



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Caffeine citrate

Proprietary Product Name: Cafnea

Sponsor: Phebra Pty Ltd

June 2010

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

I.	<i>Introduction to Product Submission</i>	4
	Submission Details.....	4
	Product Background.....	4
	Regulatory Status.....	6
	Product Information.....	6
II.	<i>Quality Findings</i>	6
	Drug Substance (active ingredient).....	6
	Drug Product.....	7
	Bioavailability.....	7
	Consideration by PSC.....	7
	Quality Summary and Conclusions.....	8
III.	<i>Nonclinical Findings</i>	8
	Introduction.....	8
	Pharmacology.....	8
	Pharmacokinetics.....	11
	Toxicology.....	12
	Nonclinical Summary and Conclusions.....	16
IV.	<i>Clinical Findings</i>	17
	Introduction.....	17
	Pharmacodynamics.....	17
	Pharmacokinetics.....	20
	Efficacy.....	37
	Safety.....	54
	Clinical Summary and Conclusions.....	60
V.	<i>Pharmacovigilance Findings</i>	63
VI.	<i>Overall Conclusion and Risk/Benefit Assessment</i>	63
	Quality.....	63
	Nonclinical.....	64
	Clinical.....	64
	Risk-Benefit Analysis.....	68
	Outcome.....	69

I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	17 March 2010
<i>Active ingredient(s):</i>	Caffeine Citrate
<i>Product Name(s):</i>	Cafnea
<i>Sponsor's Name and Address:</i>	Phebra Pty Ltd 332 Burns Bay Road Lane Cove NSW 2066
<i>Dose form(s):</i>	Injection and oral solution
<i>Strength(s):</i>	Solution for injection, 40 mg/2 mL; Oral solution, 25 mg/5 mL ([as the citrate salt)
<i>Container(s):</i>	Solution for injection: 2 mL clear vial Oral solution: 7 mL clear vial
<i>Pack size(s):</i>	Pack of 10 vials.
<i>Approved Therapeutic use:</i>	for the short-term treatment of apnoea of prematurity in infants of gestational age 28 to less than 33 weeks
<i>Route(s) of administration:</i>	Solution for injection: intravenous Oral solution: oral
<i>Dosage:</i>	Loading dose: caffeine citrate 20 mg/kg body weight Maintenance dose: caffeine citrate 5 mg/kg once a day
<i>ARTG Numbers:</i>	153873, 153874, 155059, 155060

Product Background

This is an application to register both Cafnea injection and Cafnea oral solution containing caffeine citrate. The caffeine citrate is formed *in situ* by adding anhydrous caffeine to a citrate buffer. The proposed indication is:

the short-term treatment of apnoea of prematurity in infants of gestational age 28 to less than 33 weeks.

Cafnea is designated as an Orphan Drug in Australia for the short term treatment of apnoea of prematurity in infants between 28 and 33 weeks gestational age. Caffeine is a methylxanthine derivative which is similar to theophylline, aminophylline and theobromine. Methylxanthines stimulate the central nervous system (CNS), relax smooth muscle, stimulate cardiac muscle and have a diuretic effect.

According to the proposed product information (PI), a loading dose of 20 mg/kg is given by intravenous infusion over 30 minutes. Thereupon a maintenance dose of 5 mg/kg is given once a day for 7-10 days or until apnoea ceases. The maintenance dose can be given intravenously over 10 minutes or orally using the oral solution. The maximum daily dose is 20 mg/kg (40 mg for a 2 kg infant).

Apnea of Prematurity

Apnea of prematurity (AOP) has been defined as sudden cessation of breathing lasting for at least 20 seconds or if lasting less than 20 seconds is accompanied by bradycardia or oxygen desaturation (cyanosis) in an infant younger than 37 weeks gestational age.¹ AOP is a diagnosis of exclusion. Recurrent episodes of apnoea are common in preterm infants and the incidence and severity increases at lower gestational ages.² The incidence of AOP has been reported to occur in at least 85% of infants born at less than 34 weeks of gestation.³ It has also been reported to occur in 25% of infants with a birth weight less than 2500 g and 80% of infants with a birth weight less than 1000 g.⁴ It usually ceases by 37 weeks postmenstrual age but may persist for several weeks beyond term, especially in infants born before 28 weeks.¹ Although apnoea can occur spontaneously and be attributed to prematurity alone, it can also be provoked or made more severe if there is some additional condition such as infection, hypoxemia or intracranial pathology. Prolonged AOP may require active resuscitative efforts and frequent episodes may be associated with respiratory failure requiring intermittent positive pressure ventilation.⁵

Caffeine has been used to treat AOP since the 1970s.⁵ Caffeine citrate is currently used in Australia for the treatment of AOP although it has not been approved by the Therapeutic Goods Administration (TGA) for this purpose. The sponsor, Phebra Pty Ltd, states that it was requested to manufacture caffeine citrate injection and oral formulations (Cafnea) by a number of Australian neonatal units about 8 years ago. Theophylline has also been used to treat AOP. However, caffeine is considered to have advantages over theophylline "because of its higher therapeutic ratio, once daily dosing, lack of need to assay blood levels, and fewer adverse events".⁶ The mechanisms by which caffeine reverses apnoea are uncertain. Possibilities include increased partial pressure of arterial carbon dioxide (PCO₂) chemoreceptor responsiveness resulting in increased respiratory drive, enhanced respiratory muscle performance and generalized central nervous system excitation. At a molecular level, caffeine appears to exert most of its effects by blocking adenosine receptors A1 and A2a, increasing cyclic 3,5 adenosine monophosphate, and translocating intracellular calcium.⁷

¹ AAP 2003: American Academy of Pediatrics, Committee on Fetus and Newborn. Apnea, Sudden Infant Death Syndrome, and Home Monitoring. *Pediatrics*. 2003; 111: 914-917.

² Henderson-Smart. Recurrent apnoea. In: Yu VYH editor(s). *Bailliere's Clinical Paediatrics. Pulmonary Problems in the Perinatal Period*. Vol. 3, No. 1, London: Bailliere Tindall, 1995: 203-222.

³ Schmidt B et al. Caffeine therapy for apnoea of prematurity. *N Engl J Med* 2006; 354: 2112-2121.

⁴ Scanlon JE et al. Caffeine or theophylline for neonatal apnoea? *Arch Dis Child* 1992;67: 425-428.

⁵ Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnoea in preterm infants. *Cochrane Database of Systematic Reviews*. 2000; Issue 2: CD000273.

⁶ Neonatal Handbook, Newborn Emergency Transport Service [NETS], Melbourne, <http://www.rch.org.au/nets/handbook>.

⁷ Natarajan et al. Clinical pharmacology of caffeine in the newborn. *NeoReviews* 2007; 8: e214-e220.

Regulatory Status

In Australia, caffeine citrate injection (40 mg/2 mL) and oral solution (25 mg/5 mL) were both designated as Orphan Drugs by the TGA on 2 August 2007 for "the short term treatment of apnoea of prematurity [in infants] of gestational age 28 to less than 33 weeks". The sponsor is Phebra Pty Ltd, previously named Pharmalab Pty Ltd. Caffeine citrate for the treatment of AOP has also been designated as an Orphan Drug in both the USA and the EU. The current submission to register caffeine citrate followed its Australian designation as an Orphan Drug.

The proposed Phebra formulations of Cafnea are not registered in any overseas countries. The formulations have not been submitted for approval to, or rejected by, any overseas regulatory agency. However, caffeine citrate (injection and oral solution) has been approved in the USA since September 1999 for "the short term treatment of apnoea of prematurity in infants between 28 and < 33 weeks gestational age". Caffeine citrate is also approved in France for the treatment of primary apnoea in premature newborns, and a caffeine base solution for injection (5 mg/mL) sponsored by Viridian Pharm Ltd has market authorisation in the UK for the treatment of apnoea of prematurity (granted 8 February 2008). On 23 April 2009, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) recommended that market authorisation be granted for caffeine citrate (tradename *Nymusa*) infusion and solutions, sponsored by Chiesi Farmaceutici (Italy), for "the treatment of primary apnoea of premature newborns".

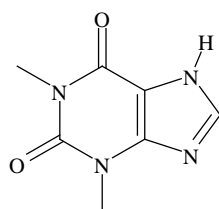
Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

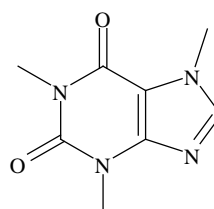
II. Quality Findings

Drug Substance (active ingredient)

Caffeine is a new chemical entity which is related to theophylline. Its structure is shown below. It is achiral.



theophylline



caffeine

caffeine (citrate)

N3,7-dihydro-1,3,7-trimethylpurine-2,6(1*H*)-dione

Formula = $C_8H_{10}N_4O_2 \cdot (C_6H_8O_7)$ MW = 194.2 (free base), 386.3 (salt)

CAS No. = [58-08-2] (free base), [69-22-7] (salt)

melting point 234-239°C

aqueous solubility = sparingly soluble, 10-33 mg/mL (1-3.3 % w/v)

It is controlled to the EP5/BP2009 monograph for caffeine which has an infrared identity test to ensure polymorphic form and limits all individual impurities and total impurities.⁸ There is also an additional test for chloroform with a limit of 60 ppm (the International Conference on Harmonization [ICH] allows 360 ppm).

⁸ EP: European Pharmacopoeia, BP: British Pharmacopoeia

Drug Product

The drug product is to be manufactured by Phebra in Sydney. Manufacture is typical for an injection solution with dissolution of the caffeine drug substance and excipients in Water for Injections followed by filling and closure. The products are terminally sterilised by steam. The Microbiology Section of the TGA's Office of Laboratories and Scientific Services (OLSS) found aspects relating to sterility acceptable.

Cafnea Oral Solution contains 25 mg/5 mL caffeine citrate presented in 5 mL vials. Each 5 mL contains caffeine base 12.5 mg, citric acid monohydrate 6.25 mg, sodium citrate 10.4 mg and water for injection to 5 mL. The solution contains no antimicrobial preservative. The formulation is proposed for oral use in one patient only. It should be stored below 30°C

Cafnea Injection contains 40 mg/2 mL caffeine citrate in 2 mL vials. Each 2 mL contains caffeine base 20 mg, citric acid monohydrate 10 mg, sodium citrate 16.6 mg and water for injection to 2 mL. The solution is clear, contains no antimicrobial preservative, sterile and adjusted to a pH of 4.2-5.2. The formulation is proposed for slow intravenous injection in one patient only. It should be stored below 30°C.

The drug products are well controlled with satisfactory expiry limits for assay and degradants.

Stability data was provided to support the proposed shelf life of 3 years when 'stored below 30°C' in the proposed vials.

The chemistry and quality control aspects of the draft PI and labels have been finalised to the satisfaction of the quality evaluator.

Bioavailability

It is claimed that the absolute bioavailability of the oral solution is 100% and that food does not affect this. The sponsor provided both a justification for not providing data in relation to the proposed formulations and relevant published papers on these issues.

The submission did not include the full details usually required, but it was accepted that overall the formulations of oral solution used in the studies were 100% bioavailable and that a special care baby formula had no effect on the bioavailability.

The justification centred on the fact that caffeine is granted a 'biowaiver' by the FDA (it was accepted where the drug substance is fully dissolved that in relation to the products it could be considered BCS Class 1) and that the clinical data sufficiently establishes the bioavailability in the clinical situation.⁹ This later matter was brought to the attention of the Delegate.

Consideration by PSC

This application was presented to the 128th meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) where:

- No objections were raised in relation to chemistry, quality control or the bioavailability on the proviso that the outstanding issues were resolved to the satisfaction of the TGA. This was the case.

⁹ The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

- The PSC considered that the literature references provided to establish the absolute bioavailability and effect of food on the bioavailability of the oral solution were sufficient for these products.

Quality Summary and Conclusions

Approval of the submission was recommended with respect to chemistry, quality control and bioavailability.

The clinical aspects of the justification for not providing bioavailability data were brought to the attention of the Delegate.

III. Nonclinical Findings

Introduction

The submission comprised published literature only. The literature search strategy used by the sponsor contained errors and was considered to be overly restrictive (for example, sets were limited to humans then further limited to animals; searches for keywords were limited to titles only). The exclusion criteria used to generate the nonclinical dossier from the retrieved citations were either unclear or based on grounds that are not scientifically sound (for example, repeat-dose toxicity studies of more than one month duration were excluded). Based on the submitted data, the toxicological assessment of the product would rely chiefly on a review article published in 1978, in which studies were frequently described in only minimal detail. It is from this article that nonclinical statements in the proposed PI document are drawn, and inconsistencies with more recent data, independently retrieved, have been found. The sponsor was advised of these issues prior to submission and/or the application's acceptance for evaluation, but the deficiencies were not rectified.

Pharmacology

Caffeine's primary pharmacological activity is as an antagonist of adenosine receptors, with secondary activities to inhibit phosphodiesterase and mobilise calcium. The submission contained a number of publications demonstrating stimulation of respiration with caffeine and investigating its mode of action in nonclinical models. In a study in pre-term baboons (~67% of term gestation), administration of two 20 mg/kg doses of caffeine citrate (route not stated, presumably intravenous [IV]) was associated with improved lung function (reduced arterial blood carbon dioxide [CO₂], reduced airway resistance, increased respiratory system compliance and decreased ventilator support) in the initial 24 hours after delivery (Yoder *et al.*, 2005).¹⁰ Two additional studies in pre-term baboons (Thomson *et al.*, 2004, 2006) were presented as primary pharmacology studies; while they involved treatment with caffeine, they did not examine the effect of the drug itself.^{11,12} IV or intracarotid infusion of caffeine citrate (3–10 mg/kg) rapidly induced transient episodes of breathing in pre-term sheep (Piercy *et al.*,

¹⁰ Yoder B., Thomson M, Coalson J. Lung function in immature baboons with respiratory distress syndrome receiving early caffeine therapy: a pilot study. *Acta Paediatr* 2005; **94**:92–98.

¹¹ Thomson MA, Yoder BA, Winter VT, Martin H, Catland D, Siler-Khodr TM, Coalson JJ. Treatment of immature baboons for 28 days with early nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2004; **169**: 1054–1062.

¹² Thomson MA, Yoder BA, Winter VT, Giavedoni L, Chang LY, Coalson JJ. Delayed extubation to nasal continuous positive airway pressure in the immature baboon model of bronchopulmonary dysplasia: lung clinical and pathological findings. *Pediatrics* 2006; **118**: 2038–2050.

1977).¹³ Respiratory rhythm generation in the medulla and its inhibition by the pons were found to be more pronounced in fetuses and pups of rats treated with caffeine¹⁴ (Herlenius *et al.*, 2002).¹⁵ Other studies in rats—involving direct dosing—showed that treatment with caffeine during the neonatal period sped development of the adenosinergic system in regions of the brain associated with respiratory control (Gaytan *et al.*, 2006) and increased neuronal activity in these centres (indicated by increased c-Fos expression; Gaytan *et al.*, 2007), and such changes were associated with increased minute ventilation in response to hypercapnia (Montandon *et al.*, 2006, 2007).^{16,17,18,19} Changes in respiratory control in rats that had been treated with caffeine as pups (at 3–12 days of age) persisted into adulthood (3–4 months old) (Montandon *et al.* 2006). The doses of caffeine used in the neonatal rat studies yield plasma drug levels comparable to the clinical level. In pre-term rabbits, lung weight, capacity and phospholipid content were not affected by maternal treatment with caffeine citrate (relative exposure in the offspring is unknown, however, and treatment was only for 2 days; Landers *et al.*, 1984).²⁰

CNS safety pharmacology studies, conducted in rats, showed that exposure to caffeine during the neonatal period produced subsequent neurological changes that were evident at juvenile and adult stages of development. These effects occurred at doses yielding plasma levels of caffeine comparable to the clinical level. Treatment was in the first week after birth; in terms of brain development, this period in the rat approximates that of humans in the third trimester (Etzel and Guillet, 1994).²¹ Notable effects included increased activity (shown in juveniles; Holloway, 1982), impaired learning, decreased stress-induced anxiety and increased sensitivity to pain (in juveniles; Pan and Chen, 2007) and altered memory retention (impaired

¹³ Piercy WN, Day MA, Neims AH, Williams RL. Alteration of ovine fetal respiratory-like activity by diazepam, caffeine, and doxapram. *Am J Obstet Gynecol* 1977; **127**:43–49.

¹⁴ Note that the offspring would have been exposed to caffeine *in utero* and through the consumption of maternal milk.

¹⁵ Herlenius E, Adén U, Tang LQ, Lagercrantz H. Perinatal respiratory control and its modulation by adenosine and caffeine in the rat. *Pediatr Res* 2002; **51**:4–12.

¹⁶ Gaytan SP, Saadani-Makki F, Bodineau L, Frugièrè A, Larnicol N, Pásaro R. Effect of postnatal exposure to caffeine on the pattern of adenosine A₁ receptor distribution in respiration-related nuclei of the rat brainstem. *Auton Neurosci* 2006; **126–127**: 339–346.

¹⁷ Gaytan SP, Giraldez-Perez RM, Pasaro R. Characterization of c-Fos expression in the respiratory-related areas of the rat following postnatal caffeine administration. *Acta Physiologica* 2007; **190**: O31.

¹⁸ Montandon G., Bairam A, Kinkead R. Long-term consequences of neonatal caffeine on ventilation, occurrence of apneas, and hypercapnic chemoreflex in male and female rats. *Pediatr Res* 2006; **59**: 519–524.

¹⁹ Montandon G., Kinkead R, Bairam A. Disruption of adenosinergic modulation of ventilation at rest and during hypercapnia by neonatal caffeine in young rats: role of adenosine A₁ and A_{2A} receptors. *Am J Physiol Regul Integr Comp Physiol* 2007; **292**:R1621–R1631.

²⁰ Landers S, Corbet A, Cregan J, Frink J, Rudolph AJ. Effect of aminophylline and caffeine on total and surfactant phospholipid in fetal rabbit lung. *Am Rev Respir Dis* 1984; **130**: 204–208.

²¹ Etzel BA, Guillet R. Effects of neonatal exposure to caffeine on adenosine A₁ receptor ontogeny using autoradiography. *Brain Res Dev Brain Res* 1994; **82**: 223–230.

in juvenile and adult males, but increased in adult females; Fisher and Guillet, 1997).^{22,23,24} Changes in neurotransmission extended beyond the adenosinergic system, with caffeine-treated animals displaying differences in responsiveness to a wide range of centrally acting agents (for example, generally decreased susceptibility to chemoconvulsants, though increased susceptibility to seizures induced by strychnine [in juveniles and adults; Guillet, 1995; Guillet and Dunham, 1995]; and decreased hyperlocomotion induced by an NMDA receptor antagonist [in juveniles; da Silver *et al.*, 2005]).^{25,26,27} Brain weight was decreased in caffeine-treated pups, most prominently in the striatum and hippocampus, with changes in biochemical composition of the brain (DNA, RNA, protein and cholesterol levels) evident (Yazdani *et al.*, 1988; body weight was unaffected).²⁸ Total dendritic length in the pre-frontal cortex was increased in juveniles and adults that had been treated with caffeine as neonates (Juárez-Méndez *et al.*, 2006).²⁹ Caffeine was shown to cause neuronal apoptosis *in vitro* in fetal mouse cortical cell cultures at concentrations $\geq 150 \mu\text{M}$ (= 29 mg/L), a concentration only moderately higher than the upper range in patients at steady-state (20 mg/L; according to the sponsor's Clinical Overview) (Kang *et al.*, 2002).³⁰ These investigators also showed induction of neuronal apoptosis *in vivo* in rat pups following acute treatment with caffeine ($3 \times 50 \text{ mg/kg}$ doses intraperitoneally [IP], 5 hours apart; relative exposure unknown).

Cardiac function and development were altered in rats treated chronically with caffeine (Temples *et al.*, 1985, 1987).^{31,32} Animals were exposed to caffeine through the consumption

²² Holloway WR. Caffeine: effects of acute and chronic exposure on the behavior of neonatal rats. *Neurobehav Toxicol Teratol* 1982; **4**: 21–32.

²³ Pan HZ, Chen HH. Hyperalgesia, low-anxiety, and impairment of avoidance learning in neonatal caffeine-treated rats. *Psychopharmacology* 2007; **191**: 119–125.

²⁴ Fisher S, Guillet R. Neonatal caffeine alters passive avoidance retention in rats in an age- and gender-related manner. *Brain Res Dev Brain Res* 1997; **98**: 145–149.

²⁵ Guillet R. Neonatal caffeine exposure alters seizure susceptibility in rats in an age-related manner. *Brain Res Dev Brain Res* 1995; **89**: 124–128.

