

NDA 20-793

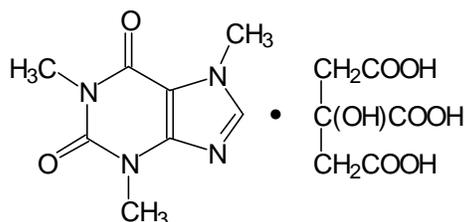
CAFCIT® (caffeine citrate) Injection

Rx only.

DESCRIPTION

CAFCIT® (caffeine citrate) Injection for intravenous administration is a clear, colorless, sterile, non-pyrogenic, preservative-free, aqueous solution adjusted to pH 4.7. Each mL of CAFCIT® Injection contains 20 mg caffeine citrate (equivalent to 10 mg of caffeine base). It is prepared in solution by the addition of 10 mg caffeine anhydrous to 5.0 mg citric acid monohydrate, 8.3 mg sodium citrate dihydrate and Water for Injection.

Caffeine, a central nervous system stimulant, is an odorless white crystalline powder or granule, with a bitter taste. It is sparingly soluble in water and ethanol at room temperature. The chemical name of caffeine is 3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione. In the presence of citric acid it forms caffeine citrate salt in solution. The structural formula and molecular weight of caffeine citrate follows.



Caffeine citrate
 $C_{14}H_{18}N_4O_9$ Mol. Wt. 386.31

NDA 20-793

Page 2

CLINICAL PHARMACOLOGY

Mechanism of Action

Caffeine is structurally related to other methylxanthines, theophylline and theobromine. It is a bronchial smooth muscle relaxant, a CNS stimulant, a cardiac muscle stimulant and a diuretic.

Although the mechanism of action of caffeine in apnea of prematurity is not known, several mechanisms have been hypothesized. These include: (1) stimulation of the respiratory center, (2) increased minute ventilation, (3) decreased threshold to hypercapnia, (4) increased response to hypercapnia, (5) increased skeletal muscle tone, (6) decreased diaphragmatic fatigue, (7) increased metabolic rate, and (8) increased oxygen consumption.

Most of these effects have been attributed to antagonism of adenosine receptors, both A_1 and A_2 subtypes, by caffeine, which has been demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically.

Pharmacokinetics

Absorption: After oral administration of 10 mg caffeine base/kg to preterm neonates, the peak plasma level (C_{max}) for caffeine ranged from 6-10 mg/L and the mean time to reach peak concentration (T_{max}) ranged from 30 minutes to 2 hours. The T_{max} was not affected by formula feeding. The absolute bioavailability, however, was not fully examined in preterm neonates.

Distribution: Caffeine is rapidly distributed into the brain. Caffeine levels in the cerebrospinal fluid of preterm neonates approximate their plasma levels. The mean volume of distribution of caffeine in infants (0.8-0.9 L/kg) is slightly higher than that in adults (0.6 L/kg). Plasma protein binding data are not available for neonates or infants. In adults, the mean plasma

NDA 20-793

Page 3

protein binding *in vitro* is reported to be approximately 36%.

Metabolism: Hepatic cytochrome P450 1A2 (CYP 1A2) is involved in caffeine biotransformation. Caffeine metabolism in preterm neonates is limited due to their immature hepatic enzyme systems.

Interconversion between caffeine and theophylline has been reported in preterm neonates; caffeine levels are approximately 25% of theophylline levels after theophylline administration and approximately 3-8% of caffeine administered would be expected to convert to theophylline.

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

Special Populations: Studies examining the pharmacokinetics of caffeine in neonates with hepatic or renal insufficiency have not been conducted. CAFKIT® (caffeine citrate) should be administered with caution in preterm neonates with impaired renal or hepatic function.

Clinical Studies

One multicenter, randomized, double-blind trial compared CAFKIT® (caffeine citrate) to placebo in eighty-five (85) preterm infants (gestational age 28 to < 33 weeks) with apnea of prematurity. Apnea of prematurity was defined as having at least 6 apnea episodes of greater than 20 seconds duration in a 24-hour period with no other identifiable cause of apnea.

