	29.3	32	3	9.4	0.045
3	28	14	50.0	19	5	26.3	0.136
4	26	14	53.8	18	2	11.1	0.005
5	24	14	58.3	16	6	37.5	0.333
6	23	12	52.2	15	5	33.3	0.326
7	22	14	63.6	14	4	28.6	0.086
8	21	14	66.7	12	4	33.3	0.083
9	20	13	65.0	11	4	36.4	0.153
10	20	12	60.0	11	6	54.5	1.000

<sup>a</sup> N = Number of patients in the double-blind group who had an observation that day.

<sup>b</sup> n = Number of patients with no apnea events

<sup>c</sup> Fishers exact test

Reference: NDA table 6.3 modified

For patients who received open-label caffeine, in general, more patients originally assigned to the placebo group had zero apnea events when compared to patients in the caffeine group. The following table shows the number of patients available (N) and the number of patients who had zero apnea events (n) by days of exposure to open-label caffeine.

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Table 14 Number of patients with zero apnea events by days. Open-label

Days of exposure	Caffeine Group (N=14)			Placebo Group (N=16)			
	N	n	%	Days of exposure	N	n	%
1	14	1	7.0	1	16	3	18.8
2	14	2	14.0	2	15	3	20.0
3	12	3	25.0	3	15	5	33.3
4	12	2	17.0	4	12	4	33.3
5	8	1	12.5	5	12	4	33.3
6	6	1	16.6	6	10	6	60.0
7	3	0	0	7	7	0	0.0
8	3	0	0	8	6	4	66.7
9	2	-	-	9	6	5	83.3
10	2	-	-	10	5	3	60.0

\* Days of exposure to caffeine in the open-label phase.  
 \* N = total number of patients transferred to open-label  
 \* n = Number of patients with zero apnea events  
 \* Patients apnea events data not available for this day.  
 Reference: NDA table 6.3 modified

It is interesting that the results obtained by the caffeine group in the double-blind phase are somewhat similar to those obtained by the placebo group that received open-label caffeine. For instance, the percentage of patients who had zero apneas after the loading dose of caffeine in the double-blind caffeine group is comparable to that of those who received open-label caffeine in the placebo group (20% versus 19%). In addition, about one third of the patients in the placebo group who received open-label caffeine no longer had any apnea events by the third day of treatment. These results are comparable to those obtained in the caffeine group in the double-blind phase. However, the percentages in the placebo group that received open-label caffeine are higher for days 8, 9, and 10 when compared to the caffeine group in the double-blind phase.

Few patients in the caffeine group, who initially had failed treatment with caffeine, eliminated their apnea events after being transferred to open-label caffeine.

These results suggest that there is a portion of the population with apnea of prematurity that responds completely to the effects of caffeine citrate.

**c) Lowest Oxygen Saturation (%) by Treatment Day.**

The mean values for lowest oxygen saturation (%) associated with apnea events by treatment day were compared between the caffeine and the placebo groups.

The mean values for lowest oxygen saturation between the caffeine and the placebo groups by treatment day were similar. In the double blind group, the mean lowest oxygen saturation associated with apnea events ranged from 78% to 84% in the caffeine-treated group and 77% to 87% in the placebo group. In the open-label phase, the mean value ranged from 73% to 89% in the caffeine group and 77% to 87% in the placebo group.

Reviewer's note: The proportion of apnea events associated with oxygen saturation <85% was not evaluated by the sponsor as proposed in the protocol.

d) **Lowest Heart rate by Treatment Day.**

The mean values for the lowest heart rates associated with apneas were evaluated between the caffeine and the placebo groups.

The mean values for lowest heart rate associated with apnea events between the caffeine and the placebo groups were similar. In the double blind group, the mean lowest heart rate associated with apnea events ranged from 67 to 78 beats per minute (bpm) in the caffeine-treated group and from 69 to 78 bpm, in the placebo group. In the open-label phase, the mean values ranged from 66 to 86 bpm in the caffeine group and from 65 to 84 bpm in the placebo group.

Reviewer's note: The proportion of apneas associated with heart rate lower than 80 was not evaluated by the sponsor, as proposed in the protocol.

e) **Duration of Apnea Events**

The duration of apnea events were grouped according to the duration of the apnea event:

1 = apnea events lasting 0 to 10 seconds beyond the apnea alarm (set at 20 sec).

2 = apneas lasting from 10 to 20 seconds;

3 = apneas lasting >30 seconds.

Reviewer's note: The events were recorded in the patients records by the attending nurse, once the alarm went off. Because the nurse was not always at bed side at the time the apnea alarm went off, the manual recording of the duration of the apnea events is unreliable.

The sponsor presented the duration of the apnea events by day for the double-blind and the open-label treatment periods for each treatment group, but did not provide the analysis of the data for this endpoint. Based on the protocol's statistical plan, the events were to be analyzed according to the average score for each group with a covariance model.

According to the statistical reviewer's calculations, the overall analysis of the summarization of duration of the apnea events submitted by the sponsor showed that there is no significant effect of caffeine on the duration of apnea events.

6. **Safety Evaluations**

The safety analysis included 85 of the 87 infants enrolled. Two infants (in the placebo group) did not receive any test drug treatment and were not included in this analysis (See table 1).

a) **Vital signs**

The mean values for temperature, respiratory rate, pulse and blood pressure were compared between the caffeine and the placebo groups.

There were no significant differences between the treatment groups.

b) **Clinical Laboratory evaluations**

Values for sodium, potassium, calcium, chloride, carbon dioxide, BUN, glucose, AST, ALT,GGTP, creatinine, and hematocrit were compared between the caffeine and the placebo groups. These values were analyzed at baseline and at the end of the study for patients who did not receive open-label caffeine therapy and at baseline, pre-open-label, and at study end for patients who received open-label caffeine.

No clinically significant differences were identified between infants in the caffeine and placebo groups or those who received open-label caffeine who had previously received caffeine or placebo during double-blind therapy.

c) **Adverse events**

Treatment emergent adverse events were captured in the CRF and classified according to the COSTART dictionary and by body system.

There were no statistically significant differences in the number and percent of patients with at least one adverse event between caffeine or placebo patients in the double-blind (p-value = 0.5).In the open-label caffeine groups, there were not clinically significant differences in the number and percent of patients with at least one adverse event between the groups .

When the adverse events were categorized by Body System, no statistically significant differences were noted for the double-blind group, or clinically significant differences for the open-label caffeine group.

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Number & Percent of Adverse Events/ Intercurrent Illnesses by Body System

Body System/ Preferred Term	Caffeine				Placebo				P-value*
	Double-Blind (N = 46)		Open-Label (N = 14)		Double-Blind (N = 39)		Open-Label (N = 17)		
	n	( % )	n	( % )	n	( % )	n	( % )	
AT LEAST ONE AE	25	(54.3)	11	(78.6)	24	(61.5)	11	(64.7)	0.5187
BODY AS A WHOLE	10	(21.7)	6	(42.9)	7	(17.9)	5	(29.4)	0.7878
ABDOMEN ENLARGED	1	( 2.2)	0	( 0.0)	1	( 2.6)	0	( 0.0)	
ACCIDENTAL INJURY	1	( 2.2)	0	( 0.0)	0	( 0.0)	0	( 0.0)	
DRUG LEVEL INCREASED	0	( 0.0)	1	( 7.1)	0	( 0.0)	0	( 0.0)	
GENERALIZED EDEMA	0	( 0.0)	0	( 0.0)	0	( 0.0)	1	( 5.9)	
HYDROCEPHALUS	0	( 0.0)	0	( 0.0)	1	( 2.6)	0	( 0.0)	
INJECTION SITE INFLAMMATION	1	( 2.2)	0	( 0.0)	0	( 0.0)	0	( 0.0)	
INJECTION SITE REACTION	4	( 8.7)	1	( 7.1)	5	(12.8)	1	( 5.9)	
PERINATAL DISORDER	4	( 8.7)	2	(14.3)	2	( 5.1)	2	(11.8)	
SEPSIS	2	( 4.3)	4	(28.6)	0	( 0.0)	2	(11.8)	
CARDIOVASCULAR SYSTEM	2	( 4.3)	4	(28.6)	2	( 5.1)	2	(11.8)	1.0000
BRADYCARDIA	0	( 0.0)	1	( 7.1)	0	( 0.0)	0	( 0.0)	
CARDIOVASCULAR DISORDER	0	( 0.0)	1	( 7.1)	0	( 0.0)	0	( 0.0)	
CEREBRAL HEMORRHAGE	0	( 0.0)	1	( 7.1)	0	( 0.0)	0	( 0.0)	
HEMORRHAGE	1	( 2.2)	0	( 0.0)	0	( 0.0)	0	( 0.0)	
PATENT DUCTUS ARTERIOSUS	1	( 2.2)	1	( 7.1)	2	( 5.1)	2	(11.8)	
TACHYCARDIA	0	( 0.0)	1	( 7.1)	0	( 0.0)	0	( 0.0)	
DIGESTIVE SYSTEM	12	(26.1)	6	(42.9)	12	(30.8)	6	(35.3)	0.6388
CONSTIPATION	8	(17.4)	2	(14.3)	8	(20.5)	3	(17.6)	
ENTEROCOLITIS	2	( 4.3)	2	(14.3)	1	( 2.6)	1	( 5.9)	
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0	( 0.0)	0	( 0.0)	1	( 2.6)	0	( 0.0)	
GASTRITIS	1	( 2.2)	0	( 0.0)	0	( 0.0)	0	( 0.0)	
GASTROINTESTINAL DISORDER	2	( 4.3)	2	(14.3)	3	( 7.7)	1	( 5.9)	
GASTROINTESTINAL HEMORRHAGE	1	( 2.2)	0	( 0.0)	0	( 0.0)	0	( 0.0)	
ORAL MONILIASIS	0	( 0.0)	0	( 0.0)	0	( 0.0)	1	( 5.9)	
SMALL INTESTINE PERFORATION	0	( 0.0)	0	( 0.0)	0	( 0.0)	1	( 5.9)	
ULCERATIVE STOMATITIS	0	( 0.0)	0	( 0.0)	1	( 2.6)	0	( 0.0)	
VOMITING	0	( 0.0)	0	( 0.0)	0	( 0.0)	2	(11.8)	

n = Number of patients experiencing adverse events  
% = n/N x 100.

\* Double-blind percentages from each body system were compared using the Fisher's exact test  
Reference: NDA table 16

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Number & Percent of Adverse Events/Intercurrent Illnesses by Body System

Body System/ Preferred Term	Caffeine				Placebo		P-value*		
	Double-Blind (N = 46)		Open-Label (N = 14)		Double-Blind (N = 39)			Open-Label (N = 17)	
	n	(%)	n	(%)	n	(%)		n	(%)
<b>HEMIC AND LYMPHATIC SYSTEM</b>									
ANEMIA	4	(8.7)	4	(28.6)	7	(17.9)	4	(23.5)	0.3313*
DISSEMINATED INTRAVASCULAR COAGULATION	3	(6.5)	3	(21.4)	7	(17.9)	4	(23.5)	
HYPOVOLEMIA	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	
LYMPHADENOPATHY	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)	
	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)	
<b>METABOLIC AND NUTRITIVE DISORDERS</b>									
ACIDOSIS	2	(4.3)	3	(21.4)	2	(5.1)	2	(11.8)	1.0000
HEALING ABNORMAL	1	(2.2)	0	(0.0)	0	(0.0)	1	(5.9)	
HYPERKALEMIA	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	
HYPOCALCEMIA	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.9)	
HYPONATREMIA	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)	
HYPOPROTEINEMIA	0	(0.0)	2	(14.3)	2	(5.1)	0	(0.0)	
	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)	
	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)	
<b>NERVOUS SYSTEM</b>									
CEREBRAL HEMORRHAGE	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	1.0000
	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	
<b>RESPIRATORY SYSTEM</b>									
APNEA	2	(4.3)	1	(7.1)	1	(2.6)	1	(5.9)	1.0000
DYSPNEA	0	(0.0)	1	(7.1)	1	(2.6)	0	(0.0)	
LUNG EDEMA	1	(2.2)	0	(0.0)	0	(0.0)	1	(5.9)	
RESPIRATORY DISORDER	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	
	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)	
<b>SKIN AND APPENDAGES</b>									
DRY SKIN	6	(13.0)	0	(0.0)	4	(10.3)	2	(11.8)	0.7478
RASH	1	(2.2)	0	(0.0)	0	(0.0)	1	(5.9)	
SKIN DISORDER	4	(8.7)	0	(0.0)	3	(7.7)	1	(5.9)	
VESICULOBULLOUS RASH	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	
	0	(0.0)	0	(0.0)	1	(2.6)	0	(0.0)	
<b>SPECIAL SENSES</b>									
CONJUNCTIVITIS	2	(4.3)	0	(0.0)	1	(2.6)	0	(0.0)	1.0000
RETINAL DISORDER	1	(2.2)	0	(0.0)	1	(2.6)	0	(0.0)	
	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	
<b>UROGENITAL SYSTEM</b>									
KIDNEY FAILURE	1	(2.2)	0	(0.0)	2	(5.1)	0	(0.0)	0.5913
KIDNEY FUNCTION ABNORMAL	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	
URINARY TRACT INFECTION	0	(0.0)	0	(0.0)	1	(2.6)	0	(0.0)	
	0	(0.0)	0	(0.0)	1	(2.6)	0	(0.0)	

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**Reviewer's note:** The above comparison of adverse events between the double blind patients allocated to caffeine versus placebo treatment is only one way of looking at the data. It does not account for the potential drug effect that caffeine could have had in all patients exposed as a group.