²⁶ Guillet R, Dunham L. Neonatal caffeine exposure and seizure susceptibility in adult rats. *Epilepsia* 1995; **36**: 743–749.

²⁷ da Silva RS, Hoffman A, de Souza DO, Lara DR, Bonan CD. Maternal caffeine intake impairs MK-801-induced hyperlocomotion in young rats. *Eur J Pharmacol* 2005; **509**: 155–159.

²⁸ Yazdani M, Hartman AD, Miller HI, Temples TE, Nakamoto T. Chronic caffeine intake alters the composition of various parts of the brain in young growing rats. *Dev Pharmacol Ther* 1988; **11**: 102–108.

²⁹ Juárez-Méndez S, Carretero R, Martínez-Tellez R, Silva-Gómez AB, Flores G. Neonatal caffeine administration causes a permanent increase in the dendritic length of prefrontal cortical neurons of rats. *Synapse* 2006; **60**: 450–455.

³⁰ Kang SH, Lee YA, Won SJ, Rhee KH, Gwag BJ. Caffeine-induced neuronal death in neonatal rat brain and cortical cell cultures. *Neuroreport* 2002; **13**: 1945–1950.

³¹ Temples TE, Geoffray DJ, Nakamoto T, Hartman AD, Miller HI. Effects of chronic caffeine ingestion on growth and myocardial function. *Proc Soc Exp Biol Med* 1985; **179**: 388–395.

³² Temples TE, Geoffray DJ, Nakamoto T, Hartman AD, Miller HI. Effect of chronic caffeine intake on myocardial function during early growth. *Pediatr Res* 1987; **21**: 391–395.

of maternal milk then, upon weaning, received diet supplemented with caffeine (to provide an estimated dose of 1 mg/kg/day, yielding drug exposure below the clinical level). Cardiac output, stroke volume and myocardial work were reduced in animals treated to 50 and 88 days of age, and heart weight was increased in 88- (but not 50-) day old animals. In an acute study in pregnant rats, the fetal electrocardiogram (ECG) was found to be more sensitive to caffeine-induced changes than was the maternal ECG (Leal *et al.*, 1990).³³ Fetal changes comprised increased heart rate, decreased QT and ST intervals, and increased frequencies of ectopic beats, and P- and T-wave abnormalities; these occurred at fetal plasma concentrations ≥ 100 mg/L (that is, ≥ 5 -times the upper clinical steady state concentration).

In a pharmacodynamic drug interaction study, increased sensitivity to theophylline-induced seizures was observed in rats that had been pre-treated with caffeine (Yasuhara and Levy, 1988).³⁴ Both drugs act as adenosine receptor antagonists.

Pharmacokinetics

Information provided by the sponsor indicated that caffeine is 100% bioavailable by the oral route in humans and laboratory animal species (rats and rabbits). The drug's area under the plasma concentration time curve (AUC)-dose relationship was linear in humans and laboratory animal species (mice, rats, rabbits and monkeys) at doses up to 10 mg/kg orally; significantly greater than dose-proportional exposure was observed in the rat and rabbit at doses exceeding 10 mg/kg orally, and, to a much lesser extent, also in the mouse.

The plasma half-life of caffeine is very much longer in human neonates than in adults (up to ~100 hours compared with 4 hours), reflecting the inability of the neonatal liver to metabolise the drug (via cytochrome P450 [CYP1]A2). The half-life decreases with age as metabolism develops, reaching adult levels at the age of 5–6 months. A similar pattern of improved clearance with age was shown for dogs and rabbits, although the magnitude of the change was not as great as in humans. No data on the plasma half-life of caffeine in young rats were identified by the sponsor.

Caffeine is widely distributed in the body (shown in dogs, rabbits and human neonates), with tissue levels approximately proportional to their water content. Serum protein binding by caffeine is low. Metabolism, when developed, involves sequential demethylation, and excretion is principally via the urine.

Pharmacokinetic drug interactions

In juvenile rats, peak levels of both caffeine and aspirin were reduced (by ~50%) with oral co-administration (Seegers *et al.*, 1980).³⁵

³³ Leal M, Barletta M, Carson S. Maternal-fetal electrocardiographic effects and pharmacokinetics after an acute i.v. administration of caffeine to the pregnant rat. *Reprod Toxicol* 1990; **4**: 105–112.

³⁴ Yasuhara M, Levy G. Caffeine as a potential risk factor for theophylline neurotoxicity. *J Pharm Sci* 1988; **77**: 745–747.

³⁵ Seegers JM, Olling M, Jager LP, van Noordwijk J. Interactions of aspirin with acetaminophen and caffeine in rat stomach: pharmacokinetics of absorption and accumulation in gastric mucosa. *J Pharm Sci* 1980; **69**: 900–906.

Toxicology

Acute toxicity

No acute toxicity studies specifically conducted in young animals were submitted. A comparison of median lethal doses (LD_{50}) values in the adult mouse, rat and rabbit, indicates a 1.3–2.6-times increase in lethal potency for caffeine with IV compared with oral administration.

Repeat-dose toxicity

Relative exposure

Exposure ratios have been calculated based on animal:human area under the plasma concentration time curve from time zero to 24 hours (AUC_{0-24h}) values for caffeine (see Table 1). Because plasma levels of caffeine achieved in repeat-dose toxicity studies were not reported, animal AUC values are based on pharmacokinetic data published in Bonati *et al.* (1985).³⁶ Specifically, exposure in rats is derived using the investigators' mathematical model for the AUC-dose relationship (a one-compartment model with Michaelis-Menten metabolism), and for mice, extrapolated from exposure data for a 100 mg/kg dose. The rat pharmacokinetic model was generated using data obtained at a maximum dose of 100 mg/kg orally; therefore, there is considerable uncertainty with regard to relative exposure in the rat at doses exceeding this. A reference value of 480 $\mu\text{g}/\text{mL}\cdot\text{h}$ has been used for the clinical AUC_{0-24h} , based on a steady-state plasma concentration in neonates of 20 mg/L (as indicated in the sponsor's Clinical Overview).

³⁶ Bonati M, Latini R, Tognoni G., Young JF, Garattini S. Interspecies comparison of *in vivo* caffeine pharmacokinetics in man, monkey, rabbit, rat, and mouse. *Drug Metab Rev* 1985; **15**: 1355–1383.

Range of studies and findings

Studies were described only as being conducted with caffeine and not, explicitly, caffeine citrate. The dossier contained no data on the repeat-dose toxicity of caffeine by the IV route. Five oral repeat-dose toxicity studies and one subcutaneous (SC) study were cited in a review article (Federation of American Societies for Experimental Biology [FASEB], 1978); all were conducted in rats.³⁷ None of these can be used to establish a No Observable Adverse Effect Level (NOAEL) as the studies were not described in sufficient detail (for example, with respect to group sizes and/or the extent of the examinations performed) to determine whether they were adequately conducted; original references were not supplied. One of the studies involved weanling rats (~21 days of age); the others are assumed to have been conducted in adults (animal ages were not specified).

The study in weanling rats (by Bachmann *et al.*, 1946) reportedly showed no effects on growth and no pathological changes with treatment at 40–50 mg/kg/day orally for 26 weeks. The types of examinations performed were not indicated, however, and systemic exposure at this dose is estimated to be subclinical (relative exposure, ≤ 0.6).

Toxicity was evident in rats at a dose of ~500 mg/kg/day orally in a 4-week study (as inhibition of body weight gain, pulmonary oedema and congestion, and hydronephrosis; relative exposure, 50; Scott and Chen, 1944) and at doses ≥ 150 mg/kg/day orally in a 100-day study (as mortality, inhibition of body weight gain and various pathological changes consistent with stress [for example, alopecia, adrenal hyperplasia and thymic atrophy]; relative exposure, ≥ 4.7 ; Boyd *et al.* 1965). Caffeine appeared to be well tolerated at a dose of ~100 mg/kg/day in a 4-week study (Scott and Chen, 1944; relative exposure, 2.2), and at 35–60 mg/kg/day for 6–7 months (study by Strubelt *et al.*, 1973; relative exposure, ≤ 0.9). Group size was inadequate in the study by Scott and Chen (at just 5 rats per dose group) and not reported for the study by Strubelt *et al.*

Higher quality data were available in the full OECD Screening Information Data Set (SIDS) on caffeine (2002), retrieved independently³⁸. Ninety-day oral studies conducted by the US National Toxicology Program (NTP) established NOAELs for caffeine of 167–179 mg/kg/day in mice (the highest dose levels tested in each sex; relative exposure, 0.8) and 151–174 mg/kg/day for rats (relative exposure, ~5–6). The high-dose level tested in the rat study (272–287 mg/kg/day; relative exposure, 15–17) exceeded the maximum tolerated dose in the species (evident as $\geq 20\%$ inhibition of body weight gain). Pathological changes in these studies were limited to alterations in the salivary gland (cellular enlargement), observed in mice treated at ≥ 167 mg/kg/day (relative exposure, 0.8) and at all dose levels in rats (≥ 20 mg/kg/day; relative exposure, ≥ 0.13). This finding is considered to be an adaptive and reversible response to the sympathomimetic action of the drug (Greaves, 2007), and is not considered to be adverse.³⁹ The age of the animals at the commencement of treatment was not stated.

³⁷ FASEB. Evaluation of the Health Aspects of Caffeine as a Food Ingredient. Select Committee on GRAS Substances, Federation of American Societies for Experimental Biology. Bethesda, MD, USA. 1978; SCOGS-89.

³⁸ A 3-page summary of this document was originally submitted in the application, but was subsequently withdrawn from the dossier by the sponsor after considering the document's minimal detail and limited value. The full data set was retrieved by the evaluator from the International Program on Chemical Safety website. <<http://www.inchem.org/documents/sids/sids/CAFEINE.pdf>>

³⁹ Greaves, P. (2007) Histopathology of Preclinical Toxicity Studies. Third Edition. Chapter 8. Digestive System. p. 349. Academic Press.

Table 1: Relative exposure at the highest and selected other doses in repeat-dose oral toxicity studies

Reference	Species & strain	Treatment duration	Sex	Dose (mg/kg/day)	AUC _{0-24h} (µg/mL·h) [#]	Exposure ratio*
Bachmann <i>et al.</i> (1946) [cited in FASEB, 1978]	Rat (strain unknown; weanling)	26 weeks	♂ / ♀	40–50	198–294	0.4–0.6
Boyd <i>et al.</i> (1965) [cited in FASEB, 1978]	Rat (Wistar)	100 days	–	150	2280	4.7
Scott & Chen (1944) [cited in FASEB, 1978]	Rat (strain unknown)	4 weeks	–	~100	1054	2.2
				~500	23904	50
Strubelt <i>et al.</i> (1973) [cited in FASEB, 1978]	Rat (Wistar)	6–7 months	–	35–60	157–409	0.3–0.9
NTP (1983) [cited in SIDS, 2002] ⁴⁰	Mouse (B6C3F1)	90 days	♂	167	367	0.8
			♀	179	394	0.8
	Rat (F344)	90 days	♂	20	62	0.13
				151	2309	4.8
			♀	272	7226	15
				23	77	0.16
			♂	174	3034	6.3
				287	8025	17
Clinical Overview	Human (preterm infant); 10 mg/kg IV loading dose + 2.5 mg/kg/day maintenance dose			480	–	

[†] * = calculated as animal:human AUC_{0-24h}; [#] = estimated values; – = not stated/not applicable; doses are expressed in terms of caffeine base; relative exposure in a 4-generation study in rats involving dosing at 100 mg/kg SC (Eichler and Mügge, 1932; cited in FASEB, 1978) has not been estimated as no pharmacokinetic data were provided for that route.

Genotoxicity

Much data exist on the genotoxicity of caffeine, its extensive study reflecting concerns due to its purine structure as well as wide human exposure. While some positive results in tests for bacterial mutagenicity, mammalian mutagenicity, and clastogenicity *in vitro* and *in vivo* (micronucleus tests in mice and hamsters) have been reported in the literature, most tests have returned negative results. Upon reviewing the data, SIDS (2002) concluded that “positive results were obtained only in studies which used extreme culture conditions, lethal doses or non-validated methods”.⁴⁰ Caffeine is therefore not considered to pose a genotoxic hazard to patients.

Carcinogenicity

Given the short duration of treatment proposed (usually ≤10 days) and the negative genotoxicity for caffeine in appropriately conducted tests, carcinogenicity studies are not required to support registration of the product under ICH guidelines. Nevertheless, because

⁴⁰ SIDS. Screening Information Dataset Initial Assessment Profile. Caffeine [56-08-2]. SIAM 14. March 2002. [full report: <<http://www.inchem.org/documents/sids/sids/CAFEINE.pdf>>].

they already exist in the literature, it is proper that such data should be submitted and the prescriber informed of relevant findings.

The 1978 review by FASEB submitted by the sponsor described a study—then yet to be published—apparently showing positive carcinogenicity findings for caffeine in rats treated at 150–250 mg/kg/day orally for 15 months. This study appears to have been published as Takayama and Kuwabara (1982), and was reviewed in SIDS (2002).⁴¹ In contrast to the preliminary claim, no increase in tumour incidence was found in rats treated with caffeine at up to ~180 mg/kg/day orally for 78 weeks. Although the sacrifice of surviving animals took place in Week 104, the treatment duration in this study was shorter than the 24 months recommended under ICH guidelines. No carcinogenicity was found for caffeine in another study in rats (by Mohr *et al.*, 1982), involving dosing for 2 years at up to 102 mg/kg/day orally in males and 170 mg/kg/day in females. This study appeared to be well conducted, and doses up to and beyond maximally tolerated levels were used (based on suppression of body weight gain); estimated relative exposure at the highest dose level is 2 for males and 6 for females. No adequately conducted mouse carcinogenicity study has been identified, but the absence of such a study is considered to be acceptable.

The International Agency for Research on Cancer (IARC) of the World Health Organization reviewed human carcinogenicity data for caffeine in 1991, concluding that “there is inadequate evidence for the carcinogenicity in humans of caffeine”.⁴² This terminology reflects that “the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available”.⁴³

Reproductive toxicity

Limited nonclinical data were available to assess the potential for neonatal exposure to caffeine to affect later fertility. No adverse effects on fertility were observed in the offspring of rats treated at 60 mg/kg/day orally (study by Pollard and Claassens, 1992; cited in SIDS, 2002) or in a 4-generation study in rats involving dosing at 100 mg/kg/day SC (Eichler and Mügge, 1932; cited in FASEB, 1978). Animals in these studies would have been exposed to caffeine during late gestation and the early postnatal period (through the consumption of maternal milk in the first, and via milk and potentially also through direct dosing in the second). Relative exposure is unknown, however, and neither study was described in sufficient detail to determine whether it was adequately conducted. No adverse effects on fertility were observed in classical fertility studies (involving treatment in adults) in mice at ≤ 88 mg/kg/day orally (relative exposure, ≤ 0.4) and rats at ≤ 50 mg/kg/day orally (relative exposure, 0.6).

Only very high maternotoxic doses of caffeine resulted in teratogenic effects in rats and mice.

In postnatal studies, no adverse effects, including on behaviour, were observed in the offspring of rats treated with caffeine at ≤ 40 mg/kg/day orally during gestation only (relative

⁴¹ Takayama S, Kuwabara N. Long-term study on the effect of caffeine in Wistar rats. *Gann* 1982; **73**:365–371.

⁴² IARC (1991) International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Coffee, Tea, Mate, Methylxanthines and Methylglyoxal. Volume 51. <<http://monographs.iarc.fr/ENG/Monographs/vol51/mono51.pdf>>

⁴³ Note that, in contrast, a conclusion of “evidence suggesting lack of carcinogenicity” is drawn where “there are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture or exposure circumstance and any studied cancer at any observed level of exposure” (IARC, 1991).

exposure, ≤ 0.4). In monkeys, the offspring of animals treated at ≥ 10 mg/kg/day orally during and after pregnancy showed impaired somatic development (at 30 days of age, but not 1 year) and behavioural alterations (feeding and/or reward; at 30–44 days of age). The behavioural alterations may reflect an acute effect of caffeine in the nursing animals (maternal and infant blood levels of caffeine were similar; estimated relative exposure ≥ 0.1) or be a consequence of exposure *in utero*.

Nonclinical Summary and Conclusions

The data contained in the nonclinical submission cannot be considered to represent a comprehensive and up-to-date review of the toxicology of caffeine. In addition, many studies were described in insufficient detail to be adequate for risk assessment.

Primary pharmacology studies with caffeine, showing improved lung function in pre-term baboons and enhanced development of respiratory control in neonatal rats, support the drug's use for the proposed indication.

CNS safety pharmacology studies in rats identify the potential for neurological changes in patients exposed to caffeine in the neonatal period, which may not become evident until later stages in development. However, these may be subtle and transient, and it is recognised that apnoea itself has neurological consequences. ECG abnormalities and altered cardiac function and development were observed in caffeine-treated rats, but, given the level of drug exposure associated with Cafnea therapy and the short duration of treatment, these findings are considered unlikely to be of clinical significance.

No adverse effects were observed in rodents treated orally with caffeine at doses yielding systemic exposure estimated to be close to (mouse; 0.8-times) or a significant multiple of (rat; ~5–6-fold) the clinical exposure level. Treatment in these studies is presumed to have commenced when animals were young adults however, and the findings may not be applicable to exposure during the neonatal period. In addition, considerable uncertainty exists with regard to the estimated relative exposure levels due to a lack of toxicokinetic data.

The drug is not considered to pose a genotoxic or carcinogenic hazard.

Registration of Cafnea was not supported due to deficiencies in the nonclinical data set. Specifically, there were no repeat-dose toxicity studies that:

- involved the IV route;
- used the citrate salt of caffeine;
- were conducted in very young animals and that were adequately documented; or
- were conducted in a second, non-rodent species.

If registration is granted on clinical grounds, the draft product information should be amended as directed.

The sponsor noted that the data available were those based on a review of the published literature. Although there were large numbers of studies available, few were specific in terms of the indication proposed for Cafnea. The development of a suitable animal model (pharmacokinetic, pharmacodynamic, safety properties etc) to match this target group of patients has not been achieved. In the hundreds of published animal studies uncovered in the literature search, there were only two studies which might approach suitability – one is in very young rats (without apnoea) and the other study used a very small number of neonatal baboons with induced apnoea. Repeat dose studies involving the IV route of administration were not found in animal studies. The animal studies (adult and young rats) presented were those available in the published literature.

IV. Clinical Findings

Introduction

The clinical component of the submission is entirely literature based and includes most of the relevant studies. The initial clinical data included 43 publications. Following discussion with the TGA the sponsor provided a further 16 publications. Consequently, the clinical component of the submission included a total of 59 publications. Of these 59 publications, 44 were original study reports, 11 were reviews (including 3 Cochrane reviews), two were letters to the editor, one was an editorial, and one was the US prescribing information (“label”) for caffeine citrate. The 44 original study reports included pharmacodynamic, pharmacokinetic, and clinical efficacy and safety studies. The pivotal efficacy and safety study is *Schmidt et al (2006 & 2007)*, a placebo-controlled study in 2006 preterm infants investigating short-term (prior to first hospital discharge) and long-term (corrected age 18-21 months) outcomes associated with caffeine citrate administered to treat or prevent AOP or to facilitate extubation.^{3,44} This pivotal study was supported by a short-term (10 day) placebo-controlled study in 85 preterm infants with AOP investigating the effect of caffeine citrate on the frequency of apnoeic episodes.⁴⁵ The submission also included a number of studies comparing the effects of caffeine (generally as the citrate) with aminophylline or theophylline for the treatment or prevention of AOP. As these studies did not include a placebo control group and neither theophylline nor aminophylline are approved for the treatment of AOP in Australia these studies are considered to provide supportive evidence for the efficacy of caffeine citrate. The submission also included studies providing dose ranging information on caffeine citrate when used to facilitate extubation or prevent AOP. These dose ranging studies did not include a placebo control group and are considered to provide supportive evidence for the efficacy of caffeine citrate.

Pharmacodynamics

Overview

The submission included six studies published between 1989 and 2006 containing information on the effects of caffeine on respiratory, cardiovascular, and central nervous system pharmacodynamic parameters when used to treat or prevent AOP.^{46,47,48,49,50,51}

⁴⁴ Schmidt B et al. Long-term effects of caffeine therapy for apnoea of prematurity. *N Engl J Med* 2007; 357: 1893-902.

⁴⁵ Erenberg A et al. Caffeine citrate for the treatment of apnoea of prematurity: a double-blind, placebo-controlled study. *Pharmacotherapy* 2000; 20: 644-652,

⁴⁶ Bucher HU. and Duc G. Does caffeine prevent hypoxaemic episodes in premature infants? A randomized controlled trial. *Eur J Pediatr* 1988; 147: 288-291.