NDA 20-793

Page 4

A 1 mL/kg (20 mg/kg caffeine citrate providing 10 mg/kg as caffeine base) loading dose of CAFKIT® was administered intravenously, followed by a 0.25 mL/kg (5 mg/kg caffeine citrate providing 2.5 mg/kg of caffeine base) daily maintenance dose administered either intravenously or orally (generally through a feeding tube). The duration of treatment in this study was limited to 10 to 12 days. The protocol allowed infants to be “rescued” with open-label caffeine citrate treatment if their apnea remained uncontrolled during the double-blind phase of the trial.

The percentage of patients without apnea on day 2 of treatment (24-48 hours after the loading dose) was significantly greater with CAFKIT® than placebo. The following table summarizes the clinically relevant endpoints evaluated in this study:

Results from a double-blind, placebo-controlled clinical trial.

	CAFKIT®	Placebo	p-value
Number of patients evaluated ¹	45	37	
% of patients with zero apnea events on day 2	26.7	8.1	0.03
Apnea rate on day 2 (per 24 hrs.)	4.9	7.2	0.134
% of patients with 50% reduction in apnea events from baseline on day 2	76	57	0.07

¹ Of 85 patients who received drug, 3 were not included in the efficacy analysis because they had < 6 apnea episodes/24 hours at baseline.

In this 10-12 day trial, the mean number of days with zero apnea events was 3.0 in the CAFKIT® group and 1.2 in the placebo group. The mean number of days with a 50% reduction from baseline in apnea events was 6.8 in the CAFKIT® group and 4.6 in the placebo group.

INDICATIONS AND USAGE

CAFKIT® (caffeine citrate) is indicated for the short term treatment of apnea of prematurity in infants between 28 and <33 weeks gestational age.

NDA 20-793

Page 5

CONTRAINDICATIONS

CAFCIT® (caffeine citrate) is contraindicated in patients who have demonstrated hypersensitivity to any of its components.

WARNINGS

During the double-blind, placebo-controlled clinical trial, six cases of necrotizing enterocolitis developed among the 85 infants studied (caffeine=46, placebo=39), with three cases resulting in death. Five of the six patients with necrotizing enterocolitis were randomized to or had been exposed to CAFCIT® (caffeine citrate).

Reports in the published literature have raised a question regarding the possible association between the use of methylxanthines and development of necrotizing enterocolitis, although a causal relationship between methylxanthine use and necrotizing enterocolitis has not been established. Therefore, as with all preterm infants, patients being treated with CAFCIT® should be carefully monitored for the development of necrotizing enterocolitis.

PRECAUTIONS

General

Apnea of prematurity is a diagnosis of exclusion. Other causes of apnea (e.g., central nervous system disorders, primary lung disease, anemia, sepsis, metabolic disturbances, cardiovascular abnormalities, or obstructive apnea) should be ruled out or properly treated prior to initiation of CAFCIT® (caffeine citrate).

Caffeine is a central nervous system stimulant and in cases of caffeine overdose, seizures have been

NDA 20-793

Page 6

reported. CAFKIT® should be used with caution in infants with seizure disorders.

The duration of treatment of apnea of prematurity in the placebo-controlled trial was limited to 10 to 12 days.

The safety and efficacy of CAFKIT® for longer periods of treatment have not been established. Safety and efficacy of CAFKIT® for use in the prophylaxis treatment of sudden infant death syndrome (SIDS) or prior to extubation in mechanically ventilated infants have also not been established.

Cardiovascular

Although no cases of cardiac toxicity were reported in the placebo-controlled trial, caffeine has been shown to increase heart rate, left ventricular output, and stroke volume in published studies. Therefore, CAFKIT® should be used with caution in infants with cardiovascular disease.

Renal and Hepatic Systems

CAFKIT® should be administered with caution in infants with impaired renal or hepatic function. (See **CLINICAL PHARMACOLOGY**, *Elimination, Special Populations*).