Because of the complexity of the design of the trial, where some patients in the placebo group received open-label caffeine at different times, the adverse event rates between the treatment groups were difficult to evaluate and had to be assessed in several ways. The following tables show the most important adverse events between the caffeine and the placebo groups analyzed from different perspectives.

The first analysis (Table 15) included all patients, analyzed by exposure to caffeine (the exposed group includes all the patients randomized to the caffeine group plus those patients in the placebo group that received open-label caffeine). No significance was noted in the incidence of the adverse events analyzed between the treatment groups. The second analysis (Table 16) compared adverse events of all patients randomized to the caffeine group (n = 46) versus the adverse events that occurred to patients randomized to the placebo group (n = 39) while they were on double-blind treatment only. The third table (Table 17) shows adverse events that occurred to patients by their randomization treatment group, regardless of their exposure to caffeine. This last analysis was done to overcome the time factor, where some patients in the placebo group were transferred to open-label caffeine quite early, with the possibility that they did not have enough time to develop some complications that may have occurred had they been allowed to continue in the same group for a longer time period.

**Table 15 Adverse events of all patients by exposure to Caffeine\*\***

Adverse Event	Exposed (N = 63)	Not Exposed (N = 22)	p-value*
Any event	43 (68%)	18 (81%)	0.589
Necrotizing enterocolitis	5 (7.9%)	1 (4.5%)	1.000
Sepsis	8 (13%)	0 (0%)	0.101
Anemia	11 (17.5%)	6 (27%)	0.381
Vomiting	2 (3%)	0 (0%)	1.000

Reference: NDA, Special request 2 table (9/22/97 submission)

\* Fisher's exact test

\*\* The exposed group constituted patients randomized to the caffeine group plus the patients in the placebo group who received open-label caffeine.

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Table 16 Adverse events by treatment \*\*

Adverse Event	Caffeine group (N = 46)	Placebo group (N = 39)	p-value*
Any event	36 (78%)	18 (49%)	0.003
Necrotizing enterocolitis	4 (8.6%)	1 (3%)	0.369
Sepsis	6 (13%)	0 (0%)	0.029
Anemia	6 (13%)	6 (15%)	0.766
Vomiting	0 (0%)	0 (0%)	1.000

\* Fisher's exact test

\*\* The adverse events reported for the placebo group are only those that occurred while the placebo patients were on placebo.

Table 17 Adverse events by original randomization\*\*

Adverse Event	Caffeine group (N = 46)	Placebo group (N = 39)	p-value*
Any event	36 (78%)	35 (90%)	0.241
Necrotizing enterocolitis	4 (8.6%)	2 (5%)	0.683
Sepsis	6 (13%)	2 (5%)	0.279
Anemia	6 (13%)	11 (28%)	0.105
Vomiting	0 (0%)	2 (5%)	0.208

\* Fisher's exact test

\*\* The adverse events are reported regardless of the patient's exposure to caffeine.

As the above tables show, no significant difference in the incidence of adverse events reported was found (except for sepsis, when the AEs of the placebo group while on placebo were compared to the adverse events of the caffeine group. When sepsis was compared by original randomization, no statistically significant difference was noted.). It is clear that the small sample size makes it difficult to pick up significant differences in safety parameters if there was any. On the other hand, we should note that the p-values calculated for the first two analyses may be somewhat biased against the caffeine treatment because of the longer time the patients in the caffeine group were on the test drug compared to those in the placebo group.

Necrotizing enterocolitis (NEC): NEC deserves special discussion in this section because of the high morbi-mortality associated with this entity, in this population. NEC has been associated in inverse relationship with gestational age and birth weight. An evaluation of the characteristics of the patients who presented with NEC in this trial (4 in the caffeine group and 2 in the placebo group) did not reveal any particular characteristic that could be associated with the development of NEC. The babies who developed NEC had a gestational age between 28 and 30 weeks and, in 5 of them, the weight at study entry was >1,000 grams. The maximum caffeine levels were between 12 and 27 mg/L, levels that are generally considered well tolerated. The APGAR scores at 5 minutes (between 6 and 9) do not represent severe neonatal distress. Unfortunately, some perinatal information, e.g., maternal treatment with steroids, birth weight and APGAR scores at 1 minute, were not available for this analysis. Regarding the route of administration of caffeine, in the caffeine group, 2 patients received double-blind treatment only, and

received the IV loading dose followed by 2 and 4 PO maintenance doses respectively. The caffeine-treated patients who received open-label caffeine were transferred on Day 3, and all of the doses were given IV for 2 to 4 days before they were withdrawn from the trial. The only placebo patient with NEC who was not exposed to caffeine received 3 days of IV placebo before being withdrawn from the trial.

The placebo patient (TAN 311) who received 8 days of open-label caffeine had ileal resection on the first day of open-label treatment. The diagnosis of NEC was not made until the autopsy, several days later. The question for this patient remains whether the patient was already having NEC on the first day of open-label treatment or the NEC changes were subsequent to the exposure to caffeine.

Table 18 Some characteristics of the patients who suffered NEC

Patient ID #	Randomized Tx.	Gestational age	Weight at entry	5 min APGAR	Pulse at birth	Max. Caffeine
205	Caffeine	30 (weeks)	705 (grams)	6	144 (bpm)	11.76 (mg/L)
321	Caffeine	28	1080	7	184	25.67
603	Caffeine	30	1163	9	142	14.14
607	Caffeine	28	1061	8	179	21.5
114	Placebo	32	1823	9	131	0
311*	Placebo	29	1435	5	181	17.84

\* Received 8 days of open-label caffeine after study Day 2.

d) **Deaths**

Three deaths were reported in this trial: 2 patients randomized to caffeine treatment and 1 patient randomized to placebo. This last patient received open label caffeine for 8 days. All deaths were secondary to complications from necrotic enterocolitis.

**Patient 205** - 30 weeks GA, male, assigned to caffeine. This patient received 5 days of treatment (the first dose was given IV and next 4 doses PO) and was then transferred to referring hospital. Three days later was readmitted for NEC and PDA. After surgery patient developed renal failure and died 6 days later.

**Patient 603** - 30 weeks GA, male, assigned to caffeine. He received 3 days of treatment (the first dose was given IV and next 2 doses PO) and was discontinued for persistent apneas. He was continued on "house caffeine" orally, for 6 more days until he developed NEC. He died next day.

**Patient 311** - 29 weeks GA, male, assigned to placebo. He was transferred to open-label caffeine on Day 2 for persistent apneas. On the first day of treatment with open-label caffeine the patient had surgery (ileal resection) for ileal perforation but was not withdrawn from the study. He continued to receive IV caffeine to complete 10 days, but hospital course was guarded and he expired 18 days later. According to an investigator's note in the CRF, "there was no

evidence" of NEC after the small bowel resection and ileal perforation. The NEC diagnosis was given later on, at the time of the autopsy.

**e) Patients' follow up**

The protocol established that the patients would be followed for 4 days after the therapy was discontinued, if they did not receive any alternative treatment. Furthermore, patients with adverse events were to be followed until resolution of the event.

Reviewer's note: The NDA did not provide any follow up information of the patients.

At the reviewer's request, the sponsor gathered and submitted the 4-day follow up data for all patients. There were no more deaths, sepsis or new NEC cases reported. However, some patients in both groups were started on 'house' caffeine after the completion of the trial.

**E. Reviewer's Comments/Conclusions Regarding Study Results**

This was a Phase III, multicenter, randomized, placebo-controlled trial, where the effects of caffeine citrate versus placebo were studied in 85 patients with apnea of prematurity.

The demographic characteristics of both groups were comparable, even though the maternal characteristics were not evaluated.

**Efficacy**

The interpretation of the results is difficult due to issues in the design of the trial. A large number of patients were transferred to open-label caffeine and/or withdrawn early from both treatment groups. This factor diminished the power of the sample size and also added a time of exposure factor into the equation. As a result, different analyses were necessary to evaluate the results, considering the changing circumstances of the patients during the trial period.

The difference between treatment groups in the primary endpoint as proposed in the protocol, change from baseline in rate of apnea episodes during hours 24 to 48 (Day 2) of the double-blind study period, was not statistically significant. However, caffeine citrate demonstrated superiority over placebo in other clinically important parameters. Patients in the caffeine group had more days without any apnea event than patients in the placebo group. The mean days with zero apneas was 3.0 for the caffeine group and 1.2 days for the placebo group (p-value = 0.005). Moreover, a total of 10 patients in the caffeine group (22%) had zero apnea events for 8 days or more, versus 0 patients in the placebo group. Six of the 10 patients (55%) did not have any other apnea event once they turned successful.

In addition, the difference in the mean number of days with >50% reduction in apnea events when compared to baseline between the caffeine and the

placebo groups was also significant, 6.8 days for the caffeine group and 4.6 days for the placebo group (p-value = 0.025).

#### **Safety**

Because several patients originally assigned to the placebo group also received open-label caffeine in the midst of the study period, at different time periods, it was difficult to compare and evaluate the incidence of adverse events between the treatment groups. It is obvious that the more time a patient is exposed to a drug, the more chances there are that unrelated events happen. At the same time, the comparisons between the treatment groups were difficult because the patients who remained in the placebo group were, for the most part, stable patients who did not have intercurrent illnesses, whereas those patients who were transferred to open-label caffeine may have had recurrence of apnea because of unrelated events common in this population, especially sepsis. The evaluation of the safety of caffeine had to be based on several analyses in order to assess each of the individual situations. Despite that fact, no significant differences were found in the incidence of adverse events except for a significant increase in the incidence of sepsis in the caffeine group, when adverse events in the placebo group while on placebo were compared to the adverse events of the caffeine-exposed group. Two patients in the placebo group went on to develop sepsis while on open-label caffeine treatment raising the question whether this finding was due to the time factor or the treatment. When the treatment groups were compared by their randomized treatment, accounting in this case for the time of exposure factor, no statistically significant differences were found between the treatment groups. It is of concern, however, that the incidence of NEC was numerically higher in the caffeine group than in the controls, even though the investigators did not associate the occurrence of these events to the study drug. As will be discussed in the review of the literature section, NEC is a relatively common and highly fatal event in this population. Its etiology has not been clearly identified yet, but its incidence has been inversely related to the gestational age of the infant and there is discussion in the literature that its incidence may be associated with several factors, xanthine use being suggested as one of them. We were not able to observe an association between the risk of developing NEC with several parameters (gestational age, APGAR scores at 5 minutes, or caffeine level) measured in this trial. NEC, however, is of such high morbidity and mortality, that its numerical increase in the treated group in this trial should not be dismissed completely without an exhaustive investigation of other possible sources of information. The sponsor should be asked to make an attempt to further investigate this issue, by assessing other large, potentially useful sources of information, i.e., the Vermont-Oxford and the NICHD Neonatal Network databases that could provide data to further elucidate any association between caffeine citrate and NEC.