⁴⁷ Saliba E et al. Effect of caffeine on cerebral blood flow velocity in preterm infants. *Biol Neonate* 1989; 56: 198-203,.

⁴⁸ Walther FJ et al. Cardiovascular effects of caffeine therapy in preterm infants. *Am J Dis Child* 1990; 144: 1164-1166.

⁴⁹ Bauer J et al. Effect of caffeine on oxygen consumption and metabolic rate in very low birth weight infants with idiopathic apnoea. *Pediatrics* 2001; 107: 660-663.

These studies were of reasonable quality, but often showed conflicting results for examined respiratory and cardiovascular pharmacodynamic parameters. These differences might reflect different doses and/or treatment regimens used in the studies.

Three of the studies showed that caffeine had no significant effects on respiratory rate, or partial pressure of arterial carbon dioxide (PaCO₂) when administered after one or two loading doses,^{47,50} or on hypoxaemic episodes after repeat maintenance doses.⁴⁶ However, *Bauer et al (2001)*, found significantly increased oxygen consumption and carbon dioxide production 48 hours after caffeine given shortly after birth.⁴⁹ This study also found that oxygen consumption was persistently high throughout the 4 weeks of treatment. It also showed that energy expenditure was significantly increased in the first 48 hours following caffeine administration. The results from this study suggest that caffeine citrate increases the metabolic rate in preterm infants.

There are conflicting data of the effect of caffeine on cerebral blood flow with *Hoecker et al (2006)* reporting a decrease, while *Saliba et al (1989)* observed no change.^{47,50} *Hoecker et al (2006)* also reported no change on left ventricular output following caffeine loading doses, while *Walther et al (1990)* reported increased left ventricular output and stroke volume over 1-7 days of caffeine maintenance treatment.^{48,50} *Hoecker et al (2006)* also observed an increase in total vascular resistance (TVR) following loading doses, and *Walther et al (1990)* reported an increase in mean arterial blood pressure (MABP), while *Saliba et al (1989)* found no significant change in this parameter. Increases in heart rate (HR) were reported by *Hoecker et al (2006)*, but not by *Walther et al (1990)* or *Saliba et al (1989)*. *Hoecker et al (2006)* reported no change in mesenteric blood flow following caffeine.

Respiratory System

Hoecker et al (2006) observed no significant changes in respiratory rate (RR) or PaCO₂ after two loading doses of caffeine citrate 12.5 mg/kg (n=16) administered 4 hours apart and assessed at 1 hour following the first dose and 1, 2, and 20 hours after the second dose. Similarly, *Saliba et al (1989)* reported no significant differences in RR, transcutaneous carbon dioxide tension (tcPCO₂), and transcutaneous oxygen tension (tcPO₂) assessed before and after caffeine citrate 20 mg/kg (n=7) administered as an IV infusion. In *Bucher and Duc (1988)*, caffeine citrate (20 mg/kg loading and 10 mg/kg/day maintenance) (n=25) had no significant effect in reducing hypoxaemic episodes (measured by tcPO₂) or bradycardia compared with controls (n=25) in spontaneously breathing preterm infants of ≤ 32 weeks gestation with mean birth weights of 1300-1400 g.⁴⁶

In *Bauer et al (2001)*, oxygen consumption (VO₂) mL/L/kg was reported to be significantly higher ($p < 0.05$) in 9 infants with AOP 48 hours after starting treatment with caffeine citrate (10 mg/kg IV loading; 5 mg/kg maintenance every 24 hours) compared with 9 controls with AOP given no treatment. In the treated group, VO₂ (mL/kg/min) increased from 7.0±0.7 before caffeine to 8.8±0.7 after caffeine with the corresponding figures for controls being 6.5±0.6 and 6.6±0.7. The significant increase in oxygen consumption was accompanied by a significant increase in carbon dioxide production (mL/kg/min) and energy expenditure (cal/kg/hr). The mean±SD (standard deviation) number of apnoeic episodes also fell from

⁵⁰ Hoecker C et al., Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; 91: F61-F64.

⁵¹ Curzi-Dascalova L et al. Sleep organization is unaffected by caffeine in premature infants. *JPea'iat N* 2002; 140: 766-771.

20±3 to 8±5 following caffeine compared with 12±4 to 11±3 with controls. The study also showed that VO₂ was statistically significantly greater (p<0.05) in caffeine treated infants compared with controls over the full 4 week treatment period, with the difference disappearing one week after treatment cessation.

Cardiovascular System

Cerebral Blood Flow: *Hoecker et al (2006)*, reported significant reductions in cerebral blood flow velocity (BFV) in the internal carotid artery (ICA) (p=0.01) and the anterior cerebral artery (ACA) (p=0.003) at 1 hour after the second loading dose of caffeine citrate 12.5 mg/kg (n=16) administered by nasogastric tube 4 hours after an initial dose of 12.5 mg/kg (17% and 19%, respectively). At 2 hours after the second dose, BFV in the ICA was still 19% lower (p=0.008) compared with pre-treatment, while BFV in the ICA was 11% lower (NS [not significant]) compared with pre-treatment. At 1 hour after the first dose and 20 hours after the second dose there were no statistically significant differences between pre- and post-treatment BFV in either the ICA or ACA. However, *Saliba et al (1989)* found that caffeine citrate 20 mg/kg IV (n=7) had no effect on cerebral blood flow (CBF) at 30, 60 and 120 minutes after administration.

Mesenteric Blood Flow: *Hoecker et al (2006)* found no significant changes in mesenteric BFV in the coeliac or superior mesenteric arteries after two loading doses of caffeine citrate 12.5 mg/kg (n=16) administered by nasogastric tube 4 hours apart and assessed at 1 hour following the first dose and 1, 2, and 20 hours after the second dose.

Left Ventricular Output (LVO): *Hoecker et al (2006)* found no significant changes in LVO after two loading doses of caffeine citrate 12.5 mg/kg (n=16) administered by nasogastric tube 4 hours apart and assessed at 1 hour following the first dose and 1, 2, and 20 hours after the second dose. However, *Walther et al (1990)* reported significant increases in LVO and stroke volume compared with controls (n=10) on days 1 to 7 of treatment with a caffeine citrate (n=10) regimen of 20/5 mg/kg with both loading and maintenance doses being administered IV.

Other Cardiovascular Variables: *Hoecker et al (2006)* reported significant increases (17% and 18%, respectively) in TVR (MBP/LVO) at 1 hour (p=0.0494) and 2 hours (p=0.0227) after a second loading dose of caffeine citrate 12.5 mg/kg (n=16) administered by nasogastric tube. In addition, *Hoecker et al (2006)* found a significant increase in mean heart rate (HR) from 149 beats per minute (bpm) pre-treatment to 158 bpm post-treatment at 20 hours after the second 12.5 mg/kg dose. However, *Saliba et al (1989)* found no significant changes in HR or MABP measured before and after IV infusion of caffeine citrate 20 mg/kg. However, in a repeat dose study *Walther et al 1990* found a significant increase in MABP in the first 3 of 7 days following caffeine citrate (n=10) 5 mg/kg IV daily preceded by a loading dose of 20 mg/IV compared with controls, but found no significant change in HR.

Central Nervous System

Sleep Organization: In *Curzi-Dacscalova et al (2002)* the effects of caffeine on "sleep organization" in neurologically normal and clinically stable preterm infants of 33 to 34 weeks postmenstrual age was assessed in 10 infants treated with caffeine citrate (20/5 mg/kg) to prevent AOP and 5 control infants who had not received caffeine.⁵¹ Polysomnographic recordings were recorded over a 10 hour period (9 am to 7 pm) at least 3 days after the loading dose. No significant difference between groups was observed in sleep-wake variables (wakefulness, active sleep, quiet sleep, indeterminate sleep), and transition between main active and quiet sleep states. In addition, no difference in sleep variables was seen between the morning (before caffeine) and evening (after caffeine) data.

Pharmacokinetics

Overview

The submission included a number of studies published between 1979 and 2008 containing pharmacokinetic (PK) data in preterm infants given caffeine citrate to treat or prevent AOP or to facilitate extubation. These studies included both large and small population pharmacokinetic (POPPK) studies as well as traditional and generally small PK studies. The PK studies were of variable quality, but overall are considered to range from satisfactory to good. The studies mostly involved Caucasian neonates of both sexes, but there was one good quality small POPPK study in Singaporean Chinese and Malays.⁵² Caffeine citrate rather than caffeine base was used in nearly all studies, and the dose varied among the studies and involved both single and repeat dose regimens. Caffeine was generally measured in plasma and/or urine using either high performance liquid chromatography (HPLC) or radio-immunoassay, and the studies generally included information on assay validation. The terms serum caffeine and plasma caffeine concentration were used interchangeably.

The submission included four large (n=364) POPPK studies analysed using NONMEM methods.^{53,54,55,56} Two of these studies were Australian and appear to have used caffeine citrate formulations supplied by the sponsor.^{53,54} The submission also included an additional eleven studies with relevant PK data on a total of approximately 300 infants.^{52,54,57,58,59,60,61,62,63,64,65} Relevant information from published data not submitted by

⁵² Lee HS et al. Caffeine in apnoeic Asian neonates: a sparse data analysis. *Br J Clin Pharmacol* 2002; 54: 31-37.

⁵³ Charles BG, Townsend SR, Steer PA, Flenady VI, Gray PH, Shearman A. Caffeine citrate treatment for extremely premature infants with apnoea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. *Ther Drug Monit* 2008; 30: 709-16.

⁵⁴ Lee TC et al. Saliva as a valid alternative to serum in monitoring intravenous caffeine treatment for apnoea of prematurity. *Ther Drug Monit* 1996; 18: 288-293.

⁵⁵ Thomson A.H, S. Kerr, and S. Wright. Population pharmacokinetics of caffeine in neonates and young infants. *Ther Drug Monit*. 1996; 18: 245-253.

⁵⁶ Falcao AC et al. Population pharmacokinetics of caffeine in premature neonates. *Eur J Clin Pharmacol*. 1997; 52: 211-217.

⁵⁷ Aranda JV et al. Pharmacokinetic profile of caffeine in the premature newborn infant with apnoea. *J Pediatr*. 1979; 94: 663-8.

⁵⁸ Le Guennec et al., Maturation Changes of Caffeine Concentrations and Disposition in infancy during maintenance therapy for apnoea of prematurity: influence of gestational age, hepatic disease, and breast feeding. *Pediatrics*. 1985; 76: 834-840.

⁵⁹ Carrier O, Pons G, Rey E, Richard MO, Moran C, Badoual J, Olive G.. Maturation of caffeine metabolic pathways in infancy. *Clin Pharmacol Ther*. 1988; 44: 145-151.

⁶⁰ Pons G et al. Developmental changes of caffeine elimination in infancy. *Dev Pharmacol Ther*. 1988; 11: 258-264.

⁶¹ Pons G et al. Maturation of AFMU excretion in infants. *Fundam Clin Pharmacol*. 1989; 3: 589-595.

⁶² Giacoia et al. Effect of formula feeding on oral absorption of caffeine in premature infants. *Dev Pharmacol Ther* 1989; 12: 205-10.

the sponsor but which complement and/or supplement the PK data from the provided studies has also been considered includes the US product information and the UKPAR.^{66,67,68} PK data from submitted studies were not included in the evaluation report if these data were not considered to be directly relevant to the submission, or if presentation of the data were unclear.^{69,70}

The PK of caffeine are summarised below, primarily from data in the submitted studies supplemented where relevant by information from non submitted studies. The four large submitted POPPK studies are discussed in detail in the final section.

Absorption

The oral bioavailability of an aqueous IV caffeine solution manufactured by the sponsor and administered by orogastric tube in the periextubation period to preterm infants of gestational age 24-29 weeks was estimated to be 100%.⁵³ The mean half-life of absorption ($t_{1/2abs}$) reported in this study was 28 minutes which was about twice that reported for adults given caffeine as an oral aqueous solution.

The effect of food on the oral absorption of caffeine in premature infants of gestational age 29-34 weeks with AOP was investigated by *Giaccoia et al (1989)*.⁶² This parallel group study showed that an infant formula administered by nasogastric tube had no significant effect on the maximal plasma concentration (C_{max}) or the area under the plasma concentration time curve from time zero to 12 hours (AUC_{0-12h}) of caffeine following a single oral dose of caffeine citrate 20 mg/kg (Table 2). The results indicate that oral caffeine citrate can be administered with or without feeding in premature infants. The mean half-life of absorption ($t_{1/2abs}$) in this study was 20 minutes in the fasted group and 38 minutes in the fed group. The study also showed that more than 90% of the absorbed dose reached the systemic circulation in less than 2 hours in both treatment groups.

Table 2: Giaccoia et al (1989) – PK parameters following single dose oral and IV caffeine citrate.

⁶³ Romagnoli C et al. Effectiveness and side effects of two different doses of caffeine in preventing apnoea in premature infants. *Ther.Drug.Monit.* 1992; 14: 14-19.

⁶⁴ De Carolis MP et al. Pharmacokinetic aspects of caffeine in premature infants. *Dev.Pharmacol.Ther.* 1991; 16: 117-122.

⁶⁵ Cattarossi L et al. Correlation between plasma and urinary caffeine levels in preterm infants. *J.Perinat.Med.* 2006; 34: 344-346.

⁶⁶ Cafcit, Inc Roxane Laboratories. Product Information. Cafcit(R), injection and oral solution caffeine citrate. 2000. Columbus, Ohio.

⁶⁷ Tassaneeyakui W et al. Caffeine metabolism by human hepatic cytochrome P450: contributions of 1A2, 2E1 and 3A isoforms. *Biochem Pharmacol* 1994; 47: 1767-76.

⁶⁸ UKPAR, caffeine 5 mg/mL solution for injection.

⁶⁹ Micallef S et al. Sequential updating of a new dynamic pharmacokinetic model for caffeine in premature neonates. *Clinical Pharmacokinetics.* 2007; 46: 59-74.

⁷⁰ Gorodischer R. Karplus M. Pharmacokinetic aspects of caffeine in premature infants with apnoea. *European Journal of Clinical Pharmacology* 1982; 22: 47-52.

Group	Oral Caffeine 20 mg/kg				
	C _{max} mg/L	T _{max} h	AUC _{0-12h} mg.L/h	ka h ⁻¹	t _{1/2} abs h
Group A [Fast] n=8	12.8±0.8	3.4±1.8	143±9	4.4±2.5	0.20±0.10
Group B [Fed] n=8	12.8±1.1	5.9±4.1	139±11	2.4±1.4	0.38±0.22

T_{max}: time to maximal plasma concentration

Distribution

Volume of distribution (Vd) values were consistent across a number of studies (Table 3), and the Vd was not significantly affected by either gestational or postnatal age. The Vd is relatively large suggesting that caffeine is extensively distributed to the tissues. No information on caffeine plasma protein binding or blood-plasma partitioning in preterm infants could be identified in the submitted clinical data.

Table 3: Volume of distribution – cross-studies comparison.

	POPKK S	N	PNA (days)	GA (weeks)	Vd (mL/kg)	
Charles et al., 2008 ⁵³	Yes	110	12	27.5	851 [365-1761]	median [range]
Lee et al., 1997 ⁷¹	Yes	89	4	28.2	970	mean
Thomson et al, 1996 ⁵⁵	Yes	80	23 [n=60] ^{1, 2.} 27 [n=20]		820 [L] ³	mean
Falcao et al., 1996 ⁵⁶	Yes	75			911	mean
Giacoaia et al., 1989 ⁶²	No	8 Fast		32	750 ± 130	mean±SD
		8 Fed		33	830 ± 230	mean±SD
Aranda et al., 1979 ⁵⁷	No	12	11.5	29.5	916 ± 70	mean±SE
Pons et al., 1988 ⁶⁰	Yes	21	15-588		784±299	mean±SD

POPKKS = Population Pharmacokinetic Study; PNA = Postnatal age; GA = Gestational Age

¹ The 80 patients were divided into two groups (population n=60 and test n=20). No overall PNA and/or GA for the 80 patients.

² Median age.

³ The population estimate of Vd was 820 L and independent of weight.

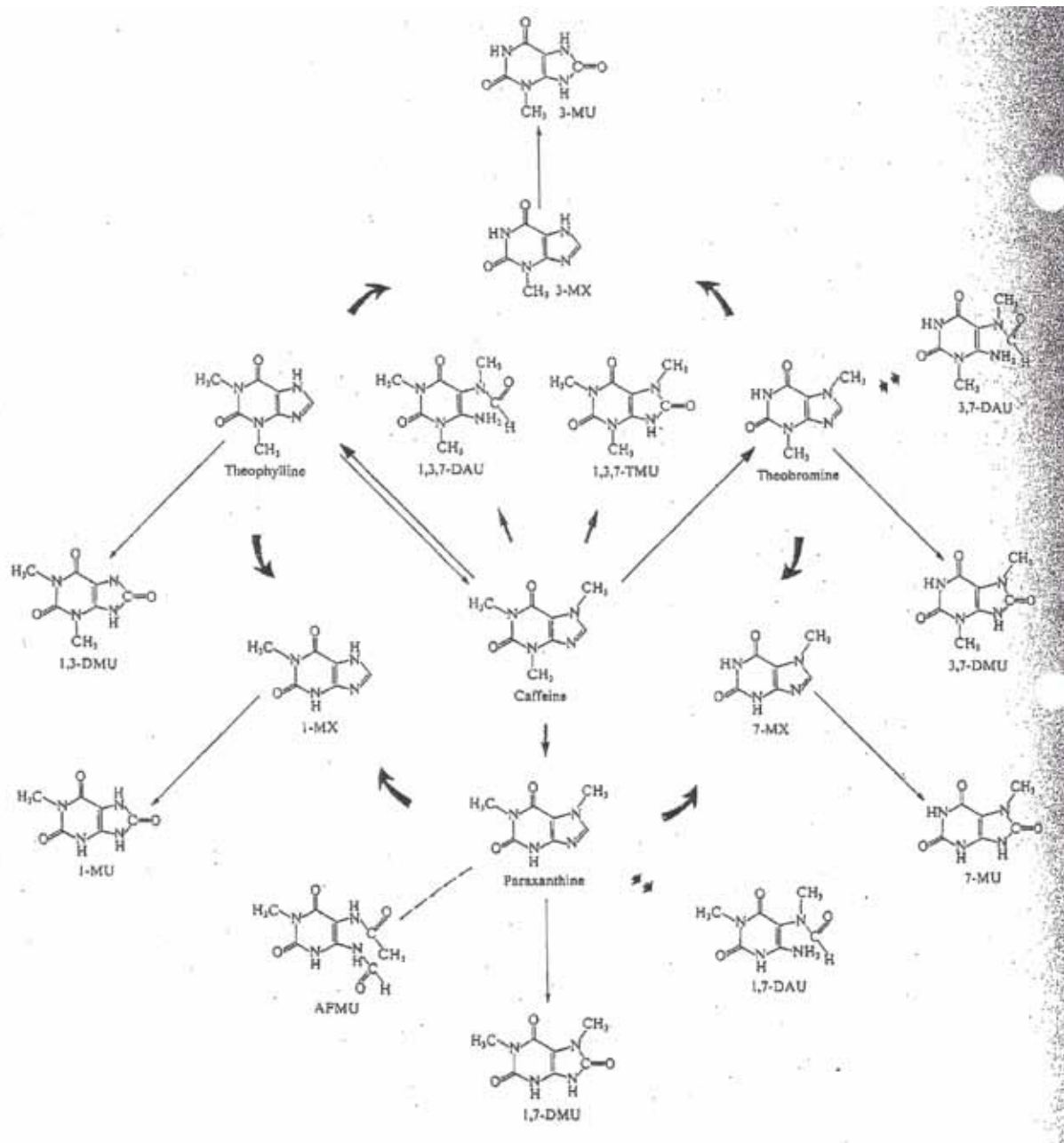
Metabolism

Caffeine is metabolised in the liver 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.⁶⁷ Data from *Carrier et al (1985)* showed that N3- and N7-demethylation of caffeine increased monoexponentially from birth to reach a plateau at a postnatal age of about 120 days, while N1-demethylation remained low and flat from birth to a postnatal age of 600 days which was the limit of observations.⁵⁹ The study also showed that 8-hydroxylation of caffeine increased linearly from birth to a postnatal age of 600 days, and the authors commented that this pathway is mature as early as a postnatal age of 1 month and may be more active in infants than adults. In *Le Guennec et al 1985*, the mean adult half-life value for caffeine of about 6 hours was reached at a postnatal age of about 5 months, while in *Pons et al (1988)* the half-life reached a plateau of 4.8 hours at a postnatal age of 4 months and clearance at a plateau of 0.127 L/kg at a postnatal age of about 6 months.^{58,60} These results are consistent with those from *Carrier et al (1985)* showing that 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. While caffeine can also be metabolised by acetylation this metabolic pathway seems to be of minor importance and data from *Carrier et al (1985)* and *Pons et al (1989)* indicate that it is immature during the first year of life.^{59,61} The metabolic pathways in humans are provided in Figure 1.⁷²

⁷¹ Lee TC et al. Population pharmacokinetics of intravenous caffeine in neonates with apnoea of prematurity. *Clin Pharmacol Ther* 1997; 61: 628-640.