Information for Patients

Parents/caregivers of patients receiving CAFKIT® (caffeine citrate) should receive the following instructions:

1. CAFKIT® does not contain any preservatives and each vial is for single use only. Any unused portion of the medication should be discarded.
2. It is important that the dose of CAFKIT® be measured accurately, i.e., with a 1cc or other appropriate syringe.
3. Consult your physician if the baby continues to have apnea events; do not increase the dose of CAFKIT® without medical consultation.

NDA 20-793

Page 7

4. Consult your physician if the baby begins to demonstrate signs of gastrointestinal intolerance, such as abdominal distention, vomiting, or bloody stools, or seems lethargic.
5. CAFKIT® should be inspected visually for particulate matter and discoloration prior to its administration. Vials containing discolored solution or visible particulate matter should be discarded.

Laboratory Tests

Prior to initiation of CAFKIT® (caffeine citrate), baseline serum levels of caffeine should be measured in infants previously treated with theophylline, since preterm infants metabolize theophylline to caffeine. Likewise, baseline serum levels of caffeine should be measured in infants born to mothers who consumed caffeine prior to delivery, since caffeine readily crosses the placenta.

In the placebo-controlled clinical trial, caffeine levels ranged from 8 to 40 mg/L. A therapeutic plasma concentration range of caffeine could not be determined from the placebo-controlled clinical trial. Serious toxicity has been reported in the literature when serum caffeine levels exceed 50 mg/L.

In clinical studies reported in the literature, cases of hypoglycemia and hyperglycemia have been observed. Therefore, serum glucose may need to be periodically monitored in infants receiving CAFKIT®.

NDA 20-793

Page 8

Drug Interactions

Cytochrome P450 1A2 (CYP1A2) is known to be the major enzyme involved in the metabolism of caffeine. Therefore, caffeine has the potential to interact with drugs that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2.

Few data exist on drug interactions with caffeine in preterm neonates. Based on adult data, lower doses of caffeine may be needed following coadministration of drugs which are reported to decrease caffeine elimination (e.g., cimetidine and ketoconazole) and higher caffeine doses may be needed following coadministration of drugs that increase caffeine elimination (e.g., phenobarbital and phenytoin).

Caffeine administered concurrently with ketoprofen reduced the urine volume in 4 healthy volunteers. The clinical significance of this interaction in preterm neonates is not known.

Interconversion between caffeine and theophylline has been reported in preterm neonates. The concurrent use of these drugs is not recommended.

NDA 20-793

Page 9

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, caffeine (as caffeine base) administered in drinking water was not carcinogenic in male rats at doses up to 102 mg/kg or in female rats at doses up to 170 mg/kg (approximately 2 and 4 times, respectively, the maximum recommended intravenous loading dose for infants on a mg/m² basis). In an 18-month study in C57BL/6 mice, no evidence of tumorigenicity was seen at dietary doses up to 55 mg/kg (less than the maximum recommended intravenous loading dose for infants on a mg/m² basis).

Caffeine (as caffeine base) increased the sister chromatid exchange (SCE) SCE/cell metaphase (exposure time dependent) in an *in vivo* mouse metaphase analysis. Caffeine also potentiated the genotoxicity of known mutagens and enhanced the micronuclei formation (5-fold) in folate-deficient mice. However, caffeine did not increase chromosomal aberrations in *in vitro* Chinese hamster ovary cell (CHO) and human lymphocyte assays and was not mutagenic in an *in vitro* CHO/hypoxanthine guanine phosphoribosyltransferase (HGPRT) gene mutation assay, except at cytotoxic concentrations. In addition, caffeine was not clastogenic in an *in vivo* mouse micronucleus assay.

Caffeine (as caffeine base) administered to male rats at 50 mg/kg/day subcutaneously (approximately equal to the maximum recommended intravenous loading dose for infants on a mg/m² basis) for four days prior to mating with untreated females, caused decreased male reproductive performance in addition to causing embryotoxicity. In addition, long-term exposure to high oral doses of caffeine (3.0 g over 7 weeks) was toxic to rat testes as manifested by spermatogenic cell degeneration.