#### **Conclusion**

Even though the caffeine treated group did not demonstrate a statistically significant improvement in the protocol-specified primary endpoint compared to placebo treated infants, there are other clinically relevant secondary endpoints that support the efficacy of caffeine citrate for the treatment of apnea of prematurity. The trial showed a similar profile of

adverse events between the treatment groups. However, the numerical increase in the incidence of NEC in the caffeine treated group in this small trial raises questions regarding whether there is an association between caffeine citrate and this adverse event. To ensure that all available data that may shed light on this question are adequately evaluated, the sponsor should be asked to assess whether existing neonatal databases contain data that could address this issue and, if they do, propose and conduct a study using this data.

### III. Review of The Literature

The sponsor conducted 3 separate literature searches to identify reference articles on the use of caffeine citrate in the treatment of apnea of prematurity.

The first search covered from 1966 to 1985. Six databases were searched: Medline, Toxline, Biosis (Biological Abstracts), Emed (Excerpta Medica), IPA (International Pharmaceutical Abstracts), and IDIS (Iowa Drug Information Systems).

The second search covered from 1985 to July 1995. Five databases were searched: MEDLINE, TOXLINE, BIOSIS, EMBASE (Excerpta Medica), and IPA. The third search was conducted in February 1996, and covered 1995 to February 1996. The previous 5 databases were searched plus IDIS.

The search identified 1072 published articles. The sponsor reviewed the abstracts of the citations in the clinical bibliography and those abstracts that satisfied the following criteria were selected for review:

- Adequate and well controlled study as defined in 21 CFR 314.126
- Prospective study
- Indication of apnea of prematurity
- Treatment with caffeine citrate
- English language.

#### A. Efficacy Summary of Published Clinical Trials

Twenty seven publications were submitted to support the efficacy of caffeine in patients with apnea of prematurity.

##### 1. Controlled Clinical Trials

All controlled trials identified by the sponsor used untreated or historical controls or compared theophylline to caffeine. No placebo-controlled trials were identified.

##### a) Trials with Historical or Untreated-Controls

There were three main trials published that studied premature infants with apnea of prematurity using untreated or historic controls.

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- The trial published by I. Murat (1981)<sup>1</sup> was the only prospective trial where untreated controls were used in parallel with treated subjects. The results of a group of 9 premature infants (29 to 35 weeks GA) randomized to caffeine sodium citrate were compared to those of 9 infants randomized to the control (not treated) group. The caffeine dose was 20 mg/Kg IM loading dose, and 5 mg/Kg oral maintenance dose<sup>2</sup>. The primary endpoint was apnea index calculated by cardiorespirographic recordings on days 1, 5 and 15. Apnea index was defined as the average number of apneic attacks per 100 minutes, obtained from the total number recorded within a 24-hour period. The apnea index in the treated group was statistically significantly lower when compared to the controls on days 1 and 5 post treatment. On day 15 the apnea index was very low in both groups; however, only 3 of the 9 patients in the control group, were studied on day 15. The other 6 control patients were considered failures, 2 received IMV and 4 received caffeine treatment. Furthermore, 8 of the 9 caffeine-treated patients had a 24-hour recording 8 days after the end of caffeine treatment; the apnea index was significantly lower than on day 15 ( $p < 0.02$  for severe and mild apneas). No adverse events were reported.
- The second trial, by Romagnoli et al. (1992)<sup>3</sup>, studied two different oral maintenance doses after an IV loading dose of 10 mg/Kg. Group I received 5 mg/Kg and Group II received 2.5 mg/Kg. In this trial, historic controls were used (a previous series of 14 untreated infants with idiopathic apneas [from 1983]) and the primary endpoint was the mean number of daily apneic spells during the first 9 days of treatment. The baseline characteristics of the 3 groups were reported to be comparable (only the birth weight and the gestational age data were published). A significant decrease in the number of apneic spells occurred in both treated groups ( $p < 0.01$ ) when compared to controls. The caffeine blood levels remained within the therapeutic range for both groups throughout the study and no significant difference was seen between the treated groups. However, adverse events like hyperglycemia, tachycardia and vomiting were more frequent in the high dose group. It is noteworthy that 1 patient in Group I and 4 in Group II were said to have been excluded from the study "because of death or other complications." No further details were given.
- The third trial, published by Anwar et al. (1986)<sup>4</sup>, is actually an

<sup>1</sup> Murat et al. The efficacy of caffeine in the treatment of recurrent idiopathic apnea in premature infants. *J. Pediatr* 1981;99:984-9.

<sup>2</sup> Reviewer's Note: The author did not specify if the stated doses were related to the caffeine citrate or the caffeine base. However, for the doses used the author referenced Aranda et al. (1977) who used 10 to 20 mg/Kg loading dose and 5 mg/Kg maintenance doses of caffeine citrate, equivalent to a loading dose of 5 to 10 mg/Kg and maintenance doses of 2.5 mg/Kg of caffeine base.

<sup>3</sup> Romagnoli et al. Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants. *Ther Drug Monit* 1992;14:14-19.

<sup>4</sup> Anwar et al. Effect of caffeine on pneumogram and apnea of infancy. *Arch Dis Child* 1986;61:891-5.

uncontrolled trial. The results of 12-hour pneumograms were compared before and after caffeine treatment. Nineteen premature infants and 4 full term infants with clinical apnea received a loading dose of 20 mg/Kg followed by an oral maintenance dose of 5 mg/Kg once daily. Each infant had 12 hour pneumogram recordings before and 7 to 10 days after administration of caffeine. The primary endpoint was: Total number of apnea attacks. There was a significant reduction in all categories analyzed ( $p < 0.05$ ), except for attacks lasting 11-15 seconds; however, there were no prolonged attacks ( $> 15$  seconds) or attacks associated with bradycardia. Eleven infants (48%) became free of apnea attacks. Six infants became irritable after treatment with caffeine was started, two of them were withdrawn from the trial.

**b) Trials Comparing Caffeine to Theophylline**

Seven trials were selected for submission. Overall, both treatment groups were not statistically significantly different from each other in reducing significantly the number or the frequency of apnea attacks from baseline.

A study by Scanlon et al. (1992)<sup>8</sup>, compared two caffeine dose regimens:

- Group A (n=16)- Caffeine citrate PO, or NG 25 mg/kg, load and 6 mg/kg every 24 hours, and
- Group B (n=14) - Caffeine citrate PO, or NG, 50 mg/kg, then 12 mg/kg every 24 hours.
- Group C (n=14) - constituted the group of patients who received theophylline PO, or NG, 7.5 mg/kg, then 3 mg/kg TID.

Both regimens were comparable to theophylline at 24 hours but Group B (the higher dose group) and the theophylline group responded better at 8 hours: 4/12 infants in Group A responded versus 10/12 in Group B and 11/12 in Group C

**2. Uncontrolled Clinical Trials**

Several small, open label, uncontrolled trials (n ranging from 5 to 34 patients) have studied caffeine under diverse conditions and have evaluated different efficacy parameters. In general, periodic breathing, number of apnea events, and/or apnea density have improved significantly after treatment with caffeine citrate at different doses.

Some investigators studied caffeine after the patient failed to improve with theophylline. These studies are hard to evaluate in many aspects of their design, e.g., their sample size are small, they were open label with soft endpoints, and the age/time factor was not taken into account. In addition, there are no crossover trials where theophylline was compared to caffeine in the same fashion.

The following tables provide a description and details of the studies submitted.

<sup>8</sup> Scanlon et al. Caffeine or theophylline for neonatal apnea? Arch Dis Child 1992;67:425-8.

**Table 19 Efficacy Summary Table--Controlled Clinical Trials. Caffeine versus historic or untreated controls**

Author	Study Design/ Drugs/Dosage	Demographics	Study Duration	Adverse events	Efficacy Results In caffeine treated infants
Anwar, <i>et al.</i> 1986	Comparison of outcomes before and after treatment/ Caffeine citrate PO 20 mg/kg load, followed by 5 mg/kg/day, 24 hours after load. /Dosage was adjusted to maintain a blood concentration of 6-15 mcg/ml.	Preterm infants with apnea (n=19): GA=32 ± 2.6 weeks BW=1.6 ± 0.6 kg Age at entry=5 ± 3.2 weeks  Full term infants with apnea (n=4): BW=2.8 ± 0.43 kg	21 of 23 infants received caffeine for 3.4 ± 1.3 months	2 infants became irritable, restless and jittery after starting Tx. And were withdrawn. 4 infants were reported irritable and restless.	<u>Total number of attacks: significant reduction in all categories analyzed (p&lt;0.05), except for attacks lasting 11-15 seconds; however, there were no prolonged attacks (&gt; 15 seconds) or attacks associated with bradycardia.</u> <u>Periodic breathing and apnea density</u> Significant reduction in (p<0.05). <u>Elimination of apneas</u> Eleven infants (48%) became free of apnea attacks.
Murat, <i>et al.</i> 1981	Randomized trial/  Group I: caffeine sodium citrate 20 mg/kg IM load, followed by 5 mg/Kg PO every 24 hours  Group II: untreated controls	Group I (n=9): GA=30.1 ± 0.6 weeks BW=1.247 ± 0.101 kg Age at entry=13.2 ± 2.3 days  Group II (n=9): GA=29.8 ± 0.5 weeks BW=1.411 ± 0.71 kg PNA=16.1 ± 3.3 days	mean 24 days (range: 15 to 40 days)	None	<u>Apnea index: significant reduction for severe (p&lt;0.01) and mild (p&lt;0.001) apnea was noted.</u> In Group I, a significant decrease in apnea index was observed from day 0 to day 1 and from day 0 to day 5 (p<0.01 for severe attacks, p<0.001 for mild attacks). No difference was found between days 5 and 15 in Group I. No difference was found from day 0 to day 1 or day 5, nor between day 1 and day 5 in Group II. Eight days after caffeine treatment, 8 of 9 infants had a significantly lower apnea index than on day 15: severe apnea p<0.02; mild apnea p<0.02.
Romagnoli, <i>et al.</i> 1992	Randomized trial/  Group I: caffeine citrate 10 mg/kg IV load, followed by 5 mg/kg PO every 24 hours  Group II: caffeine citrate 10 mg/kg IV load, followed by 2.5 mg/kg PO every 24 hours  Historical controls	Group I (n=14): GA=29.9 ± 0.9 weeks BW=1.237 ± 0.313 kg  Group II (n=10): GA=29.2 ± 1.6 weeks BW=1.140 ± 0.262 kg  historical controls (n=14): GA=30.3 ± 0.6 weeks BW=1.395 ± 0.303 kg	<u>Group I</u> 18.4 ± 3 days  <u>Group II</u> 15.1 ± 1 days	<u>Group I</u> 1 glucose (5/13), 1 BP (1/13), 1 HR (11/13), Vomiting (11/13).  <u>Group II</u> 1 glucose (2/10) Vomiting (2/10)	A significant reduction in the number of apneic spells was noted in both treated groups (p<0.01).