⁷² Arnaud MJ. The pharmacology of caffeine. *Prog Drug Res* 1987; 31: 273-313.

Figure 1: Arnaud (1987) - Metabolic pathways of caffeine in humans.



The primary metabolites of caffeine are paraxanthine (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.^{66,68} In *Romagnoli et al (1992)*, serum theophylline concentrations began to increase shortly after a loading dose of 10 mg/kg (n=23) given shortly after birth to prevent apnoea in premature infants.⁶³ Theophylline serum concentrations then increased during maintenance treatment with both 5 mg/kg/day (n=13) and 2.5 mg/kg/day (n=10). However, serum theophylline concentrations increased to a disproportionately greater extent with the higher 5 mg/kg/day dose compared with the lower 2.5 mg/kg/day dose. The report stated that serum theobromine concentrations "had a very similar trend to that of

theophylline, although...50% lower". The authors speculate that a higher caffeine maintenance dose might stimulate more rapid metabolism of caffeine to theophylline and to other xanthines. Importantly, theophylline concentrations were still well above zero three days after stopping caffeine treatment in the 5 mg/kg/day maintenance group.

In *De Carolis et al (1991)*, urinary caffeine and theophylline were collected during therapy with caffeine citrate (10 mg/kg IV loading dose, 2.5 mg/kg/day maintenance dose for 15 days) for prevention of AOP in premature neonates (n=10).⁶⁴ The percentage of theophylline of the total theophylline and caffeine collected in the urine increased from Day 6 (13.6%) to Day 15 (22.5%) and at 24 hours after dose cessation was 24%. The blood urine/ratio of theophylline was 0.38, on Days 6 and 10, and 0.39 on Day 15 and 24 hours after dose cessation. Serum caffeine concentration fell over Days 10 to 15 from 18.0 to 12.5 mcg/mL, but was still 11.5 mcg/mL at 24 hours after caffeine cessation. Serum theophylline concentration remained constant from 1.2 mcg/mL at Day 10 to 1.3 mcg/mL at Day 15, and was still 1.2 mcg/mL at 24 hours after caffeine cessation. Persistently elevated caffeine and theophylline serum concentrations after caffeine cessation have the potential to cause adverse events related to these drugs for some days after cessation of caffeine citrate therapy.

Elimination

There was a consistent pattern across PK studies in preterm infants of low caffeine clearance and long caffeine elimination half-life (Table 4). Those studies in which maturation of caffeine elimination has been investigated showed that elimination does not mature in infants until a postnatal age of about 4 to 6 months. In *Le Guennec et al (1985)*, the effect of increasing postnatal and post-conception age on the half-life of caffeine was investigated in preterm infants with AOP treated with caffeine citrate for 6 to 14 weeks (n=6) or for 21 to 34 weeks (n=17).⁵⁸ The loading dose was 20 mg/kg and the initial maintenance dose was 3-5 mg/kg/day "frequently" increasing to 12 mg/kg twice daily (bd) at 50 weeks post-conception. Half-life decreased with increasing age reaching mean adult values of about 6 hours at a post-conceptual age of about 60 weeks or a postnatal age of 5-6 months (Table 5). The mean±SD [range] half-life of caffeine was 97.9±35.3 hours [56.2-35.3] in 13 preterm infants with a post-conceptual age of < 34 weeks, and 61.7±23.3 hours [26.8-100] in 18 full term infants with a post-conceptual age of 39-42 weeks. Two infants who developed secondary cholestatic jaundice during the study had longer half-lives than mean values from about 38 to 52 weeks of post-conceptual age.

Table 4: Clearance and half-life - cross-studies comparison.

	POPK KS	N	PNA (days)	Gestational age (GA) (weeks)	CL (mL/min/kg)	t _{1/2} (hours)
Charles et al., 2008 ⁵³	Yes	110	12	27.5	0.116 [range 0.268 – 0.376] ³	101 [range 24.5 – 371]
Lee et al., 1997 ⁵⁴	Yes	89	4	28.2	0.0817 [mean]	144
Thomson et al., 1996 ⁵⁵	Yes	80	23 [n=60] ^{1,2} 27 [n=20]		0.132 ± 0.03 [mean±SD]	-
Falcao et al., ⁵⁶	Yes	75			0.127 ± 0.03	-
Le Guennec et al., 1985 ⁵⁸	No	15	0-24			97±32.7 [56 – 168]

Aranda et al., 1979 ⁵⁷	No	12	11.5	29.5	0.148±0.024 ⁴	102.9±17.9 [41-231] ⁴
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¹ The 80 patients were divided into two groups (population n=60 and test n=20). No overall PNA and/or GA for the 80 patients.

² Median age.

³ Median CL (clearance)

⁴ Mean±SE

Table 5: Le Guennec et al (1985) – Temporal change in caffeine half-life (hours).

Postnatal Age (wk)	Caffeine Half-Life	Postconceptional Age (wk)	Caffeine Half-Life
0–4 (n = 15)	97.6 ± 32.7 (56.2–168)	<34 (n = 13)	97.9 ± 35.3 (56.2–168)
5–8 (n = 18)	75.2 ± 28.8 (26.8–122.5)	35–38 (n = 20)	89.1 ± 23.4 (43.7–123)
9–12 (n = 13)	71.1 ± 32.3 (22.7–122.6)	39–42 (n = 18)	61.7 ± 23.3† (26.8–100)
13–16 (n = 13)‡	42.8 ± 25.2 (11.2–93.6)	43–46 (n = 8)	40 ± 17.7‡ (22.1–69)
17–20 (n = 11)§	28.8 ± 20.9 (7.4–83)	47–50 (n = 12)	30 ± 22§ (11.2–83)
21–24 (n = 9)§	11.7 ± 9.9 (2.2–32.7)	51–54 (n = 10)	12 ± 6.7§ (2.2–23)
25–28 (n = 7)§	12.2 ± 9.9 (2.6–30)	55–58 (n = 9)	11.8 ± 10§ (0.9–30)
>29 (n = 5)§	5.2 ± 5 (0.9–13)	59–63 (n = 7)	6.7 ± 2.9§ (4.7–13)

* Results are means ± SD (range).

† $P < 0.01$.

‡ $P < 0.05$.

§ $P < 0.001$.

In *Pons et al (1988)*, caffeine elimination half-life and clearance were found to vary linearly with gestational age and exponentially with postnatal age. These results were obtained by PK modelling using the authors' own software [TRIOMPHE] and a one compartment model. The number of samples for each subject included in the model was not given. The study used caffeine dosages calculated to maintain a steady state C_{max} of 11 mg/L [range 7.5 to 14.5]. The plateau for elimination half-life was 4.8 hours (that is, adult level) and was reached at a postnatal age of 4 months. The plateau for clearance was 0.127 L/kg and was reached at a postnatal age of about 6 months

In *Cattarossi et al (2006)*, plasma and urinary concentrations were highly correlated at a postmenstrual age of 29 to 31 weeks in infants (n=56) treated with oral caffeine citrate for AOP (10 mg/kg loading; 2.5 mg/kg maintenance).⁶⁵ In *Lee et al (1996)*, salivary caffeine concentration was found to be a convenient and valid alternative to serum caffeine concentration in preterm infants (n=35) being treated with caffeine citrate for AOP.⁵⁴

Information in the US label (product information) for Cafcit states that in neonates the amount of unchanged drug excreted in the urine (A_e) is approximately 86% (within 6 days). The origin of this figure could not be identified in the submitted data.⁶⁶ In *De Carolis et al (1991)*, 86.4% of the xanthines excreted in the urine consisted of caffeine at 6 days after starting treatment (10/2.5 mg/kg).⁶⁴ However, it was not clear if this figure is the A_e , but it is likely to be a reasonable approximation. The adult A_e of 1% is reported to be reached by 9 months of age.⁶⁶

Single Dose Intravenous Pharmacokinetics

Aranda et al (1979), investigated the PKs of caffeine following a single mean±SE IV infusion of 10.2±1.0 mg/kg [range 5–20] caffeine base to 12 pre-term infants of mean±SE [range] gestational and postnatal ages of 28.5±0.8 weeks [24–34] and 11.5±2.3 days [3–32], respectively.⁵⁷ The results are summarised below in Table 6:

Table 6: Aranda et al (1979) – PK parameters (mean±SE and [range]) following IV caffeine base administered to 12 pre-term infants with AOP.

Dose (mg/kg iv)	Cp (mg/L)	AVd (L/kg)	t _{1/2} (hours)	Kel (h ⁻¹)	CL (ml/h/kg)
10.2±1.0	11.5±1.7	0.916 ±0.070	102.9±17.9	0.009±0.001	8.9±1.46
[5-20]	[7.0-16.4]	[0.475-1.280]	[40.8-231]	[0.003-0.017]	[2.52-16.81]

Dose = dose as caffeine base; CP = plasma concentration at time zero; AVd = Apparent volume of distribution. t_{1/2} = plasma half-life; Kel = elimination rate constant

De Carolis et al (1991), reported that following a single 10 mg/kg IV infusion of caffeine citrate to premature neonates (n=5) at birth the mean±SD serum concentration of caffeine was 14.5±1.4 mcg/mL at 10 minutes, 11.3±0.1 mcg/mL at 24 hours, and 6.1 mcg/mL at 72 hours. The serum caffeine concentration at 24 hours was still high which supports the first maintenance dose being given 24 hours after the loading dose rather than before. Urine caffeine concentration decreased from 17.1±4.1 mcg/mL at 24 hours to 11.5±2.5 mcg/mL at 72 hours. The blood/urine caffeine concentration ratio decreased from 0.88 at 24 hours to 0.69 at 72 hours. The percentage of urinary caffeine in the total caffeine/theophylline concentration varied from 90% at 24 hours to 69.7% at 72 hours.

Repeat Dose Pharmacokinetics

In *Romagnoli et al (1992)*, caffeine and theophylline repeat serum concentrations were measured in premature infants treated with caffeine citrate to prevent apnoea.⁶³ There were two treatment regimens both involving a loading dose of 10 mg/kg IV given shortly after birth followed by a maintenance dose of either 5 mg/kg/day orally (n=13) for about 18 days or 10 mg/kg/day orally (n=10) for about 15 days. At 24 hours after the loading dose serum caffeine concentrations were about 17 mcg/mL with the 10/2.5 mg/kg regimen and 12 mcg/mL with the 10/5 mg/kg regimen. Serum concentration for both regimens reached steady state at about 5 days with higher concentrations being observed with the 5 mg/kg maintenance regimen. No dose proportionality between the two regimens was observed over the treatment period. The authors speculate that a higher caffeine maintenance dose might stimulate more rapid metabolism to theophylline which might account for the dose disproportionately. In both treatment groups caffeine was detected in the serum shortly after birth but before treatment suggesting placental transfer of the drug during pregnancy. At 3 to 5 days following cessation of treatment serum caffeine concentrations were still well above zero for both groups reflecting slow elimination in preterm infants. In addition, theophylline serum concentrations were still high in the 5 mg/kg maintenance group at about 3 days after caffeine had been stopped. Similar observations relating to steady state concentrations of caffeine and theophylline were reported by *De Carolis et al (1991)*. However, the results reported in *Romagnoli et al (1992)* and *De Carolis et al (1991)* are from the same group of investigators working at the same site in Rome, Italy, and the 10/2.5 mg/kg (n=10) groups in both studies look to be very similar.

In *Aranda et al (1979)*, the steady state mean [range] plasma caffeine concentration was 45.3 mg/mL [22.5-84.2] following a mean caffeine base dose of 11.2 [range 8.4-20] mg/kg/day (n=7) administered for a mean of about 10 days [range 2-20], compared with 13.7 mg/mL [7.4-19.4] following a lower caffeine base dose of 2.5 [range 2.3-2.7] mg/kg/day (n=10) administered for a mean of about 18 days [range 4-43]. In the high dose maintenance group, mild jitteriness was observed in 3 of the 7 treated infants at concentrations > 50 mg/mL (58.4, 61.7, and 84.2 mg/mL). However, in two of the infants (highest and lowest plasma concentrations) the jitteriness resolved in 24 to 48 hours despite continuation of caffeine

therapy. There were no cardiovascular or gastrointestinal adverse events seen in infants with the highest plasma concentrations. In view of the reports of jitteriness the authors concluded that the "desired" plasma concentration "probably ranges from 5 to 50 mg/mL", but noted (based on unpublished data) that "optimal ventilatory drive and control of apnoea are achievable with plasma concentrations between 5 to 20 mg/mL".

Pharmacokinetic Drug-Drug Interactions

There were no drug-drug PK interaction studies in the clinical data package. However, as CYP1A2 is the major enzyme responsible for caffeine metabolism there are potential interactions between caffeine and drugs which are substrates for this enzyme or inhibit or induce it.

Special Situation Pharmacokinetics [Race, Sex, Hepatic Impairment, Renal Impairment]

In a small population (n=18) of Singaporean Chinese and Malay preterm infants with AOP treated with caffeine citrate IV (20/5 mg/kg) the clearance (CL) was 0.00628 (CV 17.5%) L/h, the Vd 0.96 (CV 20.3%) L, and the half-life ($t_{1/2}$) 106 hours [range 72-150].⁵² In this study neonatal weight appeared to be the most important covariate explaining 64% of the variation for CL and 45% for Vd. The CL, Vd and $t_{1/2}$ values in the Singaporean neonates are consistent with those from Caucasian populations. There are no PK data on premature neonates from other racial groups. There were no PK studies in preterm infants investigating sex differences or the effects of hepatic or renal impairment.

Population Pharmacokinetic (POPPK) Studies

Charles et al., 2008

The objective of this Australian study was to develop a POPPK model for caffeine after orogastric or IV administration to preterm infants of less than 30 weeks gestational age who were about to be extubated.⁵³ A specific aim was to estimate the rate and extent of caffeine absorption in these infants. The study was approved by the human research and ethics committees of the Mater Mothers' Hospital, Brisbane, and the University of Queensland. Written informed consent was obtained from at least one parent of each infant.

Methods

The study included 110 infants of gestational age less than 30 weeks admitted to the Neonatal Intensive Care Nursery of the Mater Mothers' Hospital (Brisbane). The infants were a subset of 234 preterm infants enrolled in a large multicentre, clinical trial comparing the efficacy and safety of two caffeine citrate dosage regimens for the facilitation of extubation.⁷³ The sole inclusion criterion was that an infant be potentially eligible to participate 24 hours before a planned extubation or within 6 hours of an unplanned extubation. The exclusion criteria were major congenital abnormality, sepsis, major neurological condition, grade 3 or 4 intraventricular haemorrhage, or previous methylxanthine treatment.

There were two separate caffeine citrate treatment regimens:

- (i) a high dose regimen consisting of a loading dose of 80 mg/kg followed by a maintenance dose of 20 mg/kg; and

⁷³ Steer P et al. High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch.Dis.Child Fetal Neonatal Ed.* 2004; 89: F499-F503.

- (ii) a standard dosing regimen consisting of loading dose of 20 mg/kg followed by a maintenance dose of 5 mg/kg.

Loading doses were administered by IV infusion over 15 minutes or through an orogastric tube for infants on full enteral feeds, and maintenance doses were administered every 24 hours starting 24 hours after the loading dose. Serum caffeine concentrations were assayed using a commercial enzyme multiplied immunoassay.

The POPPK analysis was undertaken using NONMEM software (version 5.1.1) in conjunction with the G77 Fortran compiler. A one-compartment model with first-order absorption and elimination was fitted to the data using a first-order conditional estimation with interaction (FOCEI). The model parameters were clearance (CL), volume of distribution (Vd), absorption rate (Ka) and bioavailability of the orogastric dose (F). The base model estimated the parameters without the subsequently investigated covariates of post-natal age, post-conceptual age, gestational age, sex, and Apgar score, but included CL and Vd allometrically scaled to 70 kg body weight. Allometric scaling was used as the authors considered that it "has a sound theoretical basis" and provides "a useful means whereby the effects of other potentially influential covariates can be compared without being confounded by size". The effect of each of the other covariates was determined by sequentially adding them to CL and Vd and noting the effect this had on the objective function value (OFV) of the model. The OFV is a measure of the likelihood that the data fit the model ($OFV = -2 \times$ the log of the likelihood), and the lower the OFV the better the fit. Inclusion of a covariate was considered to improve the fit of the model if it resulted in a decrease in OFV of at least 6.6 compared with the model without the covariate. A decrease in the OFV of 6.6 was statistically significant ($p=0.01$, Chi-squared statistic, 1 degree of freedom). The effects of inter-individual variability (IIV) and inter-occasion variability (IOV) on the PK parameters were also assessed, as was the effect of residual unexplained variability on the observed serum caffeine concentrations.

Results

The 110 subjects (male 52%, female 58%) had a mean \pm SD gestational age of 27.6 \pm 1.3 weeks [range 24-29] and current weight of 992 \pm 192 g [range 644-1857]. The 80/20 mg/kg treatment regimen was administered to 59 subjects and the 20/5 mg/kg treatment regimen to 51 subjects. There were 145 orogastric and 877 IV doses administered. The presence of data from both orogastric and IV administration allowed the absolute oral bioavailability of caffeine citrate to be estimated. The median number of doses per infant was 7 [range 1-8]. The mean \pm SD elapsed time after a dose was 13.4 \pm 8.4 hours [range 0.033-47.8], the median number of serum samples per infant was 4 [range 1-8], and the median number of occasions per infant (that is, one or more sequential doses followed by at least one blood sampling event) was 3 [range 1-6]. The mean \pm SD serum caffeine concentration with 80/20 mg/kg was 47.4 \pm 12.4 mg/mL [range 18.9-79.8] and with 20/5 mg/kg was 14.7 \pm 3.87 mg/mL [4.8-25.1].

The data were best described by a one compartment model with no lag-time and first-order absorption from the gut to blood (for orogastric dosing). The final POPPK model was described by the following equations with CL and Vd scaled to 70 kg:

- $CL \text{ (L/h/70kg)} = 0.167 \text{ (WT/70)}^{0.75} \times \text{(PNA/12)}^{0.358}$
- $Vd \text{ (L/70kg)} = 58.7 \text{ (WT/70)}$
- $Ka \text{ (h}^{-1}\text{)} = 1.48.$
- $F = 1.0$

The median [range] estimates for CL and Vd calculated from individual estimates were 0.116 [0.0268-0.376] mL/min/kg and 851 [365–1761] mL/kg, respectively. The mean [range] elimination half-life ($t_{1/2}$) was 101 [24.5 –371] hours.

Apart from weight, the only other covariate that improved the fit of the data was post-natal age (PNA) in days on CL. The IIV (CV%) in the final model was 18.1% for CL and 22.3% for Vd. The IOV (CV%) was 35.1% for CL and 11.1% for Vd. The estimated residual unexplained variability for the residual additive error was 0.90 mg/mL and for the residual proportional error (CV%) was 6.1%. The internal validity of the model was assessed by inspection of plots of residuals, a visual predictive check (VPC) for both the low-dose and high-dose treatment regimens, and non-parametric bootstrapping (n=1000) with replacement. The goodness-of-fit scatter plots showed that the observed data were in good agreement with the model. The VPC showed that that the observed caffeine concentrations over a 7 treatment period were generally enclosed between the 2.5th and 97.5th percentile of the data generated from 100 simulations. The bootstrap estimates were in good agreement with the final model estimates, and the percentile bootstrap 95% confidence interval (CI) [2.5th, 97.5th percentile] included the corresponding final model estimate for all parameters.

Comment

This was a good quality POPPK study involving a large number of subjects and samples. Model development was well described, as were the checks for internal validity. The final model is considered to reflect the observed data. The study showed that absorption following orogastric administration was complete (that is, $F = 1.0$). This knowledge simplifies caffeine dosing as administration can be switched between orogastric and IV without having to recalculate the dose. The study used the IV formulation administered via the orogastric route rather than a specially formulated oral suspension. However, there is no reason to suspect that the oral bioavailability of the proposed oral solution will be significantly different from that in the study. The oral absorption half-life of 28 minutes was about twice that reported in adults. The authors speculate that this difference might reflect slower gastric emptying and intestinal mobility in extremely preterm infants in addition to delayed development of gastric acidity.