Pregnancy: *Pregnancy Category C*

NDA 20-793
Page 10

Concern for the teratogenicity of caffeine is not relevant when administered to infants. In studies performed in adult animals, caffeine (as caffeine base) administered to pregnant mice as sustained release pellets at 50 mg/kg (less than the maximum recommended intravenous loading dose for infants on a mg/m² basis), during the period of organogenesis, caused a low incidence of cleft palate and exencephaly in the fetuses. There are no adequate and well-controlled studies in pregnant women.

ADVERSE REACTIONS

Overall, the reported number of adverse events in the double-blind period of the controlled trial was similar for the CAFKIT® (caffeine citrate) and placebo groups. The following table shows adverse events that occurred in the double-blind period of the controlled trial and that were more frequent in CAFKIT® treated patients than placebo.

NDA 20-793
 Page 11

ADVERSE EVENTS THAT OCCURRED MORE FREQUENTLY IN CAF-CIT®
 TREATED PATIENTS THAN PLACEBO DURING DOUBLE-BLIND THERAPY

Adverse Event (AE)	CAF-CIT® N=46 n (%)	Placebo N=39 n (%)
BODY AS A WHOLE		
Accidental Injury	1 (2.2)	0 (0.0)
Feeding Intolerance	4 (8.7)	2 (5.1)
Sepsis	2 (4.3)	0 (0.0)
CARDIOVASCULAR SYSTEM		
Hemorrhage	1 (2.2)	0 (0.0)
DIGESTIVE SYSTEM		
Necrotizing enterocolitis	2 (4.3)	1 (2.6)
Gastritis	1 (2.2)	0 (0.0)
Gastrointestinal Hemorrhage	1 (2.2)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM		
Disseminated Intravascular Coagulation	1 (2.2)	0 (0.0)
METABOLIC AND NUTRITIVE DISORDERS		
Acidosis	1 (2.2)	0 (0.0)
Healing Abnormal	1 (2.2)	0 (0.0)
NERVOUS SYSTEM		
Cerebral Hemorrhage	1 (2.2)	0 (0.0)
RESPIRATORY SYSTEM		
Dyspnea	1 (2.2)	0 (0.0)
Lung Edema	1 (2.2)	0 (0.0)
SKIN AND APPENDAGES		
Dry Skin	1 (2.2)	0 (0.0)
Rash	4 (8.7)	3 (7.7)
Skin Breakdown	1 (2.2)	0 (0.0)
SPECIAL SENSES		
Retinopathy of Prematurity	1 (2.2)	0 (0.0)
UROGENITAL SYSTEM		
Kidney Failure	1 (2.2)	0 (0.0)

In addition to the cases above, three cases of necrotizing enterocolitis were diagnosed in patients receiving CAF-CIT® (caffeine citrate) during the open-label phase of the study.

Three of the infants who developed necrotizing enterocolitis during the trial died. All had been exposed to caffeine. Two were randomized to caffeine, and one placebo patient was “rescued” with open-label caffeine for uncontrolled apnea.

Adverse events described in the published literature include: central nervous system stimulation (i.e., irritability, restlessness, jitteriness), cardiovascular effects (i.e., tachycardia, increased left ventricular output, and increased stroke volume), gastrointestinal

NDA 20-793

Page 12

effects (i.e., increased gastric aspirate, gastrointestinal intolerance), alterations in serum glucose (hypoglycemia and hyperglycemia) and renal effects (increased urine flow rate, increased creatinine clearance, and increased sodium and calcium excretion). Published long-term follow-up studies have not shown caffeine to adversely affect neurological development or growth parameters.

OVERDOSAGE

Following overdose, serum caffeine levels have ranged from approximately 50 mg/L to 350 mg/L. Signs and symptoms reported in the literature after caffeine overdose in preterm infants include fever, tachypnea, jitteriness, fine tremor of the extremities, hypertonia, opisthotonos, tonic-clonic movements, nonpurposeful jaw and lip movements, vomiting, hyperglycemia, elevated blood urea nitrogen, and elevated total leukocyte concentration. Seizures have also been reported in cases of overdose. One case of caffeine overdose complicated by development of intraventricular hemorrhage and long-term neurological sequelae has been reported. No deaths associated with caffeine overdose have been reported in preterm infants.