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Table 20 Efficacy Summary Table--Controlled Clinical Trials. Caffeine versus Theophylline

Author	Study Design/ Drugs/Dosage	Demographics	Study Duration	Adverse events	Efficacy Results <u>In caffeine treated infants.</u>
Bairam, <i>et al.</i> 1987	Randomized trial/ theophylline IV: 6 mg/kg load, followed by 2 mg/kg every 12 hours  Caffeine IV: 10 mg/kg load, followed by 1.25 mg/kg every 12 hours	Theophylline group (n=10): GA=30.3 ± 0.8 weeks BW=1.5 ± 0.3 kg Age at entry=6.2 ± 3.4days  Caffeine group (n=10): GA=30.0 ± 1.5 weeks BW=1.2 ± 0.2 kg Age at entry=5.5 ± 2.5days	7 days	The theophylline group had 1 mean HR and more GI intolerance (4 infants had oral feeds stopped and 2 of them had signs of NEC) and excitability compared to the caffeine group.	Sum of cardiorespiratory abnormalities was significantly (p<0.01) and similarly decreased in both groups.
Brouard, <i>et al.</i> 1985	Rz, open label trial/ Aminophylline 5.5 mg/kg IV load, and daily IV or PO doses from 0.8 to 2.5 mg/kg every 8 hours to maintain levels between 5 to 10 mg/L  Caffeine sodium citrate 20 mg/kg IM load, and a PO daily dose of 5 mg/kg/day.	Group I (n=8): GA=30.5 ± 0.4 weeks BW=1.250 ± 0.074 kg PNA=11.7 ± 1.9 days  Group II (n=8): GA=30.5 ± 0.7 weeks BW=1.465 ± 0.101 kg PNA=11.6 ± 2.8 days	5 days	Tachycardia (165 - 210 bpm) was reported in 1/8 in the theophylline group.  No AEs were seen in the caffeine group.	Significant decreases in apnea frequency were noted in both groups (p<0.001). No significant differences between groups were reported.
Fuglsang, <i>et al.</i> 1989	Rz, double-blind trial/ Aminophylline via NG tube 7.5 mg/kg load, followed by 3.75 mg/kg every 12 hours  Caffeine citrate via NG tube 20 mg/kg load, followed by 5 mg/kg every 24 hours	Aminophylline group (n=9) GA=30 ± 2 weeks BW=1.351 ± 0.489 kg Age at entry=8 ± 11 days  Caffeine group (n=9): GA=31 ± 3 weeks BW=1.499 ± 0.467 kg Age at entry=7 ± 13 days	14 days	None	Apnea frequency and bradycardia were significantly decreased with time in both groups (p<0.001 and p<0.005). No significant differences were noted between groups.
Scanlon, <i>et al.</i> 1992	Rz, open label trial/ Group A Caffeine citrate PO, or NG 25 mg/kg, load and 6 mg/kg every 24 hours  Group B Caffeine citrate PO, or NG, 50 mg/kg, then 12 mg/kg every 24 hours  Group C: Theophylline PO, or NG, 7.5 mg/kg, then 3 mg/kg TID.	Group A (n=16): GA=28.7 ± 1.2 weeks BW=1.140 ± 0.210 kg PNA=5.6 ± 2.6 days  Group B (n=14): GA=28.2 ± 1.1 weeks BW=1.200 ± 0.260 kg PNA=6.0 ± 2.7 days  Group C (n=14): GA=27.9 ± 1.4 weeks BW=1.240 ± 0.32 kg PNA=7.6 ± 4.9 days	At least 5 days	One of 16 infants in Group A and 5 of 12 infants in Group C had dosage adjustments because of 1 HR> 195 bpm. No other AEs were reported.	Number of apnea attacks decreased significantly in all groups during the first 24 hours of treatment, occurring more rapidly (within the first 8 hours) in Group B and Group C than in Group A. Only one infant in Group A failed to respond successfully within 48 hours from start of treatment (defined as a >50% reduction in the number of apneas). Within 8 hours, 4/12 infants in Group A responded versus 10/12 in Group B and 11/12 in Group C.

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Table 21 Efficacy Summary Table--Uncontrolled Clinical Trials

Author	Drugs/Dosage	Demographics	Study Duration	Outcome Measurements	Efficacy Results
Aranda, et al. 1977	caffeine sodium benzoate 10 mg/kg (one patient/one dose)  Initial: caffeine citrate 20 mg/kg PO once or twice daily  Protocol change: caffeine citrate 20 mg/kg IV load, followed by 5-10 mg/kg once or twice daily two to three days after load	n=18 GA=27.5 ± 0.6 weeks BW=1.065 ± 0.07195 kg mean age at onset of apnea=6.5 ± 3.7 days mean age at which caffeine initiated= 18.2 ± 4.9 days	6.0 ± 1.9 days	apnea events, heart rate, respiratory rate, PO <sub>2</sub> , PCO <sub>2</sub>	Apneic spells were significantly decreased (13.6 ± 2.5 vs. 2.1 ± 0.6)(p < 0.001). Seventeen of 18 infants had a least a 50% decrease in number of apneic spells. Six of 18 had complete cessation of apnea. Blood hydrogen ion concentration (p < 0.001) and capillary PCO <sub>2</sub> (p < 0.01) were significantly decreased. Respiratory rate was significantly increased (p < 0.01). No significant changes in plasma bicarbonate and capillary oxygen tension were noted.
Cattarossi, et al. 1988	Group I: caffeine benzoate 15 mg/kg IM load, followed by caffeine citrate 2 mg/kg PO every 24 hours  Group II: caffeine citrate 15 mg/kg PO load, followed by 2 mg/kg PO every 24 hours	Group I (n=9): GA=30.6 ± 2.5 weeks BW=1.547 ± 0.3387 kg PNA=42.1 hours Apgar score at 1 and 5 minutes=6.1 and 7.7  Group II (n=9): GA=30.8 ± 1.05 weeks BW=1.552 ± 0.2042 kg PNA=77.3 hours Apgar score at 1 and 5 minutes=4.6 and 7.5	3 weeks	apnea frequency	Sixteen infants experienced a variable number of apneic attacks (1-4 episodes/day), which was considered a successful result. No resuscitatory measures were necessary. Two infants, one in each group, experienced more than 5 apneic attacks/day which required tactile stimulation or brief ventilation with a face mask for resolution.
Davis, et al. 1987	caffeine 10 mg/kg PO load, followed by 2.5 mg/kg/day	n=11 GA=31.2 ± 0.7 weeks BW=1.66 ± 0.18 kg age at diagnosis of apnea= 4.9 days age at starting theophylline= 6.5 ± 1.8 days age at starting caffeine= 20.3 ± 4.8 days study interval between switch from theophylline to caffeine= 6.0 ± 1.0 days	5 to 7 days	thermistor-pneumocardiogram (apnea duration and frequency)	Nine of 11 infants (82%) demonstrated a significant and immediate reduction in apnea frequency. Apnea frequency decreased from a mean of 22.8 episodes per 6 hour recording on theophylline to a mean of 4.8 on caffeine- (p < 0.01). Bradycardia decreased on caffeine, but was not statistically significant.

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Author	Drugs/Dosage	Demographics	Study Duration	Outcome Measurements	Efficacy Results
Haik, <i>et al.</i> 1976	caffeine ≤ 6 mg/kg IV load, followed by ≤ 2.5 mg/kg/h as continuous infusion	n=5 GA=0.7 to 1.65 weeks BW=24 to 33 kg	Not specified	apnea frequency, PA <sub>CO2</sub> , PA <sub>O2</sub> , pH	Apneic episodes were abolished in four infants and markedly reduced in one. PA <sub>CO2</sub> and pH decreased from a mean of 77 to 44 mmHg and 7.17 to 7.28, respectively. Apneic episodes returned upon caffeine discontinuation. Readministration of caffeine abolished or markedly reduced apnea and blood gases returned to normal values.
Harrison, 1992	all patients (n=61): theophylline IV, PO or gavage 5 mg/kg load, followed by 1-1.5 mg/kg every 8 hours  theophylline failures (n=16): caffeine citrate PO or gavage 20 mg/kg load, followed by 5 to 7.5 mg/kg every 24 hours	n=60 GA=32.7 ± 0.4 weeks BW=1.6 ± 0.3 kg age at diagnosis= 19 ± 11 days weight at diagnosis= 1.66 ± 0.275 kg age at theophylline start=18.7 ± 1.7 days age at caffeine start= 26.2 ± 1.6 days	4 to 10 days	pneumocardiogram (apnea density)	Apnea density was significantly and similarly decreased in theophylline and caffeine successes (p < 0.01 and 0 < 0.02, respectively). No significant differences in apnea density were noted between two groups. Forty-four of 60 (73%) theophylline-treated infants normalized their pneumocardiogram. Fourteen of 16 (88%) caffeine-treated patients normalized their pneumocardiogram. The two caffeine failures had prolonged hospitalizations for > 60 days with other medical problems.
Katsardis, <i>et al.</i> 1984	caffeine  (dose not specified)	n=9 age=38 ± 40 days	Not specified	respirogram (apnea density, periodic breathing, Quiet Sleep Breathing)	Quiet Sleep Breathing did not significantly change following caffeine administration. Apnea density was significantly decreased (44.6 ± 13.6 apneas/hr pre-caffeine to 27.5 ± 14.2 apneas/hr post-caffeine, p < 0.05). This effect was only significant in the group of apneas of intermediate duration (6 to 9.9 seconds). Caffeine did not significantly reduce the mean duration of the longest apnea (13.22 ± 4.22 pre-caffeine versus 12.56 ± 2.77 post-caffeine). Caffeine reduced the number of episodes of periodic breathing, the number of apneas in these episodes, and the duration of periodic breathing.

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Author	Drugs/Dosage	Demographics	Study Duration	Outcome Measurements	Efficacy Results
Marotta, <i>et al.</i> 1984	caffeine PO 20 mg/kg load, followed by 5 mg/kg/day	n=5 GA=33 ± 7 weeks BW=1.89 ± 0.95 kg	About 7 days	pneumo-cardiogram (% periodic breathing, apnea frequency, bradycardia)	Significant decreases were noted in periodic breathing (20.6 ± 17.9% to 2.1 ± 2.5%), apnea ≥ 15 seconds (total N)(14 to 1), and bradycardia < 100 bpm (total N)(135 to 45).
Mondestin, <i>et al.</i> 1985	caffeine citrate PO 20 mg/kg load, followed by 5 mg/kg daily	n=9 GA=32 ± 2 weeks BW=1.8 ± 1.4 kg	6.5 ± 9 weeks of age to 10 ± 9 weeks of age	pneumo-cardiogram (apnea frequency and duration, apnea density)	Caffeine treatment resulted in fewer short (<15 sec) and long apneas (>15 sec), decreased apnea density and decreased episodes and percent of periodic breathing. Number, length, or nadir of associated bradycardias were not affected.
Pearlman, <i>et al.</i> 1989	caffeine citrate IV, PO, or NG 20 mg/kg load, followed by 5-10 mg/kg once or twice daily.	n=17 GA=29.7 ± 1.9 weeks BW=1.27 ± 0.36 kg age at study= 20.7 ± 6.6 days weight at study= 1.36 ± 0.42 kg	Not specified.	apnea frequency	Caffeine citrate was administered twice daily in five patients because of failure of once daily caffeine to improve their apnea. At least a 40% reduction in the number of apneic episodes was noted in all patients.
Rothberg, <i>et al.</i> 1981	caffeine citrate 20 mg/kg IV, single dose	intravenously fed (n=6): GA=31.5 ± 3.3 weeks BW=1.185 ± 0.014 kg age at study= 4.6 ± 0.87 days  orally fed (n=6): GA=32.0 ± 3.1 weeks BW=1.391 ± .015 kg age at study= 9.5 ± 1.2 days	24 hours	pediatric pneumogram (apnea frequency)	A significant reduction in the frequency of apnea was observed (p<0.01).
Wakamatu <i>et al.</i> 1987	caffeine (10% alcoholic solution) 15 mg/kg per NG load, followed by 3 mg/kg/day	n=34 GA=28.6 ± 1.7 weeks BW=1.201 ± 0.0801 kg PNA=4.8 ± 0.7 days	7 to 35 days (mean 16.9 ± 1.5 days)	apnea frequency	Twenty-six of 34 infants had fewer apneic episodes. Apneic episodes decreased from a baseline of 7.4 ± 2.7 times/8 hours prior to caffeine to 1.3 ± 2.1 times/8 hours, 24 hours after caffeine administration.