The mean caffeine clearance (0.116 mL/min/kg) in preterm infants in this study was significantly lower than that reported in older children (4.4 mL/min/kg) and adults (1.5 mL/min/kg). However, CL for subjects at the population average weight of 0.992 kg in this study increased in a nonlinear manner from ~1 mL/min/kg on the first day of life to ~12 mL/min/kg at 45 days. The study showed that the IOV in CL was almost twice that of the IIV (CV%: 35.1 vs 18.8, respectively). The authors argue that this means that targeting a maintenance dose based on previous serum concentration data in an individual infant is "largely a futile and potentially costly exercise because of the marked day-to-day randomness in CL". The underlying reasons for IOV are considered by the authors to "remain largely unidentified and uncontrollable".

Lee et al., 1996

The objectives of this Australian study were to determine the POPPKs of caffeine after IV caffeine administration to preterm infants in order to facilitate extubation.⁵⁴ The protocol was approved by the Medical Research Ethics Committee of the Mater Hospital (Brisbane) and the University of Queensland, and conducted according to the NHMRC (Australia) Statement on Human Experimentation. Written consent was obtained from a parent or parents.

Methods

All preterm infants younger than 32 weeks gestational age who were ventilated for ≥ 48 hours were eligible. Exclusion criteria included congenital chromosomal abnormalities, infection, or neurologic conditions. Patients were randomized to one of three caffeine citrate dosage regimens consisting of a loading dose of 60, 30, or 6 mg/kg administered by IV infusion over 20 minutes either 24 hours before a planned extubation or within 6 hours of an unanticipated extubation. Maintenance doses of 30 (n=38), 15 (n=39), or 3 mg/kg (n=42) were started 24 hours after respective loading doses of 60, 30, or 6 mg, and continued daily for six days. Serum concentrations of caffeine were measured using validated HPLC.

The POPPK analysis was undertaken using NONMEM (version 4.2) software in conjunction with the Fortran 77 compiler (version 1.00). The analysis employed one and two compartment models with initial parameter estimates from a previous PK study in a smaller group of similar infants to those in the current study. The base model estimated CL and Vd without the effects of covariates, and there was no allometric scaling of these two parameters for body weight. The effect of individual covariates was determined by sequentially adding them to the base model for CL and Vd. Forward and backward estimates of the effect on the OFV of adding and then subtracting the covariates from the model were calculated. The criteria used to assess the significance of adding a covariate to the model were the same as those used in *Charles et al (2008)*. The effect of inter-patient variability on CL and Vd was assessed, as was the effect of intra-patient variability (residual error) on the observed serum caffeine concentrations. The post-analysis Bayesian predictive performance of the model in terms of precision and bias was assessed using residuals (that is, predicted minus observed serum concentrations).

Results

Data from 89 subjects were allocated for model development, and data from 30 subjects were allocated to assess predictive performance. The 89 model-development patients had a mean [range] gestational age of 28.2 weeks [24-31] and birth weight of 1167 g [571-2307]. These subjects contributed a total of 430 samples with the mean number of samples per infant being 4.8 [range 3-6]. The mean [range] of all serum caffeine concentrations at each maintenance dose was 60.7 mg/L [29.7-93.3] for 30 mg/kg (n=38), 31.1 mg/L [14.8 – 49.9] for 15 mg/mL (n=39), and 6.8 mg/L [2.5-10] for 3 mg/kg (n=42).

The final POPPK model was described by the following equations for CL and Vd:

- $CL \text{ (L/h)} = (0.0000039 \times \text{current weight [g]}) + (0.000128 \times \text{post natal age [days]})$
- $Vd \text{ (L)} = (0.000764 \times \text{current weight [g]}) + (0.0648 \times \text{post natal age [days]})$: if gest. age > 28 weeks
- $Vd \text{ (L)} = (0.000755 \times \text{current weight [g]}) + (0.0224 \times \text{post natal age [days]})$: if gest. age \leq 28 weeks

The mean estimates for CL and Vd for the study sample calculated from the final POPPK model were 0.0049 L/h/kg for CL and 0.97 L/kg for Vd, with a mean elimination half-life of 144 hours.

A two-compartment model offered no improvement over a one-compartment model. The only significant covariates found in model development were weight (influencing CL and Vd), post natal age (influencing CL and Vd) and gestational age > 28 weeks and \leq 28 weeks (influencing Vd). The inter-patient variability (CV%) in CL was 47.4% and in Vd was 26.7%. The intra-patient variability (standard deviation) in the observed serum caffeine concentrations was 3.9 mg/mL and the CV was 18.7%. Intra-patient variability in serum

caffeine concentration are attributable to such factors as timing of blood collections, dosing times, drug assay, and misspecification of the PK model. Post-analysis Bayesian predictive performance showed that there were no significant differences between predicted and observed caffeine serum concentration as assessed by measures of precision and bias.

Comment

This was a good quality POPPK study in a large number of patients contributing a large number of samples. Model development was well described. The investigators did not include allometric scaling of CL and Vd based on weight. Post-analysis Bayesian predictive performance indicated that the observed data satisfactorily fitted the model.

Thomson et al., 1996

The aim of this study was to develop a POPPK model for caffeine by utilising data collected during routine therapeutic drug monitoring in a group of preterm and term neonates.⁵⁵ It was undertaken in Scotland. No details were provided on IEC/IRB approval and/or supervision. No data were provided on consent procedures.

Methods

The study population included infants who were inpatients at Simpson Memorial Maternity Pavilion (Edinburgh) being treated with caffeine for the prevention of apnoea, the management of bronchopulmonary dysplasia, or to aid extubation. The study population included 60 infants and the median [range] demographic characteristics were: postnatal age 23 days [1-100] days; weight 1.3 kg [0.6-0.29]; and post-conceptual age 31 weeks [25-41]. The study also included a population of 20 infants in whom data was collected prospectively following analysis of the study population in order to undertake predictive performance of the model. The median [range] postnatal age and weight of this predictive performance population (n=20) was 27 days [1-74] and 1.2 kg [0.6-2.6]. POPPK analyzes in the study population (n=60), and in the combined (n=80) study and predictive populations were reported.

Treatment consisted of a caffeine citrate loading dose of 20 mg/kg (orally or IV infusion over 20 minutes) followed by a daily maintenance dose of 5 mg/kg (orally or IV bolus over 3 minutes). The dosage regimen was aimed at maintaining serum caffeine concentration within the range 25 to 100 µmol/L. The samples were analysed using a commercial enzyme multiplied immunoassay. The POPPK analysis was undertaken using NONMEM in conjunction with a Fortran compiler. Oral bioavailability was assumed to be 100% if a constant dose had been maintained for at least 7 days. The model assumed instantaneous oral absorption with a monoexponential decline in concentration. The final analysis was in the combined population (n=80) using first-order conditional estimation (FOCE). The base models included estimates of CL and Vd without covariates and without allometric scaling for weight. The effects of adding covariates to the base models were assessed using the method followed in *Lee et al (1996)*, and the statistical criteria used to assess the significance of adding a covariate were the same as those in *Lee et al (1996)* and *Charles et al (2008)*. The effect of inter-subject variability on CL and Vd was also assessed, as was the effect of the residual error (residual variability) on the observed serum caffeine concentrations. Predictive performance was based on prediction errors (that is, predicted minus observed serum concentrations) and variance parameters.

Results

There were 263 concentration measurements in the study population (n=60) with a median number of samples per subject of 3 [range 1-13]. The majority of samples (85%) were measured 18 hours after the last dose, while 3% (n=8) of samples were taken 1 hour after the loading dose. The remaining samples were measured at either 12 or 24 hours after the last dose. Of the total number of measurements, 80% were made at a post-conceptual age < 34 weeks and a postnatal age < 46 days. There were 77 concentration measurements in the predictive population (n=20) with the number of measurements per subject ranging from 1 to 9. No details were provided on sampling times in the predictive population. The final POPPK model in the combined population (n=80) was described by the following equations for CL and Vd:

- $CL \text{ (L/day)} = (0.145 \times \text{weight [kg]}) + (0.00236 \times \text{postnatal age [days]})$
- $\text{Volume (L)} = 0.818$

The individual estimates of CL and Vd were obtained using the population estimate from the combined population (n=80) and Bayesian analysis of the individual concentration measurements. The mean±SD estimated value for CL was 7.9±1.9 mL/h/kg and for Vd was 0.82 L.

The inter-subject variability (CV%) in CL was 20% and in Vd was 24%, and the residual error in the observed serum concentration was 13 $\mu\text{mol/L}$. Predictive performance showed that model predictions of serum concentration were unbiased with the mean \pm SD difference between the observed and predicted concentrations being $-2\pm 19 \mu\text{mol/L}$. The variance parameters showed that 54% of the observed individual means were within the mean ± 1 SD of the distribution generated by 100 simulations. In the final model, the only covariates significantly affecting CL were weight and postnatal age, while no covariates significantly affected Vd. Covariates found not to have an effect on CL or Vd in the final model were: Apgar score; creatinine concentration; urea concentration; infection; concurrent diuretic therapy; asphyxia at birth; concurrent phenobarbitone; and concurrent therapy with a potentially nephrotoxic drug.

Comment

This was a reasonable study but had some significant limitations. The data did not include information on the predictive population (n=20) relating to sample timing or on how subjects were chosen. The predictive performance of the model was variable with 46% of the observed individual mean serum concentrations being outside the predicted mean ± 1 SD. The investigators state that the subject population (n=60) was more variable than the predictive population (n=20) with the respective SD of residual variability being 16 $\mu\text{mol/L}$ and 12 $\mu\text{mol/L}$. The investigators noted that the raw data from the subject population (n=60) had a number of "spurious, unexpected low results that may have indicated poor absorption (perhaps due to vomiting)". The study found that no covariates influenced the Vd. This is unusual as Vd is generally dependent on body weight. The investigators acknowledged this "somewhat surprising result" but concluded that the data set held "little information" on Vd as it consisted of serum concentration measurements taken 18 hours after dosing.

Falcao et al., 1996

The aim of this study was to determine POPPK parameters for caffeine in very low birth weight infants.⁵⁶ The data were collected retrospectively from medical records and routine caffeine monitoring of 75 hospitalized patients at the University Hospitals of Salamanca (Spain) and Coimbra (Portugal), from 1988 to 1994. The study population was poorly described with frequency histograms of birth weight, current weight, gestational age, postnatal age and post-conceptual age being presented rather than tabulations. The "typical" and maintenance doses of caffeine citrate were 20 mg/kg loading followed by 5 mg/kg/day maintenance. The loading dose ranged from 17.4 to 21.3 kg/day, and the maintenance dose from 2.14 to 9.47 kg/day. The total number of samples was 145 with the average number per subject being 1.93 [range 1-9]. The majority of samples were collected 20 to 24 hours after the last dose and only 5.5% of samples were collected after the loading dose. The available caffeine serum concentrations ranged from 4.75 to 26.1 mcg/mL with a mean \pm SD of 11.8 ± 4.2 mcg/mL. Caffeine concentration was measured using a commercial enzyme multiplied immunoassay.

The POPPK analysis was undertaken using NONMEM (version IV) software. The concentration-time profile of caffeine was described using a one-compartment model with either zero or first order (infusion vs syrup) absorption and first-order elimination, assuming a permanent non-steady-state condition. Bioavailability was assumed to be complete (F=1) for oral caffeine. The description of the NONMEM analysis and model-building was comprehensive. No allometric scaling of CL or Vd was used in model building. No model validation methods were described. The final POPPK model was described by the following equations for CL and Vd:

- $CL \text{ (mL/h/kg)} = (5.81 \times \text{current weight [kg]}) + (1.22 \times \text{PNA [weeks]})$;
multiplied by 0.757 if $GA \leq 28$ weeks or 0.836 if on parenteral nutrition.
- $Vd \text{ (mL)} = 911 \times \text{current weight (kg)}$

Inter-individual variability (CV%) in CL was 14.9% and residual variability (CV%) was 18.4%. Parenteral nutrition decreased CL by about 16.5% while $GA \leq 28$ weeks decreased CL by about 26%. The variability of the Vd could not be estimated due to limited concentration data following the loading dose. Individual estimates of CL were obtained using the population estimates and a *post-hoc* Bayesian analysis of individual concentration measurements. The mean \pm SD CL was 7.6 \pm 1.5 ml/h/kg and the mean Vd was 911 ml/kg.

Comment

This was a reasonable study but has limitations relating to the problems of collecting retrospective data from medical records not specifically designed to capture study data, the poor description of the characteristics of the study population, the limited numbers of samples per individual (on average 2 per individual), the limited number of serum concentrations after the loading dose (5.5%), and the lack of information on NONMEM model evaluation. Despite these limitations the individual estimates of CL and Vd were consistent with those obtained from the three other published POPPK studies submitted by the sponsor.

Efficacy

Overview

The submission included two placebo-controlled studies which investigated the efficacy of caffeine citrate for the treatment of AOP. The pivotal study was *Schmidt et al (2006 & 2007)*, a large multinational study involving 2006 randomized preterm infants in which caffeine was compared with placebo for the treatment of AOP, the prevention of AOP or to facilitate extubation.^{3,44} The primary outcome was a composite of death or survival with neurodevelopmental disability before a corrected age of 18-21 months, and caffeine significantly reduced the risk of this outcome compared with placebo. The supportive placebo-controlled study was *Erenberg et al (2000)*.⁴⁵ It appears that US registration of caffeine citrate for the treatment of AOP was based primarily on this study. In addition, the proposed indication and the dosage and administration recommendations in the current submission appear to be primarily based on *Erenberg et al (2000)* rather than on *Schmidt et al 2006 & 2007*. Compared with *Schmidt et al 2006 & 2007*, *Erenberg et al (2000)* was a small study (n=87) of short duration (n=10 days) with short-term outcomes (reduction in apnoeic episode within 7-10 days initiation of treatment) in infants with AOP. The results showed that caffeine significantly reduced the frequency of apnoeic episodes compared with placebo. The submission also included an additional study comparing the short-term effect of caffeine citrate and placebo on preventing hypoxaemic episodes and bradycardia in 50 preterm infants [Bucher and Duc, 1988].⁴⁶ The sponsor considered this to be an efficacy study. However, it is considered that this study is primarily a pharmacodynamic study and, consequently, it has been considered in that section (see above). The study included only three caffeine citrate doses (20 mg/kg exactly 48 hours after birth followed by 5 mg/kg at 72 and 96 hours after birth). The study found no difference between caffeine and placebo on hypoxaemia or bradycardia.

The submission also included four short-term 5 to 10 day studies comparing caffeine and either aminophylline or theophylline for the treatment or prevention of AOP.^{4,74,75,76} In these four studies, effectiveness was assessed by reduction in episodes of apnoea and/or bradycardia within the first 10 days of initiation of treatment. These studies were listed by the sponsor as being pivotal efficacy and safety studies. However, none of these studies can be considered to be pivotal as regards efficacy as neither aminophylline nor theophylline are

⁷⁴ Bairam A, Boutroy MJ, Badonnel Y, Vert P. Theophylline versus caffeine: comparative effects in treatment of idiopathic apnoea in the preterm infant. *JPediatr*. 1987; 110: 636-639.

⁷⁵ Larsen PB et al. Aminophylline versus caffeine citrate for apnoea and bradycardia prophylaxis in premature neonates. *Acta Paediatr*. 1995; 84: 360-364.

⁷⁶ Brouard C et al. Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnoea in premature infants. *Am.J.Dis.Child* 1985; 139: 698-700.

approved in Australia for the treatment of AOP, and none of the studies included a placebo-control group. In the absence of a placebo control group, no definitive conclusions can be made about the efficacy of the regimens for the treatment or prevention of AOP.

Nevertheless, the four studies are considered to provide supportive evidence for the efficacy of caffeine for the treatment and prevention of AOP. It was noted that in two of the four studies [Brouard et al., 1985; and Larsen et al., 1995] the investigators considered that it would have been unethical to include a placebo control group as treatment with caffeine was considered to be of demonstrated efficacy for the treatment and prevention of AOP.^{76,77}

The submission also included three studies which can be considered to be dose ranging.^{63,74,77} *Romagnoli et al (1992)* was a small study which compared the effectiveness of two caffeine citrate dosing regimens (10/5 & 10/2.5 mg/kg) for the prevention of AOP and included a historical control of doubtful relevance of untreated preterm infants with AOP.⁶³ The study included PK data which have been considered above. *Steer et al (2003)* compared the effectiveness of three caffeine citrate dosing (L/M) regimens (6/3, 30/15, 60/30 mg/kg) for facilitating extubation in preterm infants,⁷⁷ while *Steer et al (2004)* compared the effectiveness of two caffeine citrate dosing (L/M) regimens (80/20 & 20/5 mg/kg) for facilitating extubation in preterm infants.⁷⁴ The sponsor appears to consider these three dose ranging studies to be pivotal efficacy and safety studies. However, as none of these three studies included a treated placebo control group no definitive conclusions concerning the efficacy of the regimens can be made. Nevertheless, the studies are considered to provide supportive evidence for the efficacy of caffeine to facilitate extubation and to prevent AOP.

The submission included three Cochrane reviews relating to caffeine treatment in preterm infants. In *Steer PA and Henderson-Smart DJ (1998)*, the reviewers compared caffeine with theophylline for the treatment of recurrent apnoea in a small number of preterm infants and concluded that the two drugs have similar short-term beneficial effects on apnoea and bradycardia, while caffeine treatment was associated with fewer short-term side effects.⁵ The reviewers stated that in view of the other therapeutic advantages of caffeine (that is, a higher therapeutic ratio, more reliable enteral absorption and a longer half-life) it is the preferred treatment for apnoea in preterm infants. The reviewers noted that there were no data in the reviewed studies on the long-term effectiveness and safety of caffeine or theophylline for the treatment of AOP. In *Henderson-Smart DJ and Steer PA (2001)*, the reviewers evaluated the effects of methylxanthine treatment on apnoea and the use of intermittent positive pressure ventilation (IPPV), and other clinically important effects, in preterm infants with recurrent apnoea.⁷⁸ The reviewers concluded that methylxanthines are effective in reducing the number of apnoeic attacks and the use of mechanical ventilation in 2 to 7 days after starting treatment. They also concluded that caffeine was the preferred drug in view of its lower toxicity compared with other methylxanthines. However, the reviewers noted that the safety of methylxanthine therapy was uncertain in the included studies, especially as regards the lack of long-term growth and neurodevelopmental outcomes. In *Henderson-Smart DJ and Davis PG (2003)*, the reviewers evaluated the effects of prophylactic methylxanthines for extubation in preterm.⁷⁹ The reviewers concluded that methylxanthines improve the chances

⁷⁷ Steer PA et al. Periextubation caffeine in preterm neonates: a randomized dose response trial. *J Paediatr Child Health* 2003; 39: 511-515.

⁷⁸ Henderson-Smart DJ and Steer P. Methylxanthine treatment for apnoea in preteen infants. *Cochrane Database of Systematic Reviews* 2001, Issue 3, Art. No.: CD000140.

⁷⁹ Henderson-Smart DJ and Davis PG. Prophylactic methylxanthines for extubation in preteen infants. *Cochrane Database of Systematic Reviews*. 2003. Issue 1: CD000139.

of successful extubation in within one week of commencing treatment. They also commented that there was insufficient information in the evaluated studies to assess side effects or longer term effects on child development. The three Cochrane Reviews were written before publication of *Schmidt et al 2006 & 2007*.

Pivotal Placebo-Controlled Study

Schmidt et al., 2006 and Schmidt et al., 2007

The pivotal efficacy and safety study is considered to be *Schmidt et al (2006 & 2007)*.^{3,44} The primary aim of this study was to determine whether caffeine therapy for AOP alters infant survival rate without neurodevelopmental disability at a corrected age of 18 to 21 months (age corrected for prematurity). It included 2006 infants with birth weights of 500 to 1250 g. The study was published in two parts. In the first part, *Schmidt et al (2006)* reported results for short-term secondary outcomes and in the second part *Schmidt et al (2007)* reported results for the long-term primary outcome. An integrated review of these two studies is provided below. The study was multinational, multi-centered and enrolled patients from Australia, Canada, Germany, Holland, Israel, Sweden, Switzerland, UK, and the USA. The protocol was approved by the "research ethics boards" of all clinical centres. Written informed consent was obtained from the parent or guardian of all infants. An external safety monitoring committee reviewed the data every 4 to 6 months during the enrollment phase. The study was supported by the Canadian Institutes of Health Research and by the National Health and Medical Research Council of Australia (which was a study sponsor in Australia).