Treatment of caffeine overdose is primarily symptomatic and supportive. Caffeine levels have been shown to decrease after exchange transfusions. Convulsions may be treated with intravenous administration of diazepam or a barbiturate such as pentobarbital sodium.

DOSAGE AND ADMINISTRATION

Prior to initiation of CAFKIT® (caffeine citrate), baseline serum levels of caffeine should be measured in infants previously treated with theophylline, since preterm infants metabolize theophylline to caffeine. Likewise, baseline serum levels of caffeine should be measured in infants born to mothers who consumed caffeine prior to delivery, since caffeine readily

NDA 20-793

Page 13

crosses the placenta.

The recommended loading dose and maintenance doses of CAFKIT® follow. NOTE THAT THE DOSE EXPRESSED AS CAFFEINE BASE IS ONE-HALF THE DOSE WHEN EXPRESSED AS CAFFEINE CITRATE.

	Dose of CAFKIT® (Volume)	Dose Expressed as Caffeine Citrate	Dose Expressed as Caffeine Base	Route	Frequency
Loading Dose	1 mL/kg	20 mg/kg	10mg/kg	Intravenous* (over 30 minutes)	One Time
Maintenance Dose	0.25 mL/kg	5 mg/kg	2.5 mg/kg	Intravenous* (over 10 minutes) or Orally	Every 24 hours**

* using a syringe infusion pump

**beginning 24 hours after the loading dose

Serum concentrations of caffeine may need to be monitored periodically throughout treatment to avoid toxicity. Serious toxicity has been associated with serum levels greater than 50 mg/L.

Like all parenteral drug products, CAFKIT® should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Vials containing discolored solution or visible particulate matter should be discarded.

Drug Compatibility

To test for drug compatibility with common intravenous solutions or medications, twenty (20) mL of CAFKIT® (caffeine citrate) were combined with 20 mL of a solution or medication, with the exception of an Intralipid® admixture, which was combined as 80 mL/80 mL. The physical appearance of the combined solutions was evaluated for precipitation. The admixtures were mixed for 10 minutes and then

NDA 20-793

Page 14

assayed for caffeine. The admixtures were then continually mixed for 24 hours, with further sampling for caffeine assays at 2, 4, 8, and 24 hours.

Based on this testing, CAFKIT® (caffeine citrate) Injection, 20 mg/mL (equivalent to 10 mg/mL caffeine base) is chemically stable for 24 hours at room temperature when combined with the following test products.

- Dextrose Injection, USP 5%
- 50% Dextrose Injection USP
- Intralipid® 20% IV Fat Emulsion
- Aminosyn® 8.5% Crystalline Amino Acid Solution
- Dopamine HCl Injection, USP 40 mg/mL diluted to 0.6 mg/mL with Dextrose Injection, USP 5%
- Calcium Gluconate Injection, USP 10% (0.465 mEq/Ca⁺²/mL)
- Heparin Sodium Injection, USP 1000 units/mL diluted to 1 unit/mL with Dextrose Injection, USP 5%
- Fentanyl Citrate Injection, USP 50 µg/mL diluted to 10 µg/mL with Dextrose Injection, USP 5%

HOW SUPPLIED

CAFKIT® (caffeine citrate) Injection is available as a clear, colorless, sterile, non-pyrogenic, preservative-free, aqueous solution in 3 mL colorless glass vials. The vials are sealed with a teflon-faced gray rubber stopper and an aluminum over-seal with white flip-off polypropylene disk inset.

Each vial contains 3 mL solution at a concentration of 20 mg/mL caffeine citrate (60 mg/vial) equivalent to 10 mg/mL caffeine base (30 mg/vial).

NDC 0054-8118-01: 3 mL single-dose vial, individually packaged in a carton.

Store at 15°-30°C (59°-86°F).

NDA 20-793
Page 15

**Preservative Free. For single use only. Discard
unused portion.**

Manufactured by:
Ben Venue Laboratories, Inc., Bedford, Ohio 44146.

Distributed by:
Roxane Laboratories, Inc., Columbus, Ohio 43216