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## B. Safety Summary of Published Clinical Trials

The database from published clinical trials, either submitted by the sponsor (41 articles) or from our own search (18 articles), included over 830 premature infants exposed to caffeine.

### 1. Demographic characteristics:

Gestational age ranged between 26 and 40 weeks  
Birth weight: between 0.597 Kg to 2.5 Kg

### 2. Formulation:

Caffeine citrate was used in the great majority of the cases. Other formulations used included: caffeine sodium benzoate and caffeine salt, not specified.

### 3. Dosages:

The dosages and route of administration varied widely among the trials. In a pharmacokinetic study by Lee, doses as high as 60 mg/Kg loading dose and 30 mg/Kg maintenance were used for 7 days.

- Loading dose - The most common doses used were 5, 10 and 20 mg of caffeine base/Kg, IV or PO.
- Maintenance dose: The most common dose used was 2.5 to 5 mg of caffeine base/Kg/day

### 4. Most Common Adverse events:

#### a) Stimulation of the Central Nervous system

Irritability/ cry/ jitteriness/ restlessness were reported in 21 patients. Plasma concentrations did not correlate with symptoms, and varied from 5.7 to 84 mg/L. Symptoms improved or disappeared after discontinuation of caffeine.

#### b) Seizures

Two publications have reported seizures in patients treated with caffeine:

- Davis et al., (1986)<sup>6</sup> reported 2 cases where the patients developed generalized seizures after the administration of caffeine. Both patients had received caffeine for the treatment of SIDS. The first case (a 2.5 month old boy) had received 20 mg/Kg IV loading dose of caffeine citrate and had a caffeine level of 13.7 mg/L. The EEG presented epileptiform foci over the left temporal region and had a diagnosis of seizure disorder. After 2 years of treatment with phenobarbital, had a normal EEG and a normal neurologic examination. The second case (a 4 month old girl) had received an oral loading dose of 20 mg/Kg for the treatment of SIDS. Afterwards, she had a diagnosis of myoclonic seizure disorder, and was treated with

<sup>6</sup> Davis et al. Apnea and seizures. Arch Dis Child 1986;61:791-93.

anticonvulsants. This patient had developmental delay and neurologic deficits over the next two years.

- Van den Anker et al., (1992)<sup>7</sup> reported seizures in a case of caffeine overdose. The patient was a 33.7 weeks Caucasian male, weight 1625 g, that received caffeine for the treatment of apnea of prematurity. On the 2<sup>nd</sup> day of treatment the patient presented tachypnea, tachycardia, compromised circulation, vomiting and convulsions. Serum caffeine level was 346 mg/L. (Reviewer's note: Theophylline levels were not published) Caffeine was discontinued, and after 9 days the caffeine concentration was 32.9 mg/L. At 18 months of age the follow up psychomotor examination was normal.

**c) Hearing Loss**

Koppe et al., (1979)<sup>8</sup> reviewed retrospectively 253 infants who survived ICU beyond 3 years, who were born between 1959 and 1974 with a birth weight  $\leq$  1500 g and a gestational age  $\leq$  35 weeks. Ninety four infants received caffeine for apneic spells. Until 1972 caffeine was dissolved with sodium benzoate and given subcutaneously at 5 to 25 mg, 1 to 4 times a day. After 1972, caffeine was dissolved in water and given IM or PO at 10 mg/Kg loading dose and 2.5 to 5 mg/Kg maintenance dose. (Sodium benzoate is believed to have a competitive effect with bilirubin at albumin-binding sites). The study showed that the incidence of hearing defects was higher in the caffeine treated group. When the controls were matched for birth weight, gestational age and birth date and duration of follow up, the incidence of hearing loss was statistically significantly higher in the caffeine-treated group. All patients with hearing loss, however, were born before 1972 and the authors concluded that sodium benzoate was probably responsible for the significantly higher incidence of hearing loss found in the years 1959-1972.

**d) Cardiovascular Changes**

Effects on left ventricular output, stroke volume, heart rate, and mean arterial blood pressure were evaluated in several trials, at different doses. In general, the use of caffeine was associated with tachycardia (Brouard et al. 1985, Larsen et al., 1995, Romagnoli et al., 1992, Scanlon et al., 1992), transient bradycardia (Aranda et al., 1977), increase in left ventricular output and stroke volume and higher mean arterial blood pressure (Walther et al., 1990). When the effects of caffeine and theophylline were compared, the caffeine group tended to have milder changes than the theophylline group.

**e) Gastroesophageal reflux and gastric aspirate**

The effects of caffeine in the gastrointestinal tract were evaluated in many trials. In summary, caffeine has been associated with increased gastroesophageal reflux (Skopnik et al., 1989, Vandenplas

<sup>7</sup> Van den Anker et al. Severe caffeine intoxication in a preterm neonate. Eur J Pediatr 1992;151:466-7.

<sup>8</sup> Koppe et al. Apneic spells and transcutaneous PO<sub>2</sub>: Treatment with caffeine, 19-year follow-up. Birth defects 1979;XV(4):437-45.

et al, 1986), GI intolerance, e.g., vomiting and regurgitation, (Romagnoli et al, 1992, who noticed these effects in the group with higher maintenance dose- 5 mg/Kg/day versus the lower maintenance dose 2.5 mg/Kg/day). When the effects of caffeine and theophylline were compared, gastrointestinal intolerance were reported more frequently for the theophylline group.

f) **Necrotizing enterocolitis**

Necrotizing enterocolitis is a major cause of morbidity and mortality in premature infants. Its incidence ranges from 2 to 13.5% with the highest incidence seen in the lower birth weight groups. Mortality varies from 20 to 50% according to other medical factors involved.

A paper by Grosfeld et al., (1983)<sup>9</sup> studied the effect of aminophylline in an experimental bowel ischemia model. The superior mesenteric artery was occluded for 1 minute in eighty-two weanling Sprague-Dawley rats. Group 1 were untreated controls, Group II received aminophylline (AMPH) 40 mg/Kg IP 4 hours and immediately prior to clamping. Ischemic bowel occurred in 60% of controls (43% with necrosis and 17% with perforation) versus 90% of the rats with AMPH (70% with necrosis and 19% with perforation). Mortality was 60% in the controls versus 90% in the AMPH group. However, the actual causes of mortality were similar in both groups. This study suggested that aminophylline had an adverse effect in animals with ischemic bowel insults.

Several papers have been published in the literature about the use of xanthine therapy in the infants at risk for NEC. Robinson et al., 1980<sup>10</sup>, and Williams et al., 1990 were the first to suggest the association of xanthines treatment with the development of NEC. Robinson described 3 cases (27 and 28 weeks of GA) where aminophylline was given initially IV and then orally, and developed subsequent NEC. The authors postulated that NEC, in these cases were related to bacterial overgrowth due to decreased GI motility which followed the use of xanthines. Williams reported two additional cases of NEC, in these cases following 24 hours of cessation of xanthine treatment.

The use of umbilical artery catheters; some pharmacological agents like aminophylline and Vitamin E; and high-density formulas have all been implicated with the incidence of NEC and the survival of patients with NEC (Cikrit, et al., 1984 and 1985).

McGrady in 1987<sup>11</sup> reported a study of an outbreak of NEC in a level III Neonatal Intensive Care nursery occurred in 1985. The birth weight-specific incidence of NEC in the outbreak setting was similar to that seen in endemic NEC. Transfusion of packed red blood cells was highly and significantly associated with NEC, but when birth

<sup>9</sup> Grosfeld et al. Neonatal apnea, xanthines, and Necrotizing Enterocolitis. J Pediatr Surg 1983;18:80-4.

<sup>10</sup> Robinson et al. Xanthines and necrotizing enterocolitis. Arch Dis Child 1980;55:494-5.

<sup>11</sup> McGrady et al. An Outbreak of necrotizing enterocolitis. Am J Epidemiol 1987;126:1165-72.

weight was taken into account, no association of NEC with other exposures, previously reported as risk factors, was found.

In a study by Bairam et al., 1987<sup>12</sup>, the effects of caffeine (n = 10) were compared to those of theophylline (n = 10). In this trial oral feeds were stopped in 4 infants in the theophylline group for GI intolerance. Two of them were reported to have developed signs of NEC. The caffeine group did not develop significant GI symptoms.

Larsen et al., (1995)<sup>13</sup> reported no differences in the incidence of necrotizing enterocolitis between the caffeine group (n= 82) and the theophylline group (n = 98), however, the actual incidence of NEC in each group was not published.

Finally, in a study by Davis J. et al., (1986)<sup>14</sup> 124 infants treated with theophylline had a similar incidence of NEC as did 151 infants who were not treated with theophylline. Davis studied the hospital course of 275 premature infants with birth weight  $\leq$  1500 g. He identified two groups of infants: one group received theophylline during their hospital course and the second group did not receive theophylline therapy. The incidence of NEC in the theophylline-treated group was 10% (12 cases) and in the not treated group was 11% (16 cases). Covariate analysis of risk factors for NEC in infants in whom NEC developed revealed no differences among the theophylline-treated and the non-treated group.

Reviewer's note: The findings in the literature are not conclusive whether caffeine exposure is definitely associated with an increased incidence of NEC, nor if there is a subset of patients at a higher risk of developing this disease if exposed to caffeine.

#### g) Renal effects

Several results have been reported on the effect of caffeine on the renal system. In summary, caffeine induced significant sodium loss (Bairam et al., 1987)<sup>12</sup>, significantly increased urine flow rate, water output/input ratio, and creatinine clearance (Gillot et al., 1990)<sup>15</sup> and urine calcium excretion (Zanardo et al., 1995)<sup>16</sup>.

<sup>12</sup> Bairam et al. Theophylline versus caffeine: Comparative effects in treatment of idiopathic apnea in the preterm infant. *J Pediatr* 1987;110:636-9.

<sup>13</sup> Larsen et al. Aminophylline versus caffeine citrate for apnea and bradycardia prophylaxis in premature neonates. *Acta Paediatr* 1995;84:360-4.

<sup>14</sup> Davis et al. Apnoea and seizures. *Arch Dis Child* 1986;61:791-93.

<sup>15</sup> Gillot et al. Renal effects of caffeine in preterm infants. *Biol Neonate* 1990;58:133-6.

<sup>16</sup> Zanardo et al. Methylxanthines increase renal calcium excretion in preterm infants. *Biol Neonate* 1995;68:169-74.

**h) Thyroid function**

Staib et al., (1983)<sup>17</sup> showed that T<sub>4</sub> levels were negatively correlated to circulating caffeine or theophylline in preterm infants. TSH levels, nonetheless, were within the normal range. Sourgens et al., in 1983<sup>18</sup>, also found that low T<sub>4</sub> levels did not correlate with high levels of TSH. He found that in 34 unselected preterm infants treated with caffeine citrate, and in 38 treated with theophylline, T<sub>4</sub> levels correlated with body weight (p<0.001). In both groups, the decline in serum levels of caffeine and theophylline did not correlate with the concomitant rise in serum T<sub>4</sub>.

**i) Serum Glucose**

Even when several authors have reported no changes in glucose levels during the course of the studies, Rothberg et al., (1981)<sup>19</sup> noted that 6 infants orally fed presented statistically significant drops in plasma glucose levels at 1 and 1.5 hours after a single IV dose of 20 mg/Kg of caffeine. Six infants IV fed and 4 control infants without apneas (matched for birth weight, gestational age, and age at study entry) had stable plasma glucose levels over the two-hour study period. Romagnoli et al (1992) compared two dosage levels: Group I: 10 mg/Kg IV load and 5 mg/Kg maintenance; and Group II: 10 mg/Kg IV load and 2.5 mg/Kg oral maintenance, to a group of historical controls. Hyperglycemia (blood glucose >100 mg/dl) occurred in 0/14 controls, 5/13 infants in Group I and 2/10 infants in Group II.

**j) Deaths**

The published data do not report deaths that occurred during the study period and underestimate the true mortality rate in these trials due to the exclusion from analysis of those patients who died during the trial period.

