CAFNEA®

Caffeine Citrate

1 NAME OF THE MEDICINE

Caffeine citrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cafnea Injection contains 20 mg/mL caffeine citrate (equivalent to 10 mg/mL of caffeine base).

Cafnea Oral Solution contains 5 mg/mL caffeine citrate (equivalent to 2.5 mg/mL of caffeine base).

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Both Cafnea Injection (Caffeine Citrate Injection 40 mg/2 mL) and Cafnea Oral Solution (Caffeine Citrate Oral Solution 25 mg/5 mL) are clear, colourless, preservative free sterile solutions adjusted to a pH of 4.2 - 5.2.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Cafnea Injection and Cafnea Oral Solution are indicated for the short-term treatment of apnoea of prematurity (AOP) in infants of gestational age 28 to less than 33 weeks.

4.2 DOSE AND METHOD OF ADMINISTRATION

Cafnea Injection and Cafnea Oral Solution are intended to be used in neonatal specialist units. The product is for single use in one patient only. Discard any residue.

Note:

- A prior check should be made to ensure that no other methylxanthine (e.g. theophylline and aminophylline) is being administered.
- Baseline serum levels of caffeine should be measured if mothers have consumed caffeine containing fluids prior to delivery, since caffeine readily crosses the placenta.
- The dose expressed as caffeine base is half the dose when expressed as caffeine citrate (e.g. 20 mg of caffeine citrate is equivalent to 10 mg of caffeine base).

Loading dose

Caffeine citrate 20 mg/kg body weight intravenously using a syringe infusion pump over 30 minutes.

Maintenance dose

Caffeine citrate 5 mg/kg once a day until apnoea ceases or until treatment is considered to be no longer required. The maintenance dose can be increased to a maximum of 10 mg/kg caffeine citrate once a day if apnoea persists. The maintenance dose should be adjusted weekly for changes in bodyweight. If symptoms suggestive of caffeine induced toxicity are observed such as tachycardia, tachypnoea, jitteriness, tremors and unexplained seizures and vomiting the dose of caffeine citrate can be reduced or withheld. The dose of caffeine citrate can be withheld or reduced for other clinical reasons.

Maintenance dose can be administered either intravenously (over 10 minutes) using Cafnea Injection or orally using Cafnea Oral Solution once the infant is tolerating full enteral feeds. Maintenance dose begins 24 hours after loading dose.

Compatibility

Cafnea Injection and Cafnea Oral Solution are compatible with 0.9% sodium chloride solution.

4.3 CONTRAINDICATIONS

Cafnea Injection and Cafnea Oral Solution are contraindicated in patients who have demonstrated hypersensitivity to caffeine or citrate.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prior to treatment it is essential that other causes of apnoea (e.g. CNS disorders, primary lung disease, anaemia, sepsis, metabolic disturbances, cardiovascular abnormalities, or obstructive apnoea) be ruled out or treated prior to initiation of caffeine citrate therapy.

Caffeine is a CNS stimulant and in cases of caffeine overdose, seizures have been reported. Cafnea Injection and Cafnea Oral Solution should be used with caution in infants with seizure disorders.

Clinical trials have indicated that necrotising enterocolitis may develop in neonates under treatment. Patients should be carefully monitored for the development of necrotising enterocolitis.

Cardiovascular effects

Cafnea Injection and Cafnea Oral Solution should be used with caution in infants with cardiovascular disease since caffeine has been shown to increase heart rate, left ventricular output, and stroke volume.

Gastro-oesophageal disease

Cafnea Injection and Cafnea Oral Solution may relax the lower oesophageal sphincter and increase the gastric acid excretion leading to increased episodes of gastro-oesophageal reflux in neonates.

Use in hepatic impairment

Cafnea Injection and Cafnea Oral Solution should be administered with caution in infants with impaired hepatic function. In such cases, serum caffeine should be monitored and dose administration should be adjusted to avoid potential toxicity.

Use in renal impairment

Cafnea Injection and Cafnea Oral Solution should be administered with caution in infants with impaired renal function. In such cases, serum caffeine should be monitored and dose administration should be adjusted to avoid potential toxicity.

Use in the elderly

Cafnea is not applicable to this indication. See Section 4.1. THERAPEUTIC INDICATIONS.