Methods

The study was multinational, multi-centered, randomised, placebo-controlled and double-blinded and was designed to assess the short- and long-term efficacy of caffeine therapy for the treatment of AOP in infants with very low birth weight. Infants with a birth weight of 500 to 1250 g were eligible for the study if considered by their clinicians to be candidates for methylxanthine therapy during the first 10 days of life. Indications for treatment included the prevention or treatment of apnoea and facilitation of the removal of an endotracheal tube.

Of the 5292 infants considered to be eligible, 977 were excluded (242 had dysmorphic features or congenital abnormalities likely to affect life expectancy or neurologic development; 425 were unlikely to be available for long-term follow-up; 277 had been previously treated with a methylxanthine; and 33 were excluded for unknown reasons). Of the remaining 4125 eligible infants, 2309 were not randomized (1628 because consent was not obtained and 681 were not approached). Consequently, 2006 infants were randomized, 1006 to treatment with caffeine (1005 received assigned treatment) and 1000 to treatment with placebo (999 received assigned treatment). Randomization was computer generated assigning infants to treatment groups in a 1:1 ratio, and was stratified according to study centre and balanced in random blocks of two or four patients. A designated pharmacist at each centre not otherwise involved in the study was provided with the treatment group assignments. Only the external safety monitoring committee and selected study pharmacists had access to an infant's assigned treatment group. The 2006 randomized patients were enrolled between October 1999 and October 2004. The two treatment groups were well balanced as regards both infant and maternal characteristics. The indications for caffeine included treatment of AOP in approximately 42% of infants, prevention of apnoea in approximately 22% of infants, and facilitation of removal of endotracheal tube in approximately 36% of infants.

Infants received an intravenous loading dose of either 20 mg/kg of caffeine citrate or an equivalent volume of normal saline as soon as possible after randomized treatment group

assignment. The loading dose was followed by a daily maintenance dose of 5 mg/kg or placebo equivalent. If apnoea persisted, the daily maintenance dose could be increased to a maximum of 10 mg/kg. Maintenance doses were adjusted weekly for changes in body weight and could be given orally once an infant tolerated full enteral feeding. The drug was monitored according to clinical effect with blood caffeine concentrations not being measured. Doses of the study drug were held constant or reduced for symptoms suggestive of caffeine induced toxicity (for example, tachycardia, tachypnoea, jitteriness, tremors, unexplained seizures, vomiting) or for other clinical reasons. The study drug was discontinued permanently at the discretion of the local treating clinician. However, continued therapy with the study drug was recommended until the infant had tolerated at least five consecutive days without the use of positive airway pressure. Caffeine citrate for injection was supplied by Sabex, apart from the single US study site which used Cafcit (Roxane Laboratories). The study protocol discouraged the use of open-label methylxanthines and the use of the respiratory stimulant doxapram. Non pharmacologic therapies such as continuous positive airway pressure could be used as necessary to control apnoea.

Primary Outcome

The primary outcome was a composite of death or neurodevelopmental disability occurring before a corrected age of 18 to 21 months. Disabilities contributing to the composite endpoint were one of more of cerebral palsy, cognitive delay, hearing loss requiring amplification, and bilateral blindness. Cerebral palsy was diagnosed if the child had a non-progressive motor impairment characterized by abnormal muscle tone and decreased range or control of movement. The level of gross motor function was determined using the Gross Motor Function Classification System. This system assigns a normal level of 0 if the child is able to walk 10 steps independently at 18 months, while levels between 3 and 5 (the highest possible score) indicate progressively more serious limitations of gross motor function. Cognitive delay was defined as a Mental Development Index score of less than 85 (1 SD below the mean of 100) on the Bayley Scales of Infant Development II. The score was assumed to be less than 85 if the child could not be tested because of severe developmental delay. Audiometry was performed to assess hearing and blindness was defined as a corrected visual acuity less than 20/200. Follow-up was targeted for a corrected age of 18 months, but the protocol allowed a window of 18 to 21 months (12 to 21 months for audiometry).

A sample size of 1000 infants in each group gave the study a statistical power of 80% to detect a 25% relative reduction in the risk of death or disability due to caffeine compared with placebo. Analyses of the primary outcome and of all other dichotomous outcomes were adjusted with the use of a logistic regression model that included terms for treatment and study centre with results from smaller centres being combined. The regression coefficient associated with treatment in the fitted model gave a point estimate for the treatment effect expressed as an odds ratio with a 95% confidence interval. The quotient of the estimated coefficient and its standard error was used as a z-test statistic for the null hypothesis of no treatment effect. The mean differences between the two groups for quantitative outcomes were adjusted according to centre with the use of multiple linear regression. All p values were two-sided, but were not adjusted for multiple testing.

Secondary Outcomes

The results for the protocol specified secondary short-term outcomes were reported before the results for the primary outcome became available following a recommendation from the external monitoring committee to the steering committee. The secondary short-term outcomes occurring before first discharge home included bronchopulmonary dysplasia, ultrasonographic signs of brain injury, necrotizing enterocolitis, retinopathy of prematurity

and growth. Other outcomes occurring before the first discharge home reported in *Schmidt et al (2006)* were death and drug or surgical closure for PDA. The use of drug or surgical closure for PDA was not a protocol specified outcome. The report does not indicate whether death before discharge home was a protocol specified outcome.

Bronchopulmonary dysplasia was defined as the need for supplemental oxygen at a postmenstrual age of 36 weeks. Cranial ultrasonography was recommended between 14 and 28 days of life, and between 34 and 36 weeks of postmenstrual age if the infant was still hospitalized in the study centre at that time. Scans were read locally, and copies of the written reports were sent to the coordinating center. The following conditions were considered indicative of brain injury and were analyzed as a group: intraparenchymal echodense lesions; cystic periventricular leukomalacia; porencephalic cysts; and ventriculomegaly with or without intraventricular hemorrhage. Necrotizing enterocolitis was diagnosed during surgery, at autopsy, or by a finding of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air on radiography. Retinopathy was recorded according to the international classification system of retinopathy of prematurity. Data on retinopathy were incomplete before the first discharge home. Weight and head circumference were recorded weekly.

Results

Subjects

Of the 2006 infants enrolled between 11 October 1999 and 22 October 2004, 994 were enrolled in Canada, 58 in the United States, 520 in Australia, and 434 in Europe and Israel. Six infants (four in the caffeine group and two in the placebo group) did not meet the eligibility criteria but were included in the analysis. The median [interquartile range] postmenstrual age at which infants randomized to caffeine received their first dose was 28.1 weeks [26.2-29.3] compared with 27.7 weeks [26.4-29.1] for placebo. The median [interquartile range] postmenstrual age at which infants randomized to caffeine received their last dose was 34.4 weeks [33.0-35.9] compared with 34.7 weeks [32.9-36.1] for placebo. The median [interquartile range] duration of treatment was 37 days [24-46] for caffeine and 36 days [23-46] for placebo; $p = 0.68$. Dose reduction due to suspected caffeine toxicity occurred more frequently with caffeine (2.3%) than with placebo (1.4%); $p=0.18$. Co-interventions related to respiratory support were used, on average, 1-2 weeks longer (depending on the type of support) in the placebo group than in the caffeine group and the differences were statistically significant ($p<0.001$ for each intervention). In addition, the use of postnatal corticosteroids and doxapram was statistically significantly higher with placebo than with caffeine. Similarly, the use of open-label methylxanthines and permanent switch to these agents occurred statistically significantly more frequently with placebo than with caffeine.

Primary Outcome

Of the 1006 infants randomized to caffeine, 937 (93.1%) had adequate data for the primary outcome analysis compared with 69 without adequate data (36 with incomplete assessments, one with data on vital status only, and 32 lost to follow up). Of the 1000 infants randomized to placebo, 932 (93.2%) had adequate data for the primary outcome analysis compared with 68 without adequate data (36 with incomplete assessments, three with data on vital status only, and 30 lost to follow up). There were no data on infants lost to follow up. However, these numbers were relatively small and did not differ between treatment groups making it highly unlikely that the infants lost to follow up biased the results. The results for the composite endpoint of death or disability and the individual components are summarised below in Table 7.

The results showed that caffeine treatment was associated with a statistically significant 23% reduction in the risk of death or disability when compared with placebo (odds ratio [OR] adjusted for centre). The absolute difference between caffeine and placebo was 6%, and the number of infants needed to be treated with caffeine to prevent one event of death or disability (NNT) was 16 [95% CI: 9-56%]. The results (OR adjusted for centre) were statistically significant for the individual components of cerebral palsy and cognitive delay. There were no statistically significant differences for the individual components of death before 18 months (odds ratio adjusted for centre), severe hearing loss (OR unadjusted for centre), and bilateral blindness (OR unadjusted for centre). The ORs for severe hearing loss and bilateral blindness were not adjusted for centre because of the small number of events.

The study included a *post-hoc* exploratory analysis using step-wise logistic regression of variables which might explain the effect of caffeine on the rate of survival without neurodevelopmental disability. Six variables were included in the regression model: postmenstrual age at which positive airway pressure through an endotracheal tube was last administered; postmenstrual age at which any positive pressure was administered; postmenstrual age at which oxygen therapy was last administered; postnatal use of corticosteroids; surgical closure of a PDA; and bronchopulmonary dysplasia. All six variables grouped together explained 55% of the observed benefit of caffeine therapy on the primary composite outcome at 18 months. Each of the individual variables (apart from surgical closure of PDA) explained between approximately 20% to 50% of the effect of caffeine on the composite outcome. As the variables are correlated the total variability accounted for by the six variables (55%) on the primary outcome is less than the total of their individual variabilities. The most important individual variable was postmenstrual age at which positive airway pressure was last administered which explained about 49% of the beneficial effect of caffeine on the primary composite outcome. On average, infants in the caffeine group were treated with positive airway pressure for about one week less than infants in the placebo group.

Table 7: Schmidt et al (2007) – Primary outcome of death or disability at a corrected age of 18 to 21 months.

Outcome	Caffeine Group no./total no. (%)	Placebo Group no./total no. (%)	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value	Odds Ratio Adjusted for Center and Patient Characteristics (95% CI) ^a
Composite						
Death or disability	377/937 (40.2)	431/932 (46.2)	0.78	0.77 (0.64–0.93)	0.008	0.79 (0.65–0.96)
Components						
Death before 18 mo [†]	62/974 (6.4)	63/970 (6.5)	0.98	0.97 (0.67–1.40)	0.87	0.99 (0.65–1.50)
Cerebral palsy [‡]	40/909 (4.4)	66/901 (7.3)	0.58	0.58 (0.39–0.87)	0.009	0.59 (0.39–0.89)
Cognitive delay [§]	293/867 (33.8)	329/858 (38.3)	0.82	0.81 (0.66–0.99)	0.04	0.83 (0.67–1.02)
Severe hearing loss [¶]	17/909 (1.9)	22/905 (2.4)	0.77	0.77 (0.40–1.45)	0.41	0.81 (0.43–1.55)
Bilateral blindness [‡]	6/911 (0.7)	8/905 (0.9)	0.74	0.74 (0.26–2.15)	0.58	0.79 (0.27–2.31)

* The odds ratio has been adjusted for the gestational age and sex of the infant, the mother's education at the time of the assessment, antenatal administration of corticosteroids, and multiple birth.

[†] This outcome is for children whose vital status was known at a corrected age of 18 months.

[‡] Data for this outcome exclude children who died before the scheduled tests and those who were alive but were not tested.

[§] Cognitive delay was defined as a Mental Development Index score of less than 85.

[¶] These data are for children who underwent audiometry (810 in the caffeine group and 805 in the placebo group) and for those who did not undergo audiometry but who had no indication of severe hearing loss during the clinical examination and the Bayley Test (99 in the caffeine group and 100 in the placebo group).

[|] The odds ratio for this outcome was not adjusted for center because there were too few events.

Secondary Outcomes

The secondary outcomes in the randomized infants (n=2006) are summarised below in Table 8 [Schmidt et al., 2006]. The results showed that caffeine treatment statistically significantly reduced the risk of bronchodysplasia before first discharge home by 37% compared with placebo (OR adjusted for centre). The absolute difference between treatments in the bronchodysplasia rate was 10.6%. The differences between treatments for all other protocol specified outcomes were statistically non-significant. The differences between both drug and surgical treatments for PDA were statistically significantly lower in the caffeine group compared with placebo. However, the study report indicated that treatment for PDA was not a protocol specified secondary outcome. Weight gain was lower in the caffeine group than in the placebo group over the first 3 weeks following randomization, but by the end of the fourth week weight change between groups was no longer significantly different. The mean difference [95%CI] in weight gain (g) after 1, 2, and 3 weeks after randomization was: -16 [-25, -7], p<0.001; -23 [-32, -13] p<0.001; -13 [-25, -0.4], p=0.04; respectively.

Table 8: Schmidt et al (2006) - Outcomes before the first discharge home.

Outcome	Caffeine Group (N=1006)	Placebo Group (N=1000)	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value	Odds Ratio Adjusted for Center and Patient Characteristics (95% CI) [†]
Death — no. (%)	52 (5.2)	55 (5.5)	0.94	0.93 (0.63–1.38)	0.73	0.96 (0.64–1.44)
Bronchopulmonary dysplasia — no. (%) [‡]	350 (36.3)	447 (46.9)	0.65	0.63 (0.52–0.76)	<0.001	0.64 (0.52–0.78)
Retinopathy of prematurity — no. (%) [§]	322 (39.2)	362 (43.2)	0.84	0.84 (0.68–1.03)	0.09	0.88 (0.70–1.10)
Brain injury — no. (%) [¶]	126 (13.0)	138 (14.3)	0.90	0.90 (0.69–1.18)	0.44	0.97 (0.74–1.28)
Necrotizing enterocolitis — no. (%)	63 (6.3)	67 (6.7)	0.93	0.93 (0.65–1.33)	0.63	0.94 (0.65–1.34)
Drug therapy only for closure of patent ductus arteriosus — no. (%) ^{**}	293 (29.3)	381 (38.1)	0.67	0.67 (0.55–0.81)	<0.001	0.67 (0.54–0.82)
Surgical closure of patent ductus arteriosus — no. (%) ^{**}	45 (4.5)	126 (12.6)	0.33	0.32 (0.22–0.45)	<0.001	0.29 (0.20–0.43)

[‡] CI denotes confidence interval.

[†] The odds ratio has been adjusted for the gestational age and sex of the infant, as well as for the presence or absence of antenatal administration of corticosteroids, a multiple birth, and an endotracheal tube at randomization.

[‡] This outcome is for infants who were alive at a postmenstrual age of 36 weeks (963 in the caffeine group and 954 in the placebo group).

[§] This outcome is for infants who were examined for retinopathy in the 35 study centers where the infants were enrolled (322 in the caffeine group and 338 in the placebo group). A total of 531 infants (53 percent) in the caffeine group and 490 infants (49 percent) in the placebo group were transferred to another hospital before their first discharge home. Data on retinal examinations performed after those transfers will be collected at the 18-month follow-up.

[¶] This outcome is for infants who underwent cranial ultrasonography at least once after randomization (967 in the caffeine group and 966 in the placebo group). In the caffeine group, 33 infants had intraparenchymal echodense lesions, 24 had cystic periventricular leukomalacia, 6 had a porencephalic cyst, and 93 had ventriculomegaly (with or without intraventricular hemorrhage); in the placebo group, 41 infants had intraparenchymal echodense lesions, 37 had cystic periventricular leukomalacia, 16 had porencephalic cysts, and 99 had ventriculomegaly (with or without intraventricular hemorrhage).

[|] Fourteen infants in each group received ibuprofen, and 282 in the caffeine group and 372 in the placebo group received indomethacin.

^{**} This outcome excludes infants who underwent surgical closure of a patent ductus arteriosus before randomization (five in the caffeine group and one in the placebo group).

Comment

This was a good quality study which supports the use of caffeine for the treatment of AOP, the prevention of AOP, and the facilitation of endotracheal removal in infants with birth weights 500 to 1250 g. The composite primary outcome of death or survival with neurodevelopmental disability at a corrected age of 18 to 21 months was statistically significantly lower with caffeine treatment compared with placebo. The individual components of the composite primary outcome of cerebral palsy and cognitive delay occurred statistically significantly less frequently with caffeine treatment compared with placebo, while there were no statistically significant differences between treatments for the individual components of death, severe hearing loss, or bilateral blindness. The authors' comment that outcomes at 18 to 21 months may not accurately predict function later in childhood and indicate that follow-up of the study cohort to a corrected age of 5 years is in progress with detailed assessments of cognition, gross and fine motor function, vision, hearing, behavior, and general health.

The analyses of the secondary outcomes showed that the rate of bronchodysplasia (BPD) before first discharge home (a protocol specified secondary outcome) was statistically significantly lower with caffeine treatment compared with placebo. The study used a clinically based definition of BPD (the need for supplemental oxygen at a postmenstrual age of 36 weeks) which is a surrogate measure of future poor pulmonary or neurological outcomes. It has been estimated that the accuracy of BPD as a predictor of poor pulmonary or neurologic outcomes at 18 months of age in preterm infants with birth weights between 500

and 999 g is 63% for both outcomes [Davis et al., 2002].⁸⁰ The differences between treatments for the other secondary outcomes of retinopathy of prematurity, brain injury and necrotizing enterocolitis were statistically non-significant. Weight gain was statistically significantly lower in the first three weeks after randomization in the caffeine group compared with placebo, but mean head circumferences were stated to have remained similar over the 6 week initial observation period. It is possible that the lower rate of weight gain over the first three weeks following randomization in the caffeine group might reflect higher oxygen consumption and metabolic rate due to the drug [Bauer et al., 2001].⁴⁹ However, by corrected age of 18-21 months there were no significant differences between treatment groups in height, weight, or head circumference. There were no outcomes assessing the effect of caffeine on the number and duration of apnoeic episodes or on episodes of hypoxaemia or bradycardia. The authors state that data on the frequency and severity of apnoea was not collected from nurses' charts "because such records have been shown to be inaccurate". In addition, the authors state that "there is no agreement about the change in oxygen saturation or the severity of bradycardia that represents prognostically important apnoea".

Infants in the caffeine group received their first and last dose at a median postmenstrual age [interquartile range] of 28.1 weeks [26.6-29.3] and 34.4 weeks [33.0-35.9], respectively. The median [interquartile range] duration of caffeine treatment was 37 days [24 to 36]. The study drug could be discontinued permanently at the discretion of the local clinicians. However, it was recommended that therapy with the study drug continue until the infant had tolerated at least five consecutive days without the use of positive airways pressure. There are no data on whether this recommendation was adhered to. The study analyzed the study population as a group rather than as individual subgroups. This has important implications for the proposed indication as the study is considered pivotal as regards approval for registration. Similarly, the duration of treatment used in this study is also considered to be directly relevant to the approved dosage and administration recommendations.

The main limitation of the study was lack of individual detail on the three treated subgroups in the study population (that is, treated for AOP; treated to prevent AOP; and treated to facilitate extubation). No information was provided on the definition of AOP or on the criteria for initiating preventive treatment or on the time between treatment and extubation. The decision to enrol an infant in the study depended on local clinicians at individual study centres. Consequently, it is likely that different criteria for each of the treated subgroups were applied depending on clinical practice followed at the study centres. No information was provided on differences in outcome or treatment duration for each of the three treated subgroups. It is possible that outcomes and treatment duration differ depending on the reason for treatment. There are also no data on the possible effect of differences in age at the time of starting treatment and outcomes. The median age of the infants in both treatment groups was 3 days and the study enrolled infants in the first 10 days of life. It is possible that outcomes might differ in infants first treated at ≤ 3 days or > 3 days.

Supportive placebo-controlled study

Erenberg et al., 2000

This is considered to be the primary supportive clinical efficacy and safety study. Its aim was to evaluate the efficacy and safety of caffeine citrate for the treatment of AOP.⁴⁵ It was

⁸⁰ Davis PG et al. Evaluating old definitions for the new bronchodysplasia. *J Pediatr.* 2002; 140: 555-60.

undertaken in the USA in nine neonatal intensive care units. The protocol was approved by the investigational review board at each participating centre and written consent was obtained from parents or legal guardians. The study appears to have been sponsored by Roxane Laboratories as part of its submission to the FDA to register Cafcit (caffeine citrate) for the treatment of AOP. The full study report appears to have been provided to the FDA rather than the published paper as FDA approval occurred before the *Erenberg et al., 2000* paper.