**C. Reviewer's Comments on Published Clinical Trials**

**Efficacy**

There is a large body of information in the literature regarding the efficacy of caffeine in premature infants with apnea of prematurity. The great majority of the trials published showed that using the various endpoints studied, patients improved after treatment with caffeine or that the effect of caffeine was clinically comparable to that of theophylline. Most of these trials, however, can not be considered adequate and well controlled, were small, used open-label treatment, and were conducted without a parallel control group. In addition, several of them compared apnea rates before and after treatment using cardiorespiratory monitors without recordings.

<sup>17</sup> Staib et al. do methylxanthines influence T<sub>4</sub> levels and TSH levels in premature infants as compared to healthy newborns and asthmatics? Naunyn Schmiedeberg Arch Pharmacol 1983;324 (SUPPL):78R. (Abstract #311).

<sup>18</sup> Sourgens et al. T<sub>4</sub> levels in methylxanthine-treated premature newborns. Pediatr Pharmacol 1983;3:267-72.

<sup>19</sup> Rothberg et al. The metabolic effects of caffeine in the newborn infant. Pediatr Pharmacol 1981;1:181-6.

The ICU nurses were to count and measure the length of the apnea spells, with the potential misrepresentation of these events. Many of the studies compared the apnea index before and after the first few days of therapy, without following the patients after the observation period for possible recurrence of apneic attacks or presentation of late adverse events. The prospective study by Murat et al, conducted in 1981, deserves special mention because the author tried to address many of these issues. Even though it was an open-label trial, it is probably one of the best designed studies that provided strong evidence to support the efficacy of caffeine for the treatment of apnea of prematurity. The fact that this trial was unblinded is mitigated by the use of cardiorespirographic recordings on days 1, 5 and 15 which is an objective evaluation of the primary endpoint, the apnea index. The cardiorespirographic recordings on day 8 after cessation of therapy provided needed information regarding possible recurrence of apnea after the treatment period was completed.

#### **Safety**

The target population is in a way so unique in that they have multiple risk factors for adverse outcomes (e.g., different insults at the time of delivery, immaturity of the different body systems, exposure to a variety of pharmacological agents and other treatment regimens, medical complications, etc.) that the identification of specific drug-related adverse events is difficult and may require prospective, large and well designed studies to identify them.

In general, the adverse events reported in the literature for caffeine are similar to those reported for theophylline, but milder and less frequent for the most part.

The increased hearing loss reported by Koppe has not been confirmed in other more recent studies; moreover, the author attributed this finding to the use of caffeine sodium benzoate before 1972.

Caution should also be exercised when evaluating reports that assessed the suggested association of increased incidence of NEC with the use of xanthines in infants at high risk of developing NEC (very low birth weight). The question of such association was based mainly on anecdotal reports or on non-controlled trials using theophylline. Other authors, on the other hand, have not found such association in their trials. This question raised in the published literature is important, however, because, even though the difference was not statistically significant, the small, placebo-controlled, clinical trial conducted by the sponsor did show a numerical increase of NEC in the caffeine treated group.

#### **D. Reviewer's Conclusions of Published Clinical Trials**

There is a large body of evidence in the literature that provides supplementary support for the efficacy and safety of caffeine citrate for the treatment of apnea of prematurity. Altogether, the prospective trial by Murat et al can be considered the strongest contributor to this body of evidence in the literature. The published data addressing the question regarding the association of methylxanthine use and necrotizing enterocolitis, although

mainly anecdotal or consisting of not well controlled trials, are not conclusive in either direction.

#### IV. ~~Audit Report from the Division of Scientific Investigations (DSI)~~

The Division of Scientific Investigations audited the following investigational sites:

Table 22 Investigational sites audited by DSI.

Investigational Sites	Name of Principal Investigator	Number of patients
U. of Colorado School of Medicine.	Adam Rosenberg, M.D.	19
University of California Irvine Medical Center.	Feizal Waffarn, M.D.	17
Medical College of Georgia	Jatinder Bathia, M.D.	14
U. of Texas Health Science Center at San Antonio	Daniel Casto, Pharm. D.	12

DSI audited the requested four study sites. The center in California, had several discrepancies between the nursing flow sheets at bed side and the CRFs. The discrepancies primarily involved the duration of the events and their categorization by different personnel. Another widespread problem was the lack of consistency between the nurses flow charts to record concomitant medications and the computer generated patient records. These problems had been already pointed out to the investigator by the sponsor's own monitors and their notes were provided to this agency by the DSI inspector. Overall, however, no major violations were found in the patients' records reviewed by the auditors (57 patients in total), that could potentially affect the final outcome of the study.

#### V. Advisory Committee Meeting

The Pulmonary and Allergy Drugs Advisory Committee met on December 15, 1997 to discuss the safety and efficacy of Cafcit for the treatment of apnea of prematurity. After an extensive discussion, the panel, that included 3 practicing neonatologists, concluded that the totality of evidence available supported the efficacy of Cafcit for the proposed indication. The panel also concluded that there was enough evidence to support Cafcit's safety, when used for the proposed indication under the conditions followed in the placebo-controlled trial, but recommended that further efforts be made to clarify the controversy on the association of methylxanthine use and necrotizing enterocolitis. The committee also raised questions regarding the pharmacokinetic and pharmacodynamic relationship of Cafcit in the premature infant, and concluded that further studies were necessary to identify the optimal dose and the therapeutic caffeine concentrations in this population.

## VI. Reviewer's comments on the Integrated Summary Of Efficacy and Safety.

Study OPR-001 is the only randomized, double-blind, placebo controlled trial where caffeine citrate was studied for the treatment of apnea of prematurity. It showed modest, though clinically relevant, evidence of efficacy of caffeine citrate in the treatment of apnea of prematurity. The impact of its failure to show a statistically significant difference in the primary endpoint (i.e., apnea rate on day 2 after the loading dose) is lightened, in part, by showing a substantial effect in reducing by 50 or 100% the number of apnea events from baseline, in the target population. Although these calculations were not adjusted for multiple variables, the clinical relevance of the findings supports the efficacy of caffeine citrate. In addition, when the original primary endpoint for the study is evaluated statistically, the resultant P value is .07, and thus this outcome is also supportive of the efficacy of caffeine citrate. These results are supported by the large body of evidence collected in the literature over the years over different endpoints. In particular, the study conducted by Murat et al can be considered the main contributor to this body of evidence.

Study OPR-001 showed no statistically significant differences in adverse events by body system between caffeine and placebo treated patients. The data in the literature were consistent with the findings in the clinical trial, showing that caffeine was well tolerated by most patients in the population studied. However, the numerical increase in the incidence of NEC found in the caffeine-treated group is of concern, in particular because the association of methylxanthines with an increased risk of NEC has previously been questioned in the literature. In concurrence with the recommendation of the Advisory Committee, the sponsor should be asked to make a significant effort to address this concern.

Considering that conducting another placebo-controlled trial may not be feasible, because the use of methylxanthines for apnea of prematurity is considered standard of care by a wide margin of neonatologists, and that a clinical trial with NEC or mortality as primary endpoints would probably require an unreasonably large number of patients, the sponsor should be asked, prior to approval of this NDA, to evaluate other sources of data already available, e.g., the Vermont-Oxford and the NICHD Neonatal Networks, to determine whether they contain data that could address this issue and, if they do, propose and conduct a study using these data.

## VII. Reviewer's conclusion

There is enough evidence to conclude that Cafcit is safe and effective for the short term treatment of apnea of prematurity. From the clinical standpoint, this application is approvable pending the evaluation of other sources of data already available, e.g., the Vermont-Oxford and the NICHD Neonatal Networks, to determine whether they contain data that could further assess the existing question regarding the relationship between caffeine use and the incidence of NEC. This would ensure that all available data that may shed light on this question are adequately evaluated.

I concur with the Advisory committee recommendation that the sponsor further evaluate the pharmacokinetic/pharmacodynamic relationship of Cafcit to determine the optimal dose and the therapeutic concentrations of caffeine citrate in the target

population. The sponsor should be requested to conduct these studies as phase 4 commitments.

### **VIII. Comments to be sent to the sponsor:**

- 1. The numerical increase in the incidence of necrotic enterocolitis found in the caffeine-treated group is of concern, particularly since the association of methylxanthines with an increased risk of NEC has previously been questioned in the literature. To ensure that all available data that may shed light on this question is adequately evaluated, we request that you assess whether existing neonatal databases, such as the Vermont-Oxford and the NICHD Neonatal Networks contain data that could address this issue. If they do, we would like you to propose and conduct a study using this data to evaluate the association of caffeine citrate with necrotizing enterocolitis. The results of these evaluations and the protocols that were followed in carrying out the analyses should be submitted to this agency for review.**
- 2. To identify the optimal dose and the therapeutic concentrations of caffeine citrate in premature infants, we request that you commit to conduct additional phase 4 pharmacokinetic/pharmacodynamic studies in the target population.**
- 3. Comments regarding the labeling will be discussed at a later date, but we recommend that you design a patient's package insert to be given to care-takers of patients that are sent home on Cafcit. This package insert should include:**
  - instructions about the administration of Cafcit,**
  - a warning about discarding vials with unused medication**
  - a warning about dosage increases only after medical consultation, and**
  - relevant, expected adverse events.**

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ON ORIGINAL**

**MEDICAL ABUSE LIABILITY CONSULT REVIEW**

NDA: 20793  
Drug Product: Cafcit  
Sponsor: OPR Development, LP  
Referring Division: HFD 570 (Division of Pulmonary Drug Products)  
Reviewer: E Douglas Kramer  
Peer Reviewer: Michael Klein  
Date Received: 12 Dec 1997  
Date Assigned: 19 Dec 1997  
Date Due: 12 Jan 1997

Material Received: The consult package includes: a Draft copy (undated) of the medical review of the NDA; a copy of the Clinical Pharmacology/Biopharmaceutics Review (dated 11/12/97), copies of the NDA overview (8 pages), the copies of the Human Pharmacokinetics and Bioavailability and Integrated Non Clinical Summary portions of the NDA global summary.

**BACKGROUND**

Caffeine citrate has been used extensively for the treatment of neonatal apnea. It is also widely used in the treatment of infants with Apparent Life Threatening Events (ALTE's or "near-miss" SIDS), although such use is not the subject of the current NDA which only proposes to make caffeine citrate (Cafcit) available as a 10mg/mL solution for use in the treatment of apnea of prematurity. Caffeine citrate is currently compounded by hospital pharmacies.

The purpose of this review is to assess the data on withdrawal syndromes associated with caffeine use and determine whether there is evidence of a withdrawal syndrome associated with use of caffeine in treatment of neonates.

**CAFFEINE AS A DRUG OF DEPENDENCE IN ADULTS**

Caffeine dependence and withdrawal have been examined in abuse liability studies. Much of this work has been done by Griffiths and earlier work is reviewed by him.<sup>1</sup> The data pertaining to human caffeine consumption in this reference are summarized below:

Griffiths and Woodson's 1988 review cites estimates that 82-92% of North American adults regularly consume caffeine. In the US and Canada, daily per capita caffeine consumption is estimated at 211 and 238mg. In the UK and Sweden, daily consumption estimates are 444mg and 425mg, respectively.

<sup>1</sup> See, for example, RR Griffiths and PP Woodson, Caffeine Physical Dependence. PSYCHOPHARMACOLOGY (1988) 94:437-451.

They summarize 37 reports (case reports, experimental studies and surveys) that describe withdrawal syndromes following chronic caffeine administration. 12 additional reports are excluded because it was unclear whether caffeine withdrawal was explicitly looked for or documented. An additional 12 reports dealing with withdrawal from combination products were also excluded. A final report was excluded because it was not clear to the authors that it involved a meaningful duration of caffeine abstinence.

Eighteen of the reports involved case reports or clinical observations. In all but 2 cases, the number of patients observed was reported. All but one of these reports involved 1 or 2 cases. The last report involved 36 men in a starvation experiment with periodic caffeine and fluid deprivation. Nineteen experimental and survey studies were identified that studied approximately 1500 people (range 1 to <430, median 32).