Paediatric use

Cafnea is indicated for use in pre-term infants of gestational age 28 to less than 33 weeks. See Section 4.1 THERAPEUTIC INDICATIONS and Section 5.1 Clinical Trials.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There is little data on drug interactions with caffeine in preterm neonates. However, CYP1A2 is the major enzyme responsible for caffeine metabolism and there is potential for interactions between caffeine and drugs that are substrates for this enzyme or inhibit or reduce it. Studies in adults show that co-administration of mexiletine, cimetidine, fluvoxamine, oral idrocilamide, oral methoxsalen and 5-methoxypsoralen, enoxacin, tiabendazole, artemisinin, fluconazole and terbinafine, verapamil may decrease caffeine elimination. Co-administration of phenytoin may increase caffeine elimination. Caffeine antagonises the effects of benzodiazepines. Caffeine increases the levels of both endogenous and orally administered melatonin as well as clozapine. Caffeine may cause a reduction in the bioavailability of fluvoxamine.

Caffeine elimination half-life has been reported to be increased and clearance decreased by concomitant administration of antibacterials such as ciprofloxacin, enoxacin and pipemidic acid, lomefloxacin, norfloxacin and olfloxacin.

Other methylxanthines (theophylline, aminophylline) should not be used concomitantly.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies in animals are limited but suggest that neonatal exposure to caffeine does not pose a hazard to later fertility.

Use in pregnancy

Not applicable.

Use in lactation

Not applicable. If mothers are drinking caffeine containing fluids, this should be taken into consideration when determining the dose for the neonate.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Necrotising enterocolitis is a common event in preterm infants and must be investigated whether or not the infant is receiving caffeine.

Table 1: Percentages of most frequently reported adverse events from Erenberg et al[1]

Adverse Event	Treatment group	
	Caffeine citrate	Placebo
Injection site reaction	8.7	12.8
Perinatal disorder (trace aspirates, feeding intolerances)	8.7	5.1
Constipation	17.4	20.5
Gastrointestinal disorder (gastroesophageal reflux, dilated loops of bowel)	4.3	7.7
Anaemia	6.5	17.9
Hyponatraemia	0	5.1
Rash	8.7	7.7

In non-controlled studies the following effects have been reported:

CNS stimulation: i.e. irritability, restlessness, jitteriness.
Cardiovascular effects: tachycardia, increased left ventricular output and increased stroke volume.
Gastrointestinal effects: i.e. increased gastric aspirate, gastrointestinal intolerance.
Alterations in serum glucose: hypoglycaemia and hyperglycaemia.
Renal effects: increased urine flow rate, increased creatinine clearance and increased sodium and calcium excretion.

Adverse effects observed in the Schmidt et al[2,3] controlled clinical trials have included tachycardia, tachypnoea, jitteriness, tremors, unexplained seizures and vomiting. Caffeine reduced weight gain temporarily.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Up to three times the usual dose has been given without noticeable side effects except an increase in jitteriness and a loss in weight which returns to normal following cessation of therapy. Higher doses may result in fever, irritability, poor feeding, insomnia, tachypnoea, jitteriness, fine tremor of the extremities, hypertonia, opisthotonos, tonic-clonic movements, nonpurposeful jaw and lip movements, vomiting, hyperglycaemia, elevated blood urea

nitrogen, and elevated total leukocyte concentration, seizures, neurological sequelae, tachycardia, respiratory distress, heart failure, gastric distention and acidosis.

Treatment of overdose

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.

Treatment of withdrawal

Caffeine withdrawal: no withdrawal symptoms have been reported following short-term therapy (less than three weeks).

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

NOTE: The pharmacology, dosage regimens and clinical descriptions apply only to preterm infants with apnoea.

Caffeine is a methylxanthine and is structurally related to other methylxanthines such as theophylline.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Caffeine is a centrally acting respiratory stimulant. It increases respiratory rate (breaths/minute) significantly in premature infants and significantly reduces the number of short and prolonged attacks of apnoea. There is evidence that caffeine has a direct effect on the myocardium. In ventilator dependent pre-term infants, caffeine has been shown to reduce pulmonary resistance and increase lung compliance with a concomitant reduction in the requirement for inspired oxygen.

The following pharmacodynamic effects of caffeine were found in preterm infants with apnoea.

- caffeine increases heart rate
- caffeine increased respiratory rate in some studies but not others
- mean arterial blood pressure, $TcPO_2$, $TcPCO_2$ are unchanged
- blood flow volumes in the coeliac artery and superior mesenteric artery, LVO, PCO_2, do not change significantly
- caffeine increases cerebral blood flow in some studies but not in others.