Methods

The study was randomized, double-blind, and placebo-controlled in design with an open-label, caffeine rescue arm. Preterm infants of 28-32 weeks post-conceptional age and more than 24 hours postgestational age who had six or more apnoea episodes (> 20 seconds duration) in a 24-hour period were eligible for enrollment. All infants were hospitalized in the neonatal intensive care unit at each centre throughout the study. Infants were excluded if apnoea was due to CNS disorders, primary lung disease, generalized disturbances (hemoglobin < 10 g/dL, untreated sepsis, untreated shock), metabolic disturbances, cardiovascular abnormalities, abnormal temperature, and obstructive apnoea. Infants were also excluded if blood urea nitrogen was more than 20 mg/dL, serum creatinine was above 1.5 mg/dL, and, after the first 48 hours of life, urine output was less than 1 mL/kg/hour; serum aspartate transaminase (AST) or alanine transaminase (ALT) was more than 3 times the upper limit of normal; mechanically assisted ventilation was required; methylxanthines had been given within 7 days before enrollment or treatment with histamine H₂ antagonists for regurgitation within 7 days before enrollment had been given; treatment with CNS active drugs was being given at the time of enrollment; or effects of CNS active drugs were present at the time of enrollment. The study also included a PK component.

A total of 87 infants randomized to treatment using computer generated random numbers in blocks of six. Of these 87 infants, 46 were randomized to caffeine (1 withdrawn due to < 6 apnoea episodes during baseline observations) and 41 to placebo (2 withdrawn because they did not receive the study drug, 2 withdrawn due to < 6 apnoea episodes during baseline observations). The population for efficacy analysis included 82 infants, 45 treated with caffeine and 37 with placebo. The two treatment groups were reasonably well balanced. Infants randomized to caffeine received a loading dose of caffeine citrate 20 mg/kg IV over 30 minutes with a syringe infusion pump. Infants randomized to placebo received a solution indistinguishable in appearance and containing the same excipients (citric acid/sodium citrate) as in the caffeine citrate solution. Approximately 24 hours after the loading dose, a daily maintenance dose of caffeine citrate 5 mg/kg or equal volume of placebo was administered intravenously over 10 minutes or orally through an orogastric or nasogastric tube. Initially, double-blind treatment was continued for up to 10 days, but the protocol was amended to allow up to 12 days of double-blind treatment. However, as only four infants received more than 10 days of treatment the 10 day results rather than the 12 day results were analysed for efficacy. Infants failing double-blind therapy after day 1 and before day 8 were eligible to be "rescued" with open-label caffeine citrate. All infants transferred to open-label "rescue" received an additional loading dose of caffeine citrate 20 mg/kg followed by a daily maintenance dose of caffeine citrate 6 mg/kg IV or orally and given until double-blind treatment would have been completed (that is, up to 12 days). The active and placebo products were prepared by Ben Venue Laboratories, Bedford, OH, USA.

Outcome

Apnea was defined as cessation of breathing for an interval > 20 seconds. Successful treatment was defined as at least a 50% reduction in apnoeic episodes. Infants with at least a 50% reduction in apnoeic episodes included those with elimination of apnoea. Successful treatment was summarized as number (%) of infants who were successes on each study day, and number of days (0-10) that an infant was classified as a success. Infants were withdrawn from the study if mechanical ventilation or continuous positive airway pressure was required; the number of apnoea episodes in a 24 hour period was greater than 50% of baseline events and, in the investigators' opinion, the infants would be at risk to continue; significant protocol violations or noncompliance; parents or guardians refused to allow infants to continue

treatment and/or assessments in accordance with the protocol; unacceptable toxicity; investigators decided withdrawal from the study was in the infant's best medical interests; or unrelated medical illnesses or complications arose that could cause apnoea.

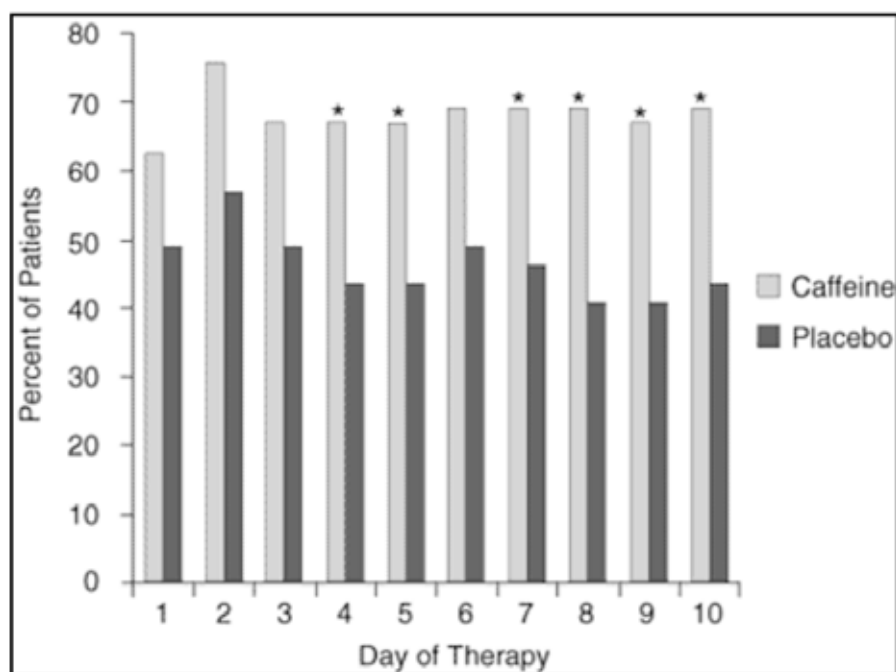
The sample size was based on the assumption that, compared with baseline, 70% or more caffeine citrate treated infants and 20% or fewer placebo treated infants would experience at least a 50% reduction in apnoeic episodes during the 24 to 48 hours after the double-blind loading dose. A significance level of 5% and a power of 95% required a total of 46 infants (23 per treatment group). The number (%) of successes and failures was analyzed by Chi-squared test for each study day. Infants who did not complete the double-blind treatment period were classified as successes or failures on the day of withdrawal and this observation was carried forward (LOCF). The number of days that infants were rated as a success or failure was analyzed by the t-test. In relation to baseline characteristics, the analysis of response was based on three ordered success categories among infants randomized to caffeine citrate: no days with zero apnoea events; 1-6 days of zero apnoea events; and at least 7 days of zero apnoea events.

Results

A greater percentage of infants treated with caffeine completed at least 10 days of double-blind therapy than placebo treated patients: 46.7% (21/45) vs 32.4% (12/37); $p=0.19$. The percentage of infants transferred to open-label caffeine was greater in the placebo group than in the caffeine group: 43.3% ($n=16$) vs 31.1% ($n=14$). The withdrawal rate from the double-blind treatment period was greater with placebo than with caffeine: 24.3% ($n=9$) vs 22.2% ($n=10$). The most frequent reason for withdrawal from the double-blind period for both treatments was recurrence of apnoea and this occurred more frequently with placebo than with caffeine: 16.2% ($n=5$) vs 11.1% ($n=5$).

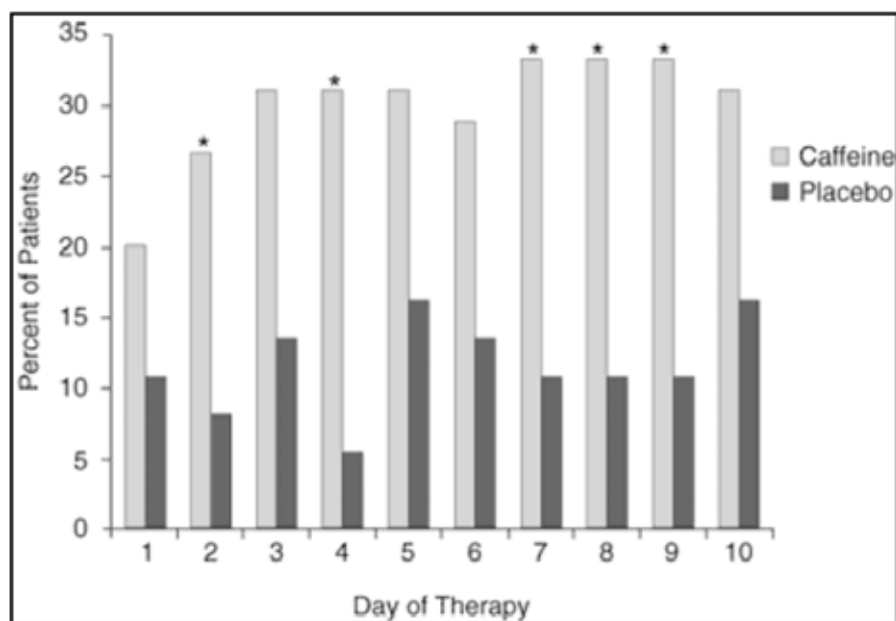
The $\geq 50\%$ reduction rate in apnoea episodes for an aggregate of 7 to 10 days treatment was statistically significantly higher in caffeine treated infants compared with placebo: 68.9% vs 43.2%; $p=0.02$. Similarly, the incidence of no apnoea for an aggregate of 7 to 10 days treatment was statistically significantly higher in caffeine treated infants compared with placebo: 24.4% vs 0%; $p=0.005$. The percentage of infants with at least a 50% reduction in apnoea events was statistically significantly greater ($p<0.05$) with caffeine compared with placebo on days 4, 5, 7, 8, 9, and 10 of treatment (Figure 2). The percentage of infants with elimination of apnoea was statistically significantly greater ($p<0.05$) with caffeine compared with placebo on days 2, 4, 7, 8, and 9 (Figure 3). No statistical association was found between response to therapy and gestational age, post-conceptual age, number of baseline apnoea events, gender, race, or weight at study entry.

Figure 2: Erenberg et al (2000) - The percentage of infants with at least a 50% reduction in apnoea events on each of the respective double-blinded phase study days.



* = statistical significance ($p < 0.05$) between groups on days 4, 5, 7, 8, 9, and 10.

Figure 3: Erenberg et al (2000) - The percentage of infants with elimination of apnoea events on each of the respective double-blinded phase study days.



* = statistical significance ($p < 0.05$) between groups on days 2, 4, 7, 8, and 9.TT

Follow-up information was obtained for 20 infants randomized to caffeine citrate and 10 randomized to placebo who had a 50% or greater reduction in the number of apnoea events on completion of 10 days of double-blind therapy. Of these infants, 11(55%) and four (40%), respectively, continued to have apnoea episodes but did not receive further treatment, while 4 (20%) and one (10%), respectively, had no further apnoea episodes. Six infants continued to receive caffeine citrate, four (20%) and two (20%) from the caffeine citrate and placebo

groups, respectively. One infant (5%) from each group received theophylline. Follow-up data were not available for five infants (25%) in the caffeine citrate group and two (20%) in the placebo group.

The PK component of the study showed that in the double-blind and open-label phases of the study 90% of 284 samples from 43 caffeine treated infants had plasma caffeine concentrations of ≤ 20 $\mu\text{g/mL}$. The authors considered that the literature indicated that therapeutic concentrations were 8 to 20 $\mu\text{g/mL}$. However, the authors found no association between mean plasma concentration and success. No samples were above a level of 50 $\mu\text{g/mL}$, which the authors state have been reported with serious toxicity

Comment

This small study provided satisfactory supportive evidence for the efficacy of short-term (10 day) treatment with caffeine for the reduction of apnoea episodes in infants with AOP. However, the placebo response rate for infants with a $\geq 50\%$ reduction in apnoea episodes from baseline for an aggregate of 7 to 10 days treatment was high (43.2%), although statistically significantly lower than for placebo. The reason for this is high placebo response is unknown. The number (%) of withdrawals in the double-blind treatment for both treatment groups was also high for such a short-term study.

Comparative Studies (Caffeine vs Theophylline)

Brouard et al., 1985

This small, randomized, open-label, French study (n=16) compared the effects of caffeine citrate and aminophylline on the number of severe apnoeic attacks on days 1 and 5 in a 24 hour recording period relative to baseline in preterm infants with apnoea (AOP) with a mean gestational age of 30.5 weeks.⁷⁶ Severe apnoeic attacks were defined as cessation of breathing for more than 10 seconds, with heart rate below 80 bpm for more than 30 seconds or below 60 bpm for more than 15 seconds. In each 24 hour recording period (days 0, 1, and 5), "apnoea frequency" was defined as the average number of apnoeic attacks per 100 minutes. Caffeine citrate (n=8) was given as a loading dose of 20 mg/kg intramuscularly (IM) followed by 5 mg/kg/day orally with the aim of maintaining caffeine plasma concentration between 8 and 16 mg/mL. Theophylline (n=8) was given as a loading dose of 5.5 mg/kg IV followed by a maintenance dose of 0.8 to 2.5 mg/kg every 8 hours IV or orally and adjusted to maintain plasma theophylline concentration between 5 and 10 mg/mL. Both treatments were administered for 5 days. Compared with baseline (day 0), apnoeic attacks on both Day 1 and 5 were statistically significantly lower ($p < 0.01$ and $p < 0.001$, respectively), for both caffeine citrate and aminophylline. The Day 0 results were 1.42 ± 0.7 and 1.02 ± 0.4 apnoeic attacks per 100 minutes for caffeine and aminophylline, respectively, and the corresponding results for the two treatments on Day 1 were 0.13 ± 0.11 and 0.12 ± 0.04 , and on Day 5 were 0.07 ± 0.02 and 0.06 ± 0.02 . There were no statistically significant differences between caffeine citrate and aminophylline on Day 1 or 5. No adverse effects were observed with either caffeine or aminophylline.

Comment: This small study showed that both caffeine citrate and aminophylline reduced the frequency of apnoeic episodes to a similar extent on Day 1 and 5 of treatment in infants with AOP. The study was not blinded and included no placebo control. Therefore, no definitive conclusions regarding efficacy can be made. The authors considered that addition of a control group would have been unethical given the results of a previous study that they had undertaken which found that the spontaneous course of severe apnoeic attacks was "unfavourable" and that caffeine was able to modify such attacks. The caffeine citrate dosing regimen was similar to that being proposed for approval and the aminophylline dosing

regimen was consistent with that recommended in Australian guidelines. Dosage was adjusted to maintain plasma concentrations between pre-specified limits rather than on clinical grounds. The study is considered to provide supportive evidence for the efficacy of caffeine citrate for the treatment of AOP.

Bairam et al., 1987

This small, randomized, double-blind, French study (n=20) compared the effects of caffeine (n=10) and theophylline (n=10) on "cardiorespiratory abnormalities" in preterm infants with apnoea (AOP) (mean gestational age of approximately 30 weeks).⁷⁴ Caffeine (formulation not specified) was given as a loading dose of 10 mg/kg IV followed by a maintenance dose of 1.25 mg/kg IV every 12 hours, and theophylline (n=10) was given as a loading dose of 6 mg/kg IV followed by a maintenance dose of 2 mg/kg IV every 12 hours. Efficacy was assessed by comparing the sum of the number of cardiorespiratory abnormalities per 100 minutes recorded within a 12 hour period before treatment with those recorded on days 3 and 7 of treatment. Cardiorespiratory abnormalities were defined as apnoea lasting for ≥ 15 seconds, episodes of bradycardia of < 80 bpm, and apnoea plus bradycardia < 100 beats bpm. The results were expressed as mean \pm SE. From baseline to day 3, the number of cardiorespiratory abnormalities per 100 minutes was reduced from 0.7 ± 0.3 to 0.4 ± 0.2 with caffeine (n=8) and from 0.6 ± 0.2 to 0.2 ± 0.1 with theophylline (n=10), $p < 0.01$. On Day 7, the number of cardiorespiratory abnormalities was 0.2 ± 0.3 with caffeine and 0.3 ± 0.1 with theophylline, $p < 0.01$.

Comment: This was a reasonable study indicating that caffeine and theophylline have similar beneficial effects on "cardiorespiratory abnormalities" following short-term (7 days) treatment of AOP. However, the study had no placebo control and, consequently, no definitive conclusions can be made about efficacy. The study did not specify the caffeine formulation used. The adverse events of tachycardia, arousal and gastrointestinal intolerance occurred less frequently with caffeine than with theophylline suggesting that caffeine is better tolerated. The theophylline dosing regimen used in the study was similar to that recommended in Australian guidelines. The study is considered to provide supportive evidence for the efficacy of caffeine for the treatment of AOP.

Scanlon et al., 1991

This randomized, UK study (n=44) compared the effects of two caffeine and one theophylline dosing regimen on the number of apnoeic episodes over a 24 hour period in oxygen dependent preterm infants (< 31 weeks gestational age) with AOP.⁴ Apnea was defined as ≥ 10 attacks in 8 hours, or 4 attacks in 1 hour, in spontaneously breathing infants, or a drop in heart rate to < 40 bpm below the resting rate in infants not breathing and who required stimulation to correct the problem. Infants were randomized to one of the three dosing regimens (usually given orally or via a nasogastric tube): n=16 "standard dose" caffeine citrate 25 mg/kg loading followed by 6 mg/kg/day maintenance aimed to give a caffeine plasma concentration of 15 mg/mL [range 13-20 mg/mL]; n=14 "high dose" caffeine citrate loading 50 mg/kg followed by 12 mg/kg/day maintenance 30 mg/mL [range 26-40 mg/mL] aimed to give a plasma concentration of 30 mg/mL [range 26-40 mg/mL]; and n=14 theophylline 7.5 mg/kg loading dose followed by a maintenance dose of 3 mg/kg three times daily aimed to give plasma concentration of 15 mg/mL [range 13-30 mg/mL]. The number of apnoeic attacks fell from baseline over the 2 days following initiation of treatment with each of the three treatments with the highest reduction being seen with theophylline (~ 20 episodes) followed by "high" dose caffeine (~ 17 episodes) and "standard" caffeine (~ 12 episodes). The number of infants achieving a $> 50\%$ reduction in the number of apnoeic attacks at 8 hours was 11/14 (78.6%) for theophylline, 10/14 (71.4%) for "high" dose caffeine

and 4/16 (25%) for "standard" dose caffeine. More dosage adjustments for tachycardia were required with theophylline treatment than with caffeine treatment.

Comment: This was a reasonable study in infants with AOP. It showed that reduction in apnoeic episodes was similar at 8 hours and at 48 hours for "high" dose caffeine and theophylline dosing regimens. The total duration of treatment appeared to be 10 days. The study was not blinded nor was it placebo controlled. Therefore, no definitive conclusions can be made about efficacy. The caffeine dosing regimens used in the study were higher than those being proposed and the theophylline dosing regimen was higher than that recommended in Australian guidelines. Caffeine and theophylline doses were adjusted to maintain pre-specified plasma concentrations. Caffeine appeared to be better tolerated than theophylline. The study is considered to provide supportive evidence for the efficacy of caffeine for the treatment of AOP.

Larsen et al., 1995 [Caffeine vs Aminophylline]

This randomized, double-blind, Danish study (n=180) compared caffeine citrate (n=82) with aminophylline (n=98) for the prevention of apnoea in preterm neonates with a gestational age of ≤ 33 weeks being routinely treated for apnoea and bradycardia prophylaxis with mononasal continuous positive airway pressure (NCPAP).⁷⁵ Caffeine citrate was given as a 20.2 mg/kg IV loading dose followed by a maintenance dose of 2.5 mg/kg given IV or by gastric tube twice daily for 10 days, and aminophylline was given as a 6.2 mg/kg loading dose followed by 3.1 mg/kg IV or by gastric tube twice daily for 10 days. In 10 days of treatment, the number of apnoea episodes was similar for caffeine and aminophylline [2.5 vs 2.0; p=0.28, respectively], as was the number of bradycardia episodes [5.0 vs 4.5; p=0.15, respectively].

Comment: This was a satisfactory study. It showed that the number of episodes of both apnoea and bradycardia over a 10 day treatment period was similar for both the caffeine and aminophylline dosing regimens. The caffeine citrate regimen was similar to that being proposed and the aminophylline regimen was similar to that recommended in Australian guidelines. There was no placebo control group so no definitive conclusions can be made about the efficacy of the regimens. The authors considered that it was unethical to include a placebo group as "both aminophylline and caffeine citrate have a well documented effect on apnoea and bradycardia in neonates". The study is considered to provide supportive evidence of the efficacy of caffeine for the prevention of apnoea in preterm infants.