Among these 37 reports headache was identified as a withdrawal symptom in 19, with 2 additional case reports describing fullness in the head and pressure in the head or facial flushing. This is noted to be distinct from migraine. Next on the list is fatigue with 15 reports. These describe symptoms such as mental depression, weakness, apathy, etc. Symptoms of anxiety (anxious, nervous, jittery, shaky, muscle tension, restless and insomnia) were noted in 8 of 37 reports. Individual reports of other symptoms, some possibly related to anxiety, are also noted. It is noted that the frequency of headache associated with caffeine withdrawal identified in prospective studies is higher than the frequency of headache in surveys.

The authors note that withdrawal generally begins at 12-24 hours peaks by 2 days and lasts about a week. This is believed to be a specific pharmacological withdrawal syndrome because: it appears that persons who consume more caffeine at baseline tend to have the most severe withdrawal; withdrawal can be caused by caffeine given in beverages or in capsules. Withdrawal may also be relieved by caffeine regardless of the method of administration. The ability of caffeine to precipitate and relieve withdrawal appears to be dose-related.

More recent work by Griffiths and his colleagues<sup>2</sup> elaborates on these findings and has included controlled observations of caffeine withdrawal.

The first of these studies describes the emergence of caffeine withdrawal symptoms among 7 drug abuse researchers who had been maintained on

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<sup>2</sup> RR Griffiths et al., Low Dose Caffeine Physical Dependence In Humans. J PHARMACOL EXP THER (1990) 255:(3) 1123-1132

K Silverman et al., Withdrawal Syndrome After The Double Blind Cessation Of Caffeine Consumption N ENGL J MED (1992) 327:(16) 1109-1114

Strain EC et al., Caffeine Dependence Syndrome. Evidence From Case Histories And Experimental Evaluations. JAMA (1994) 272:(13) 1043-1048

100mg/day caffeine (as capsules) for the preceding 116 to 264 days during prior drug discrimination experiments with caffeine. During the first month of the study, subjects (who are also the authors of the report) randomly underwent placebo substitution for 12 days. In the second phase of the study subjects underwent at least 5 random 1 day placebo substitutions separated by at least 5 days. During phase 1 subjects completed a 33 item withdrawal questionnaire. In phase 2 they completed the Profile of Mood States (POMS) in addition to the withdrawal questionnaire. Results: Subjects were 3 men and 4 women in good health with a mean age of 37 (range 29-42), mean weight 66kg, mean duration of regular caffeine exposure was 16.7 years (range 12-25 years), and a mean daily caffeine exposure of 384mg/day (range 223-791). All were nonsmokers. Placebo substitution for 12 days resulted in a withdrawal syndrome in subjects 1, 4, 5, and 7 that peaked in the first 2 days and returned to baseline over about a week. This included headache, lethargy or fatigue, decrease in energy and ability to concentrate. These subjects also experienced muscle aches and chills. The group as a whole (N=7) experienced significant changes in similar measures also reported statistically significant changes in other symptoms such as impaired work/thought, decreased urge to work and decreased satisfaction. Much of the data is presented as tables of statistical significance based on repeated measures ANOVA such that the magnitude of the effects is difficult to discern. During the second phase, POMS ratings showed increased vigor and confusion and decreased fatigue and friendliness in addition to showing significant ratings on many of the same caffeine withdrawal measures seen in the first period.

The second report described changes in standard measures of mood and performance during a crossover study of adults aged 18 to 50 who consumed caffeine daily (but not more than 600mg/day based on a 7 day diary), had a normal blood pressure and EKG and had no physical condition which contraindicated caffeine, were not taking medication or using illicit drugs. In one period of the crossover, daily caffeine intake was replaced with caffeine capsules for 2 days (in the subject's average daily dose), in the other, it was replaced with placebo. Observations were made on the second day of each 2 day crossover period. Subjective measures included Beck Depression Inventory, the State-Trait Anxiety Inventory, the Profile of Mood States (POMS), a 33 item questionnaire on symptoms of caffeine withdrawal (including headache), Performance tasks included a digit symbol substitution, reaction time, number recall and a numerical Stroop, and tapping tasks. Results: 138 subjects were screened; 44 did not meet criteria; 32 refused to participate but were eligible; 62 participated. Participants had a mean age of  $30 \pm 8$ . 71% were women. They had a mean caffeine intake of  $235 \pm 126$ mg/day, with 45% consuming <200mg caffeine per day and 48% of subjects consuming 200-399mg/day. Salivary caffeine confirmed compliance with dietary caffeine restrictions during this study. Most of the data is presented in tables of statistical significance that do not provide an estimate of the magnitude of the effects

observed. Positive mood outcomes based on the proportion of abnormal scores (defined from published normal values except for headache) are shown below:

Measure	Placebo Substitution	Caffeine Substitution
High Scores on Beck Depression Inventory	11%	3%
High Scores on Trait Scale of the State-Trait Anxiety Inventory	8%	2%
Low Vigor Score (POMS)	11%	2%
Hi Fatigue Score (POMS)	8%	0%
Headache (moderate or severe)	52%	6%

Other results: 13% of patients took an analgesic during the placebo period vs. 2% during the caffeine period ( $p=0.038$ ). A total of 14 items on the caffeine withdrawal questionnaire did not differ during caffeine and placebo substitution periods. Tapping rate was the only one of the performance tests that differed during placebo and caffeine administration. Average tapping rate (taps per minute) in 3 tries was between 355 and 360 during baseline and caffeine periods and between 340 and 345/minute during placebo substitution.

The final report in this series describes the results of a structured psychiatric interview for caffeine dependence and subsequent placebo substitution of caffeine in those volunteers who met criteria for dependence on caffeine. Subjects were 18 to 50 years old with at least a high school diploma and a normal blood pressure, heart rate and EKG who consumed caffeine on a daily basis and reported problems with their caffeine use based on a diagnostic interview based on the DSM III R criteria for psychoactive substance dependence. To meet the diagnostic criteria of this study subjects needed to meet 3 of the 4 following criteria: 1) Tolerance; 2) Withdrawal; 3) Persistent Desire Or Unsuccessful Efforts To Cut Down Or Control Use; And 4) Use Continued Despite Knowledge Of A Persistent Or Recurrent Physical Or Psychological Problem That Is Likely To Have Been Caused Or Exacerbated By Substance Use. Subjects then underwent double blind administration of caffeine (subjects usual daily dose) or placebo tablets during 2 2-day crossover study periods during which they followed caffeine-free diets. They were evaluated on the 2nd afternoon of each period with instruments used in the previous studies. In the afternoon of the second day. Results: A total of 99 volunteers were screened by telephone. 27 were eligible and willing to participate in a diagnostic interview; 16 of these were diagnosed as dependent on caffeine; 1 of these was medically disqualified and 11 underwent a double-blind caffeine withdrawal evaluation. Ten of the 16 subjects had previous histories of substance use disorders, with 2 currently meeting criteria for anxiety disorders; Their average age was 38 years old. 88% were women. 5 subjects were current daily

smokers. Median daily caffeine consumption was 357mg (range 129 to 2548mg/day). 94% of them reported withdrawal symptoms. Among the 11 subjects who underwent placebo substitution, at least 1 withdrawal symptom was identified in 9: 7 had maximal ratings of headache during placebo substitution; 7 had alterations in fatigue, depression or vigor (from the Beck Depression Inventory or POMS); 5 subjects used an analgesic; 6 had decreases in tapping velocity, and 8 patients reported functional impairment of varying degrees.

#### **REVIEWER'S ASSESSMENT OF CAFFEINE WITHDRAWAL SYNDROMES IN ADULTS**

The results of this series of experiments can be taken as confirming the existence of a caffeine withdrawal syndrome in adults who may or may not have clear-cut dependence on caffeine. Features of this syndrome would appear to include headache, lethargy/fatigue and anxiety or depression of mood. This may also be associated with minor somatic complaints such as muscle aches or feeling flu-like.

This data suggests that the prevalence, frequency and severity of withdrawal will vary from one group of people to another and to some extent over time within a given person. Looking across the studies, however, there is a suggestion of a dose relationship in the severity and frequency of withdrawal symptoms.

Finally, it is important to note that the nature of the methods used to detect the relatively high prevalence of subjective effects of caffeine withdrawal in these studies means that it is unlikely that casual observation will detect such symptoms nor will a clinical trial that is not designed to detect them. Yet such effects are clearly detected in a population of trained observers.

#### **USE OF CAFFEINE IN NEWBORNS**

Infants may experience a number of respiratory disorders for which caffeine has been included in the treatment regimen. These include apnea of prematurity, and infants at risk for sudden infant death syndrome (SIDS).

Apnea of prematurity is characterized by periods of prolonged apnea not due to identified causes such as obstruction of the respiratory tree, sepsis, etc. Apnea episodes may occur with or without bradycardia. The frequency of apnea is inversely related to gestational age.

Infants who have experienced an "Apparent Life Threatening Event" (ALTE or "near-miss" SIDS) are also treated with caffeine. This particular use of caffeine is not discussed in the materials received, but it is an important use in a small population of newborns and infants both because SIDS is the leading cause of death in infants under 1 year of age and because the duration of treatment may be longer than that used to treat uncomplicated apnea.

## CAFFEINE PHARMACOKINETICS IN ADULTS AND NEWBORNS

In adults, caffeine is well absorbed orally and peak serum levels tend to be observed about 30 minutes after dosing. Half life is 3 to 5 hours

Pharmacokinetic information on the use of caffeine in newborns is available. This information is well summarized by Roberts<sup>3</sup> based on studies of apnea of prematurity. In-general, the half-life of caffeine is 60 to 130 hours, but drops off with increasing age. Volume of distribution in newborns is generally 0.8 to 0.9 L/kg. Loading doses of 10mg/kg PO or IV produce serum concentrations ranging from 5.6±4.8, 12±2, 6-10, or 17mg/L. The half life and volume of distribution gradually decrease to adult levels over the first several months of life.

## CLINICAL TRIALS IN THE NDA

The NDA includes a single new 9-center placebo controlled trial of caffeine in the treatment of neonatal apnea. The goals of the study were to determine the efficacy of caffeine citrate in the treatment of apnea of prematurity by comparing the rate of apnea episodes in patients treated with caffeine to those treated with placebo, to determine the safety of caffeine citrate in apnea of prematurity and to obtain plasma concentrations of caffeine in infants treated for up to 12 days. The primary outcome variable in the protocol as amended was the rate of apnea episodes at 24 - 48 hours post loading dose where an apnea episode was defined as cessation of breathing for  $\geq 20$  seconds. Prior to the last amendment, the primary success criterion was having a  $\geq 50\%$  reduction in the number of apnea episodes during the 24-48 hours after the double blind loading dose as compared to baseline.

Eligible infants were post conceptual age 28 weeks to  $\leq 32$  weeks 6 days who were  $>24$  hours after birth and who had at least 6 episodes of apnea ( $>20$  seconds) in a 24 hour period or less. Infants were excluded for: 1. identifiable causes of apnea; 2. BUN $>20$  mg/dL, creatinine  $>1.5$ mg/dL after 48 hours, urine output  $< 1$ mL/kg/hr; 3. AST and ALT $>3$ x ULN; 4. requiring mechanical ventilation; 5. Previous treatment with xanthines or H2 blockers within 7 days; 6. Receiving CNS active medication.

Loading dose was 10mg/kg IV over 30 minutes. This was followed by a maintenance dose of 2.5mg/kg/day (PO or IV) starting 24 hours after the loading dose. Patients could be rescued with open label caffeine citrate if 24 hours after the loading dose and before day 8, the number of apnea events did not remain  $<50\%$  of the patient's baseline and continued double blind treatment placed the

<sup>3</sup>Roberts, RJ. Drug Therapy In Infants. WB Saunders Co. 1984, pp 119-138.

patient at unacceptable risk. The loading dose for rescue was 10mg/kg IV followed by 3mg/kg/day PO or IV. The total duration of participation was 12 days, including both double-blind treatment and rescue treatment. Patients were to be followed for 4 days after the end of the study, if they did not receive alternative treatment.