Clinical trials

Efficacy study

The randomised double blinded placebo controlled trial by Erenberg et al[1] evaluated the efficacy and safety of caffeine citrate for the treatment of AOP. The study included a total of 87 preterm infants of 28-32 weeks post-conceptional age. Infants randomised to caffeine received a loading dose of 20 mg/kg caffeine citrate IV. A daily maintenance dose of caffeine citrate 5 mg/kg was administered by IV or orally for 10 days.

The primary efficacy end point was at least a 50% reduction in apnoeic episodes from baseline events and elimination of apnoea. Caffeine citrate was significantly more effective than placebo in reducing apnoeic episodes by at least 50% in 6 days ($p < 0.05$). The percentage of patients with 50% reduction in apnoeic episodes was 68.9% active treatment vs 43.2% placebo ($p=0.02$). Caffeine citrate was also significantly better at eliminating apnoea in 5 days ($p < 0.05$). The percentage of patients with elimination of apnoeic episodes was 24.4% active treatment vs 0% placebo ($p=0.005$).

Safety study

The long term safety study by Schmidt et al[2,3] was a large multinational study involving 2006 randomised preterm infants with birth weights of 500 to 1250 g in which caffeine was compared to placebo for the short and long term safety of caffeine treatment for apnoea of prematurity (AOP), the prevention of AOP or to facilitate extubation. Treated infants received an intravenous loading dose of 20 mg/kg of caffeine citrate followed by a daily maintenance dose of 5 mg/kg IV or orally. If apnoea persisted, the daily maintenance dose could be increased to a maximum of 10 mg/kg. Maintenance dose was adjusted weekly for changes in body weight.

Table 2: Primary and secondary outcomes from Schmidt et al clinical study[2]

PRIMARY OUTCOME (at corrected age 10 to 21 months)	P Value	OTHER OUTCOMES (at corrected age 10 to 21 months)	P Value	SECONDARY SHORT-TERM OUTCOMES (before the first discharge home)	P Value
Composite		Retinopathy of prematurity		Death	0.75
Death or disability	0.008	All stages	0.06	Bronchopulmonary dysplasia	<0.001
Components		Severe retinopathy	0.01	Retinopathy of prematurity	0.09
Death before 18 mths	0.87	Cerebral palsy	0.2	Brain injury	0.44
Cerebral palsy	0.009	Seizure disorder	0.85	Necrotising enterocolitis	0.63
Cognitive delay	0.04	Height percentile	0.88	Drug therapy only for closure of patent ductus arteriosus	<0.001
Severe hearing loss	0.41	Weight percentile	0.66	Surgical closure of patent ductus arteriosus	<0.001
Bilateral blindness	0.58	Head circumference	0.12		

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following an oral dose of caffeine citrate solution, the time to reach peak concentration ranges from 30 minutes to 2 hours. Absorption following oral administration is complete. Feeding does not affect the rate or extent of oral caffeine absorption in premature infants. Following an intravenous (IV) loading dose of 20 mg/kg of caffeine citrate, the mean peak plasma level for caffeine is 12 mg/L. Following a single 10 mg/kg IV infusion of caffeine citrate, the mean ± SD serum concentration of caffeine was 14.5 ± 1.4 micrograms/mL at 10 minutes, 11.3 ± 0.1 micrograms/mL at 24 hours and 6.1 micrograms/mL at 72 hours. After a loading dose of 10 mg/kg of caffeine citrate and maintenance dose of either 5 mg/kg/day orally or 10 mg/kg/day orally, serum concentrations reached steady state at about 5 days with higher concentrations being observed with the 5 mg/kg maintenance regimen[4] (see Figure 1 below). Following maintenance doses of caffeine citrate 5 mg/kg, caffeine plasma levels range from 5 to 15 mg/L.

Distribution

Caffeine is distributed rapidly in infants with a volume of distribution, V = 0.8 to 0.9 L/kg.

Metabolism

Caffeine is poorly metabolised in preterm infants. The primary metabolites of caffeine are paraxanthines (main metabolite), theobromine, and theophylline. Interconversion between caffeine and theophylline has been observed in premature infants and approximately 3% to 8% of administered caffeine is expected to be converted to theophylline.

Caffeine is metabolised in the liver by cytochrome P450 enzymes, primarily by CYP1A2. This enzyme catalyses N1, N3, and N7-demethylation of caffeine. In addition, CYP2E1 also catalyses N1 and N7-demethylation, while CYP3A catalyses 8-hydroxylation. The N3 and N7 metabolic pathways are not mature until a postnatal age of about 4 months and explain the long half-life and low clearance in infants younger than this age.

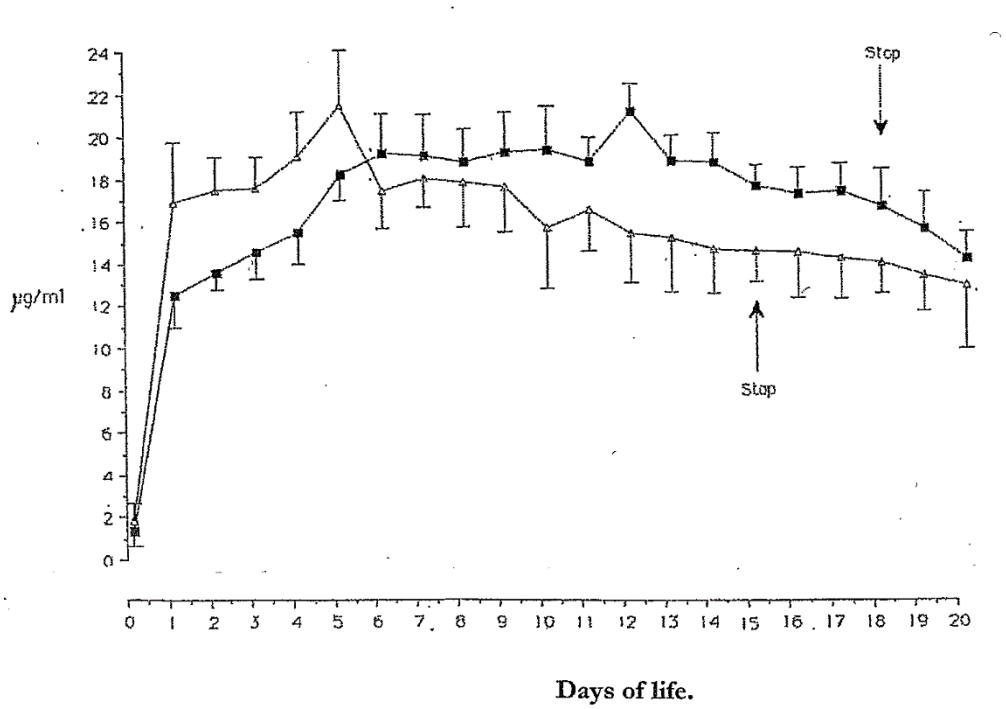


Figure 1: Mean±SD serum concentrations for caffeine following caffeine citrate 10/5 (loading/maintenance) mg/mL [■] to 13 premature neonates and caffeine citrate 10/2.5 (loading/maintenance) mg/mL [Δ] to 10 premature neonates.[5]

Excretion

More than 85% of caffeine is excreted unchanged in the urine. Preterm infants from 28 to 32 gestational weeks excrete 85% to 97% of caffeine unchanged. The terminal half-life in infants decreases from birth until it reaches adult values at approximately 60 weeks. Premature neonates have a significantly longer caffeine half-life than neonates born at term. The mean terminal life in neonates ranges from 65 to 102 hours. Excretion of caffeine in preterm infants is slow with a half-life of 80 to 120 hours. Following cessation of treatment serum concentrations of caffeine are likely to remain elevated due to the long elimination half-life of the drug (see Figure 1 above).

Special groups

Neonates of Asian background tolerated an IV loading dose of 20 mg/kg caffeine citrate with a maintenance dose of 5 mg/kg/day caffeine citrate IV. A higher maintenance dose resulted in an increase of hyperglycaemia and tachycardia[6].

Other studies have found no effect of gender or race on volume of distribution of caffeine. Hepatic impairment as measured by serum creatinine or serum urea levels did not influence volume of distribution.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Assays for bacterial and mammalian mutagenicity *in vitro,* and for clastogenicity *in vitro* and *in vivo* generally show negative results for caffeine. Positive responses have been observed in some tests, but these studies use extreme concentrations, lethal doses or non-validated methods. Cafnea is not considered to pose a genotoxic hazard to patients.

Carcinogenicity

In a small number of animal studies caffeine did not show carcinogenicity or tumorigenicity. In a two year carcinogenicity study conducted in rats, caffeine (administered as base) did not increase tumour incidence at oral doses up to 102 mg/kg/day in males and 170 mg/kg/day in females. Systemic exposure in animals at these doses is estimated to be 2-6 times higher than that in neonates at the recommended maintenance dose of 5 mg/kg/day caffeine citrate.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cafnea Injection contains the excipients citric acid monohydrate and sodium citrate dihydrate in water for injections. The injection contains no preservatives.