Caffeine levels were obtained at the following times: 1 hour prior to and 1 hour after the loading dose of the double blind phase (and the open label phase if necessary); prior to dosing on days 2 to 12; on days 5 and 8 at a time left to the discretion of the investigator; at the time any patient was withdrawn from the study due to nonresponsiveness or recurrence of apnea episodes; at the time of adverse events associated with study drug administration.

#### **RESULTS OF THE NDA STUDY**

87 infants were enrolled (46 randomized to caffeine, 41 on placebo). Five patients were excluded from the efficacy analysis, 1 caffeine and 2 placebo patients were withdrawn from the study for having less than 6 apnea episodes during the 24 hour baseline period. Two placebo patients were reintubated and were never treated. Gestational age at birth was 30 weeks for both groups. Patients were enrolled at a mean gestational age of 31 weeks. The mean number of baseline apnea attacks was 10 in each group. Weight at entry was slightly more than 1200 grams.

#### **EFFICACY**

The primary efficacy analysis (which failed to show efficacy over placebo) was not submitted by the sponsor, who claimed that they did not anticipate the high dropout rate. They submitted the original 50% reduction success outcome instead. The disposition of patients and the outcome based on the sponsor's analysis is shown in the following table:

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Day	Caffeine				Placebo				p value
	DbI Blind N(%)	Open label	D/C	% Success	DbI Blind N (%)	Open label	D/C	% Success	
BL	45(100)				37(100)				
1	41(91)	2	2	62	32(86)	5		49	0.21
2	28(62)	11	2	76	19(51)	9	4	57	0.07
3	26(57)	1	1	67	18(48)		1	49	0.09
4	24(53)		2	67	16(43)		2	43	0.03
5	23(51)		1	67	15(41)	1		43	0.03
6	22(48)		1	69	14(38)	1		49	0.06
7	21(47)		1	69	12(32)		2	46	0.03
8	20(44)		1	69	11(30)		1	41	0.01
9	20(44)			67	11(30)			41	0.01
10	20(44)			69	11(30)			43	0.01

Tables 5 and 7 of the Medical Officer's review, except listing patients who discontinued at day 7 (caffeine) and day 8 (placebo). Patients were listed as stopping treatment per hospital protocol. The placebo patient was noted by the medical reviewer to have had a recurrence of apnea. (p values not corrected) % success based on last Double Blind analysis carried forward.

The medical reviewer (Dr Pina, HFD-570) notes the following (statistically significantly different) outcomes for patients with at least 1 day with apnea rate reduced  $\geq 50\%$  of baseline by treatment group:

#### Patients With At Least 1 Day With Apnea Reduced $\geq 50\%$ Of Baseline

Outcome	Caffeine (N=36)	Placebo (N=24)
Maintained $\geq 50\%$ reduction once achieved (among completers)	20 (55%)	7 (29%)
Reduction not maintained once achieved	6 (17%)	11 (46%)
Patients transferred to open label or D/C with a carry-over reduction $\geq 50\%$	10 (28%)	6 (25%)

Table 8 of Medical Officer's Review.

Among the patients transferred to open label treatment or D/C (3rd line of the table); the reviewer notes that some of them had bradycardia without apnea or had persistent apnea even though less than at baseline. Also noted is that among patients switched to open label caffeine (N=14 for caffeine, N=16 for placebo), more patients on placebo had a  $\geq 50\%$  reduction in apnea events from baseline than those originally on caffeine.

The pharmacokinetics review notes that among the 11 infants on caffeine who were transferred to open label caffeine, all of them had plasma caffeine levels that were above the traditional therapeutic range of 8 to 20mg/L, with the highest level being 43mg/L.

**SAFETY**

The safety database includes 85 of 87 infants (The 2 placebo patients who did not receive medication are not included in the safety analysis).

No significant differences were noted for mean values of temperature respiratory rate, pulse, and blood pressure between the treatment groups. No clinically significant differences were identified between treatment groups in Na, K, Ca, Cl, CO<sub>2</sub> BUN, glucose, AST, ALT, GGTP, creatinine or Hct. (Values analyzed at baseline and study end. Values were also analyzed pre-open label for patients transferred to this treatment).

**ADVERSE EVENTS**

In what appears to be the sponsor's listing of adverse events, there is no difference noted in adverse event rates by treatment. Of note, there are no behavioral symptoms that one might expect to see from a methylxanthine (such as irritability, insomnia, increased wakefulness). There is only 1 report of Drug Level Increased, not surprisingly in the open label caffeine group, presumably in a patient who received 2 loading doses of caffeine. The drug level in this case is not reported.

As an alternative analysis, the medical reviewer analyzed adverse events based on caffeine exposure with the following results:

Adverse Event	Exposed to Caffeine (N=63)	Not Exposed (N=22)
Any Event	68%	81%
NEC (Necrotizing Enterocolitis)	7.9%	4.5%
Sepsis	13%	0%
Anemia	17.5%	27%
Vomiting	3%	0%

Table 15 of Medical Officer's Review.

**DEATHS**

Three deaths occurred in this trial. All involved patients exposed to caffeine who developed NEC.

**FOLLOW-UP**

Data from post-treatment follow-up is incomplete. At the reviewers request, the sponsor reported follow-up data on all patients from 5 of 9 centers. Of note, some patients in both groups were placed on caffeine after the conclusion of the study. Doses, blood levels and duration of treatment are not reported.

**PUBLISHED LITERATURE**

The Medical Officer's Review includes a summary of selected published literature covering the efficacy and safety of caffeine in neonatal apnea. Including 18 of the reviewer's own references, this database includes over 830 neonatal exposures to caffeine, mostly caffeine citrate. Gestational age ranged from 26 to 40 weeks and birthweight from 0.6 to 2.5kg. The most common loading doses were 5, 10 or 20 mg/kg of caffeine base, followed by 2.5 - 5 mg/kg as a maintenance dose. However, loading doses as high as 60mg/kg with maintenance doses of 30mg/kg/day for 7 days were noted. Irritability, crying, jitteriness were reported in 21 patients. Cardiovascular changes, including tachycardia, were also observed. These were generally noted to be milder than seen with theophylline in those trials that used an active control. Like the NDA trial, most of these studies appear to have been of short duration. The studies presented in most detail in the NDA review are the following:

Trial N Duration of Rx	Dose	Adverse Events
Murat 1981 N=9, 15-40d	20mg/kg IM (LD) 5mg/kg PO Maint	None
Romagnoli 1992 N=37 15-18d	10mg/kg IV (LD) 2.5 mg/kg PO Maint vs. 5 mg/kg PO Maint	Hyperglycemia, Tachycardia and vomiting more frequent in high dose group
Anwar 1986 N=23 (including 4 full term) 3.4+/-1.3 months	20mg/kg 5mg/kg PO	4 infants became irritable, restless; 2 others irritable, restless, jittery withdrawn from the study.
Scanlon 1992 (N=14-16/group) At least 5 d	25 mg/kg PO or NG (LD) 6 mg/kg Maint vs. 50mg/kg PO or NG (LD) 12mg/kg Maint vs. 7.5 mg/kg Theop (LD) 3mg/kg Theop TID Maint	1 on low dose caffeine, 5 on theophylline had dose adjustment for HR>195

The information from published studies is particularly important in assessing the possibility of a withdrawal syndrome following caffeine treatment in newborns. It is especially important to note:

That the caffeine doses employed in these studies were often higher than those traditionally recommended. Indeed Scanlon's medline abstract notes: "If used in very preterm infants, however, it is suggested that a higher dose regimen than that previously recommended be used to achieve a faster response".

In some of these studies, subjects were noted to have irritability, excitability or other symptoms that are typical of methylxanthine treatment. To the extent that infants may become tolerant to such effects, it is not unreasonable that some of them may experience behavioral changes when caffeine treatment is discontinued.

## CONCLUSIONS

Unfortunately information available from the review division (either from the NDA itself or from the review of the published literature) cannot confirm or rule out the existence of a withdrawal syndrome among infants treated with caffeine for many reasons: The observation period in most studies, including the NDA trial, did not necessarily follow infants to the end of their caffeine treatment, in which case it would be impossible to observe any withdrawal-associated behavioral changes. In the case of the published trials reviewed by the division – and in the NDA trial – it is not clear how rigorously nonserious adverse events that might be markers for a withdrawal syndrome – such as irritability or insomnia – were assessed. The short term use of caffeine in these studies does not necessarily reflect a potentially significant clinical use, namely longer term use in home monitored settings in infants at risk for SIDS. Some studies – including the NDA study – may have used relatively low doses of caffeine which data from adults suggests may be less likely to result in a withdrawal syndrome than higher doses. The likelihood that relatively higher doses will be used in actual practice is reflected in the relatively high proportion of infants in the caffeine group of the NDA study were switched to open label caffeine early in the study. Such infants were given 2 loading doses within a 24 to 48 hour period.

Although it was not observed in available data, a change in behavior following withdrawal of caffeine in newborns or infants would appear to be well more than a theoretical possibility. A self-limited, dose-related caffeine withdrawal syndrome has been well described in adults. Symptoms such as irritability have been reported among infants treated with caffeine in published studies of apnea. This is considered to be consistent with centrally mediated CNS stimulation in this setting. In addition, actual doses may be higher and duration of treatment may be longer than is appreciated from the types of short term trials conducted in neonatal apnea. Thus, under conditions of actual use, the possibility of tolerance development to the CNS stimulating effects of caffeine would be increased. Such a situation would be compatible with behavioral changes emerging at the end of treatment.

## RECOMMENDATIONS

It is recommended that the possibility of observing behavioral changes on withdrawal of caffeine treatment be noted in the label. This possibility would appear to be greatest among infants treated over a period of weeks to months as

outpatients in home-monitored settings for refractory apnea of prematurity or an ALTE. As such, it would be particularly important for physicians to share this information with parents of these infants who might reasonably be expected to be quite concerned that any behavioral change may be a harbinger of recurrent apnea.

Symptoms may occur either as a result of discontinuation of therapy, as a result of inadequate therapeutic monitoring of infants whose maintenance dose is inadequate to maintain a stable blood concentration, or as a consequence of metabolic maturation. It is not clear that such behavioral changes would constitute a true withdrawal syndrome (i.e. the emergence of new symptoms following the discontinuation of drug treatment) or merely the absence of a pharmacologic effect (e.g., decrease in alertness or wakefulness). It should also be noted that the symptoms of such withdrawal may be minor and self-limited as appears to be generally the case in adults.

#### Phase IV Recommendations

It is recommended that the division ask the sponsor to explore the possibility of withdrawal-emergent behavioral changes in infants treated with caffeine over extended periods of time (e.g. infants with ALTE's). It is not clear that a placebo-controlled study would be necessary to assess this. A carefully controlled observational study where infants are treated in accordance with an established protocol such as that described by Children's Hospital of Philadelphia<sup>4</sup> may provide a suitable environment for these observations (for example during periodic pneumograms during which the children's reactions to cessation of caffeine are assessed). Such a study should try to assess dose-relatedness of any behavioral findings by grouping the infants based on their caffeine level at time of withdrawal.

It is also recommended that the division ask the sponsor to conduct a PK/PD analysis of the relationship of caffeine levels to effect. This information may be available from the clinical trial. Data that is available from the review division suggests that many patients will need a second loading dose. Should larger doses of caffeine come into regular long term use (e.g. with levels of 20 to 40 mg/L), this may be associated with both increased CNS stimulation and subsequent behavioral changes on withdrawal.

Finally, it is recommended that the division ask the sponsor to survey major children's hospitals that have extensive involvement of clinical pharmacists in the management of caffeine in children with apnea. If they can identify large programs that include full pharmacist participation in outpatient follow-up, this may be an additional source of information on CNS effects of caffeine in infants

<sup>4</sup>Spitzer, AW, Fox WW. Infant Apnea. An Approach To Management. CLINICAL PEDIATRICS. (1984) 23(7):374-380.

and possible effects of caffeine withdrawal with relatively well documented blood levels.

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