Cafnea Oral Solution contains the excipients citric acid monohydrate and sodium citrate dihydrate in water for injections. The solution contains no preservatives.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[7]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

The product is for single use in one patient only. Discard any residue. Store below 30°C.

[7] AUST R 153873 (injection); AUST R 153874 (oral solution)

6.5 NATURE AND CONTENTS OF CONTAINER

Cafnea Injection: 40 mg caffeine citrate (equivalent to 20 mg caffeine) per 2 mL injection presented in a 2 mL clear vial available as a pack of 10 vials.

Phebra product code - INJ101

Cafnea Oral Solution: 25 mg caffeine citrate (equivalent to 12.5 mg caffeine) per 5 mL of sterile solution presented in a 7 mL clear vial available as a pack of 10 vials.

Phebra product code - SOL026

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

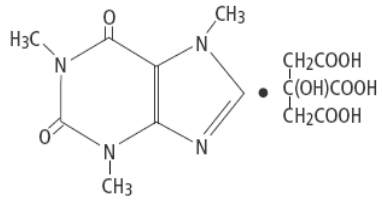
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Caffeine citrate

The molecular weight of the compound is 386.3.
The molecular formula is $C_8H_{10}N_4O_2,C_6H_8O_7$.

Chemical structure of caffeine citrate

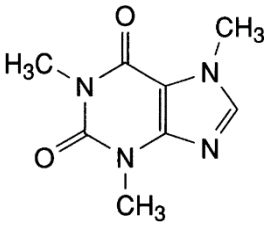


Caffeine citrate
$C_{14}H_{18}N_4O_9$ Mol. Wt. 386.31

Caffeine

Caffeine in the presence of citric acid forms caffeine citrate in solution.
The molecular weight of caffeine is 194.2.
The chemical name for caffeine is 1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione.
The molecular formula is $C_8H_{10}N_4O_2$.

Chemical structure of caffeine:



CAS number

69-22-7 (caffeine citrate); 58-08-2 (caffeine)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled

8 SPONSOR

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Telephone: 1800 720 020

9 DATE OF FIRST APPROVAL

17 Mar 2010

10 DATE OF REVISION

03 May 2021

11 REFERENCES

1. A. Erenberg, R. D. Leff, D. G. Haack, K. W. Mosdell, G. M. Hicks, and B. A. Wynne. Caffeine citrate for the treatment of apnoea of prematurity: a double-blind, placebo-controlled study. Pharmacotherapy 20 (6):644-652, 2000.
2. B. Schmidt, R. S. Roberts, P. Davis, L. W. Doyle, K. J. Barrington, A. Ohlsson, A. Solimano, and W. Tin. Caffeine therapy for apnoea of prematurity. N.Engl.J.Med. 354 (20):2112-2121, 2006.
3. B. Schmidt, R. S Roberts, P. Davis, L. W Doyle, K. J Barrington, A. Ohlsson, A. Solimano, W. Tin. Long-term effects of caffeine therapy for apnoea of prematurity. N Engl J Med. 357 (19):1893-902, 2007
4. M. P. De Carolis, C. Romagnoli, U. Muzii, G. Tortorolo, M. Chiarotti, Giovanni N. De, and A. Carnevale. Pharmacokinetic aspects of caffeine in premature infants. Dev. Pharmacol.Ther. 16 (3):117-122, 1991.
5. C. Romagnoli, M. P. De Carolis, U. Muzii, E. Zecca, G. Tortorolo, M. Chiarotti, Giovanni N. De, and A. Carnevale. Effectiveness and side effects of two different doses of caffeine in preventing apnoea in premature infants. Ther.Drug Monit. 14 (1):14-19, 1992.
6. H. S. Lee, Y. M. Khoo, Y. Chirino-Barcelo, K. L. Tan, and D. Ong. Caffeine in apnoeic Asian neonates: a sparse data analysis. Br.J.Clin.Pharmacol. 54 (1):31-37, 2002.

[8] Cafnea, Phebra and the Phi symbol are trademarks of Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.

PRODUCT INFORMATION
Cafnea® Injection and
Cafnea® Oral Solution

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	PI reformatted to align with new form
4.2	Inserted Compatibility section with: Cafnea Injection and Cafnea Oral Solution are compatible with 0.9% sodium chloride solution.
6.1	Update excipient name from sodium citrate to sodium citrate **dihydrate** as per AAN.