Dose Ranging Studies

Romagnoli et al., 1992 [Two Caffeine Dosing Regimens]

This small, randomized, Italian study compared the effectiveness of two caffeine citrate dosing regimens for prevention of apnoea in preterm neonates of gestational age < 32 weeks.⁶³ The two caffeine dosing regimens involved a loading dose of 10 mg/kg IV followed by an oral maintenance dose of either 5 mg/kg/day (n=13) continued for a mean of 18 days [range 14-21] or 2.5 mg/kg/day (n=10) continued for a mean of 15 days [range 14-16]. The study also included an "historical control" group of 14 preterm infants of similar gestational age with AOP which had not been treated pharmacologically. The study compared the effects of the two caffeine regimens on the mean \pm SD number of daily apnoeic episodes and compared these with results from the historical control. The number of apnoeic episodes was statistically significantly decreased from baseline in both caffeine groups (p<0.01). Only 5 infants in the 10/5 mg/kg group and 3 in the 10/2.5 mg/kg group had one or two daily apnoeic episodes during the first few days of life and none occurred after the fifth day of life. Following treatment none of the infants in the two caffeine citrate groups required additional

treatment. In the historical control group, all infants except 1 had three or more daily apnoeic attacks with a progressive decrease in frequency over the first nine days of life. Adverse events occurred more commonly in the high than in the low maintenance dose group. In the high maintenance dose group, 11/13 infants experienced tachycardia (> 100 bpm) and 11/13 experienced vomiting or other feeding problems with the respective numbers in the low dose maintenance group being 0/10 and 2/10. Hyperglycaemia and hypertension also occurred more frequently with high compared with low dose maintenance treatment: 5/13 vs 2/10; and 1/13 vs 0/10; respectively. No severe adverse events of nervousness, seizures, abdominal distension or renal effects were observed in either caffeine treatment group and treatment did not affect weight.

Comment: This was reasonable study. It showed that both the high and low dose maintenance regimens had similar effects on the number of apnoeic episodes in preterm infants treated with caffeine to prevent apnoea. Neither regimen was identical to that being proposed for registration, although the 10/5 mg/kg used the same maintenance dose as that being proposed. Compared with the number of apnoeic episodes occurring in a historical control group of untreated preterm infants with AOP, both caffeine dosing regimens were associated with a lower number of such episodes. The study was not blinded nor did it include a contemporaneous placebo control group. Therefore, no definitive conclusions about efficacy can be made. The inclusion of an historical control involving infants with AOP is of doubtful relevance. The use of an historical control of infants without AOP followed up to observe the number of infants in whom AOP developed without treatment would have been a more appropriate historical control. The incidence of adverse events was higher in the high compared with the low dose maintenance group. The authors state that treatment can be stopped after 14 days as the long half-life of caffeine maintains satisfactory serum levels to 20 days after which the risk of apnoea is markedly reduced. The study is considered to provide supportive evidence of the efficacy of caffeine citrate for the prevention of apnoea in preterm infants.

Steer et al., 2003 [Three Caffeine Dosing Regimens]

This randomized, double-blind, Australian study (n=127) was designed to determine if there was an optimal caffeine dosing regimen to facilitate extubation and prevent AOP in preterm infants of gestational age of < 32 weeks.⁷⁷ The three caffeine citrate loading/maintenance dosing regimens were 6/3 mg/kg (n=42), 30/15 mg/kg (n=40), and 60/30 mg/kg (n=45). Loading doses were administered over 15 minutes by IV infusion and maintenance doses were given IV or via nasogastric tube at 24 hour intervals for the next 6 days. The primary outcome was failure of extubation from mechanical ventilation defined as either: (i) an inability to extubate from mechanical ventilation within 48 hours of caffeine loading for a planned extubation; or (ii) the use of reintubation or doxapram within 7 days of commencing caffeine therapy. Failure of extubation rates were 45% (n=19), 25% (n=10), and 24% (n=11) for the respective treatment groups 6/3, 30/15, and 60/30 mg/kg; p=0.06. The secondary outcome was the median [range] number of apnoea attacks per day and the results were 1.3 [0-14], 0.4 [0-11], and 0.2 [0-13] for the respective treatment groups 6/3, 30/15, and 60/30 mg/kg; p=0.01. The median starting day for caffeine treatment was similar in the high and standard dose groups (4.0 vs 3.9 days, respectively), as was the mean duration of treatment (32.7 vs 32.8 days, respectively).

Comment: This was a good quality study. No statistically significant difference was seen in failure of extubation rates for the three treatment groups, although the failure rate was numerically higher in the lowest dose group. There was a statistically significant difference in the median number of apnoeic attacks per day for the three treatment groups, with more

apnoeic attacks being reported in the lowest dose group. The results of treatment were similar for the two highest dose groups and better than the lowest dose group. Tolerability was better with 30/15 mg/kg group than with 60/30 mg/kg. There was no placebo control group so no definitive conclusions can be made about the efficacy. None of the three caffeine citrate treatment regimens was similar to that being proposed for approval. The study is considered to provide supportive evidence for the efficacy of caffeine citrate to facilitate extubation in preterm infants and to prevent AOP.

Steer et al., 2004 [Two Caffeine Dosing Regimens]

This multicentred, randomized, double-blind, Australian study (n=234) compared the effectiveness of two caffeine dosing regimens for the facilitation of extubation in preterm infants of gestational age of < 30 weeks.⁷³ The two caffeine citrate loading/maintenance regimens were 80/20 mg/kg (high dose) (n=113) and 20/5 mg/kg (standard dose) (n=121). Loading doses were administered over 15 minutes by IV infusion and maintenance doses were also given by IV infusion over 15 minutes for the duration of caffeine administration. The primary outcome measure was failure of extubation from mechanical ventilation, defined as either: (i) an inability to extubate from mechanical ventilation within 48 hours of caffeine loading for planned extubation (decision by treating neonatologist not to attempt extubation based on the clinical condition of the infant) or (ii) the use of reintubation or doxapram within 7 days of caffeine loading. Failure of extubation rates were 15% (n=17) for the 80/20 mg/kg dosing regimen and 29.8% (n=36) for the 20/5 mg/kg dosing regimen; RR=0.51 [95% CI: 0.31-0.51], p<0.01. There was also a significant decrease in the median [range] in the number of episodes of apnoea (secondary outcome) within 7 days of the start of treatment in the high dose compared with the low dose treatment regimen (4 [0-92] vs 7 [0-56], respectively, p<0.01). The short-term adverse effects suggest that the standard dose group is better tolerated than the high dose group.

Comment: This was a good quality study. It showed that high dose regimen (80/20 mg/kg) was more effective than standard dose regimen (20/5 mg/kg) in facilitating extubation in preterm infants, while the standard dose regimen was marginally better tolerated. The study included no placebo control group so no definitive conclusions can be made about the efficacy of the two treatment regimens. The study is considered to provide supportive evidence for the efficacy of caffeine citrate to facilitate extubation in preterm infants and to prevent AOP.

Safety

Safety data from each placebo-controlled, comparative caffeine versus theophylline or aminophylline, and dose ranging study have been considered separately. No integrated safety summary was provided, but this is not unusual given that the submission was literature based. Caffeine was generally well tolerated in all studies and the studies give rise to no significant safety concerns relating to the use of the drug in preterm infants. The adverse effects of caffeine were largely predictable as they relate to the known pharmacological effects of the drug. There were only limited data on potential changes in haematological and biochemical parameters following caffeine treatment in preterm infants.

Placebo-Controlled Studies

The primary and secondary outcomes in the pivotal study, *Schmidt et al (2006 & 2007)*, are essentially safety outcomes.^{3,44} The caffeine citrate dosing regimen used in this study was identical to that proposed for approval. Infants in the caffeine group received their first dose at a median postmenstrual age of about 28 weeks and their last dose at a median postmenstrual age of about 35 weeks. The median [interquartile range] duration of caffeine

treatment (n=1006) was 37 days [24 to 36] compared with 36 days [23 to 46] for placebo (n=1006); p=0.68. In the caffeine group, 23 (2.2%) infants had the drug withheld or the dose reduced because of signs and symptoms of caffeine toxicity compared with 14 (1.4%) infants in the placebo group; p=0.18. The primary composite outcome of death or survival with neurodevelopmental disability at a corrected age of 18 to 21 months was 40.2% in the caffeine group (377/937) and 46.2% in the placebo group (431/932); p =0.008. Of the five individual components or the primary outcome, both cerebral palsy (4.4% vs 7.3%, p=0.009) and cognitive delay (33.8% vs 38.3%, p=0.04) were statistically significantly lower with caffeine compared with placebo. While the incidence of each of the remaining three individual components (death before 18 months, severe hearing loss, bilateral blindness) of the primary outcome was lower with caffeine compared with placebo the differences were statistically non-significant. The incidences of the short-term secondary outcomes occurring before discharge home were all lower with caffeine (n=1006) than with placebo (n=1000). However, only the incidence of bronchodysplasia (defined by the use of supplemental oxygen at a postmenstrual of age of 36 weeks) was statistically significantly lower with caffeine compared with placebo (36.3% vs 46.9% p <0.001). The short-term outcomes for which the differences between treatments were statistically non-significant were death, retinopathy of prematurity, brain injury, and necrotizing enterocolitis. Overall, the pivotal study gives rise to no significant short or long-term serious safety concerns associated with caffeine treatment.

In the supportive efficacy and safety study safety analyses were conducted in 85 infants of post-conceptual age 28 to 33 weeks, of whom 46 received caffeine citrate and 39 placebo [Erenberg et al., 2000].⁴⁵ The caffeine citrate dosing regimen used in this study was identical to that proposed for approval. In this study, over 90% of the infants treated with caffeine had serum caffeine concentrations of 20 µg/mL or lower and none had concentrations greater than 50 µg/mL. Caffeine and placebo were compared after 10 days of double-blind treatment. Of the 45 infants randomized to double-blind treatment with caffeine, 21 (46.7%) completed at least 10 days of double-blind treatment, 14 (31.1%) transferred to open-label caffeine, and 10 (22.2%) withdrew from double blind treatment (2 [4.4%] due to an adverse effect (AE); 5 [11.1%] due to recurrence of apnoea; two [4.4%] at the investigator discretion; and one [2.2%] transferred to referring hospital). Of the 37 infants randomized to double-blind treatment with placebo, 12 (32.4%) completed at least 10 days of double-blind treatment, 16 (43.3%) transferred to open-label caffeine, and nine (24.3%) withdrew from double-blind treatment (one [2.2%] due to an AE; six [16.2%] due to recurrence of apnoea; and two [5.4%] at the investigator discretion). During the double-blind and open-label treatment phases, it was stated that no clinically significant differences were found between groups as regards vital signs, body weight, or laboratory tests. However, the numerical results for vital signs, laboratory tests, and body weight were not included in the study report. No clinically significant differences were seen in number and percentage of adverse events between groups during double-blind and open-label treatment (Table 9).

Table 9: Erenberg et al (2000) – Most frequently occurring adverse events in the double-blind and open-label phases.

Adverse Event	Caffeine citrate (n=46)	Placebo (n=39)
Constipation	17.4%	20.5%
Injection site reaction	8.7%	12.8%
Perinatal disorder (trace aspirates, feeding intolerance)	8.7%	5.1%
Rash	8.7%	7.7%

Necrotizing enterocolitis	8.7%	5.1%
Anemia	6.5%	17.9%
Gastrointestinal disorder (gastroesophageal reflux, dilated loops of bowel)	4.3%	7.7%
Hyponatraemia	0	5.1%

The number of infants discontinuing in the double-blind treatment phase due to adverse events was similar in the two treatment groups: two (4.4%) in the caffeine group (one for dyspnoea; one for septicemia); and one (2.7%) in the placebo group was for necrotizing enterocolitis. Necrotizing enterocolitis occurred in 4 (8.7%) infants treated with caffeine and 2 (5.1%) with placebo. This adverse event was considered to be possibly related to caffeine treatment in one infant and unrelated in the three others. Three deaths due to necrotizing enterocolitis occurred within 30 days of discontinuation of the study drug with none of the deaths being attributed to caffeine. Two of the deaths were in infants in the double-blind caffeine group, and one was in infant originally in the double-blind placebo group transferred to open-label caffeine on the same day that surgery was required for an ileal perforation. Overall, this study showed that caffeine citrate at the proposed dose was generally well tolerated and that the adverse event profile did not significantly differ from that of placebo.

Dose Ranging Studies

In *Steer et al (2004)*, a high dose caffeine citrate treatment regimen (80/20 mg/kg [n=113]) was compared with a standard dose treatment regimen (20/5 mg/kg [n=121]) to facilitate extubation in preterm infants less than 30 weeks gestation ventilated for more than 48 hours.⁷³ The median treatment starting time and mean duration of treatment were 4.0 and 32.7 days, respectively, in the high dose group and 3.9 and 32.8 days, respectively, in the standard dose group. Tachycardia (>200 bpm) occurred more frequently in the high dose group compared with the standard dose group (4% vs 1%) as did caffeine being withheld due to tachycardia (3% vs 0%). The incidence of jitteriness was identical in both groups (2%) and no infants had their caffeine dose reduced due to jitteriness. Caffeine was withheld more frequently in the high dose compared with the standard dose group (8% vs 4%, p=0.24). The results for adverse events are summarised below in Table 10.

Table 10: Steer al (2004) – Adverse events.

	20 mg/kg (n=113)	5 mg/kg (n=121)	p Value
Tachycardia	4	1	
Caffeine withheld	3	0	
Jitteriness	2	2	
Caffeine withheld	0	0	
Total in whom caffeine was withheld*	9 (8)	5 (4)	0.24
Feed intolerance*	40 (35)	37 (31)	0.44
Total parenteral nutrition (days)†	14.3 (8.26)	15.5 (10.8)	0.80
Weight gain (g/kg/day)‡	12.2 (6.5–15.2)	12.6 (9.2–15.2)	0.35
Time to regain birthweight (days)††	14.8 (5.3)	12.9 (5.0)	<0.01

*Values are number (%).
†Values are mean (SD).
‡Values are median (interquartile range).
††Data available for 116 infants in the 5 mg/kg group, and 110 infants in the 20 mg/kg group.

There were no significant differences between the high and standard dose groups in major morbidity and death before hospital discharge (Table 11).

Table 11: Steer et al (2004) – Major morbidity and death.

	20 mg/kg (n=113)	5 mg/kg (n=121)	RR (95% CI)	p Value
Proven infection	52 (46)	60 (50)	0.93 (0.71 to 1.21)	0.59
Necrotising enterocolitis	0	5 (4)		
Intraventricular haemorrhage				
Data available	n=112	n=121		
Total	33 (30)	34 (28)	1.04 (0.68, 1.58)	0.86
Grades 3 or 4	5	1		0.11
Major cerebral abnormalities at 6 weeks of age*	7 (7)	10 (11)	0.64 (0.26 to 1.61)	0.34
Data available	n=97	n=89		
Retinopathy of prematurity	21 (23)	34 (33)	0.68 (0.43 to 1.09)	0.11
Stage 3 and 4	3	8	0.42 (0.11 to 1.52)	0.22
Data available	n=92	n=102		
Pulmonary air leak	5 (4)	7 (6)	0.77 (0.25 to 2.34)	0.64
Chronic lung disease				
Chronic lung disease, 28 days†	64 (66)	80 (74)	0.89 (0.74 to 1.07)	0.22
Data available	n=97	n=108		
Chronic lung disease, 36 weeks‡	33 (34)	51 (48)	0.72 (0.51 to 1.01)	0.06
Data available	n=96	n=107		
Death before hospital discharge	5 (4)	7 (6)	0.77 (0.25 to 2.34)	0.64

Values are number (%).

*Major cerebral abnormality at 6 weeks defined as one or more of the following: cerebral cystic formation (parencephalic cysts or periventricular leucomalacia or encephaloclastic porencephaly) or hydrocephalus.

†Oxygen requirement at 28 days of postmenstrual age in survivors at hospital discharge. ‡Oxygen requirement at 36 weeks of postmenstrual age in survivors at hospital discharge.

The results for neurological assessment at corrected age of 12 months for the high (n=80) and standard (n=78) dose groups are summarised below in Table 12. The General Quotient (Revised Griffith developmental scale) was non-significantly higher in the high dose group (p=0.08), while death or disability were non-significantly lower in the high dose group (p=0.08) as was major disability (p=0.05). Overall, developmental assessment at a corrected age of 12 months favoured the high over the standard dose treatment regimen. However, the number of patients lost to follow up at corrected age of 12 months (26%) was high and, consequently, the difference in developmental assessment between the high and standard dose regimens should be interpreted cautiously.

Table 12: Steer et al (2004) – Outcomes at 12 months corrected for prematurity (mean±SD).

	20 mg/kg (n=87)	5 mg/kg (n=78)	RR [95% CI]	p value
Development assessment	n=80	n=78		
General Quotient (GQ) *	96.6±13.2	92.2±17.3 **		0.08
Major Disability	6	4	0.42 [0.17, 1.05]	0.05
Death up to 12 months of age	7	8		
Death or Disability	13	22	0.58 [0.32, 1.08]	0.08

Major disability defined as one or more of cerebral palsy, bilateral blindness, nearing for hearing aids, GQ < 75.

* Revised Griffiths developmental scale. ** Two infants for whom testing was not possible were excluded.

In *Steer et al (2003)*, the effects of three caffeine dosing regimens were compared for facilitation of extubation in preterm infants less than 31 weeks of age expected to be

ventilated for at least 48 hours.⁷⁷ Infants were randomized to one of three dosing regimens 24 hours prior to a planned extubation or within 6 hours of an unplanned extubation. The three dosing regimens were 6/3 mg/kg (n=42), 30/15 mg/kg (n=40) and 60/30 mg/kg (n=45) and the duration of therapy was 7 days after which routine management for apnoea was commenced as required. None of the three regimens was identical to that being proposed. Tachycardia (>200 bpm) occurred more frequently in the high (17.8%, n=5) than in the middle (12.5%, n=8) or low (2.4%, n=1) dose groups (p=0.07), but only one patient (middle dose group) had caffeine withheld due to tachycardia. Jitteriness occurred infrequently with only two infants being reported with these adverse events (one in each of the middle and low dose groups). Feed intolerance was reported more frequently in the high (47%), than in the middle (35%) or low (31%) dose groups; p=0.29. In all three groups weight decreased but to a lesser extent in the low compared to the two other dose groups; p=0.09. Sepsis occurred more frequently in the low (19.0%, n=8) than in the middle (12.5%, n=5) or the high (15.5%, n=7) dose groups, but the difference was statistically non-significant. Intraventricular haemorrhage (grade 3 or 4) occurred only in the high dose group (4.4%, n=2). Necrotising enterocolitis occurred only in the middle dose group (5%, n=2). Overall, this study showed caffeine to be well tolerated in the short-term with each of the three dosing regimens.

In *Romagnoli et al (1992)*, two caffeine citrate dosing regimens were compared for the prevention of AOP.⁶³ The two regimens were 10/5 mg/kg (n=13) and 10/2.5 mg (n=10) and the mean±SD [range] of treatment duration was 18.4±3 days [4-21] and 15.1±1 days [14-16], respectively. Neither of these two regimens was identical to the one being proposed for approval. Tachycardia (> 180 bpm) occurred significantly more frequently with the high than the low dose regimen (84.6% [n=11] vs 0%; p<0.001). Vomiting and other feeding problems occurred more frequently with the high than the low dose regimen (84.6% [n=11] vs 20% [n=2]; NS), as did hyperglycaemia (38.5% [n=13] vs 2% [n=2]; NS) and hypertension (7.7% [n=1] vs 0%; NS). Infants in the high dose group were treated on average for three days longer than those in the low dose group which might have contributed to the more frequently observed adverse events in the high dose group. No severe adverse events such as excessive central nervous system stimulation, nervousness, seizures, abdominal distension, or adverse renal effects (particulars not provided) were observed in either group. The weight gain curve was unaffected by either dose.

Caffeine vs Other Methylxanthine Studies

In *Brouard et al (1985)*, there were no adverse events reported by Day 5 in infants with AOP treated with either caffeine citrate 20/5 mg/kg (n=8) or aminophylline 5.5 mg/kg loading dose followed by 0.8-2.5 mg/kg tds maintenance dose (n=8).⁷⁶ On Day 6 (the first day after treatment cessation) one infant who had been treated with aminophylline was reported to have experienced tachycardia (165-210 bpm) for 24 hours. No severe adverse events were observed with either treatment. In *Bairam et al (1987)*, caffeine (formulation not stated) 10 mg/kg followed by 2.5 mg/kg every 12 hours was compared with theophylline 6 mg/kg followed by 2 mg/kg every 12 hours for the treatment of AOP over a 7 day treatment period.⁷⁴ Theophylline, but not caffeine was associated with tachycardia. There were no significant differences reported between the two treatments in mean weight change, fluid load, diuresis (percent of fluid intake), plasma and urine sodium concentrations or creatinine clearance. However, no numerical values were reported for these parameters. There was a two to three fold increase in sodium excretion in both treatment groups compared with expected values, ranging from 4.8 to 5.6 mmol/kg/day for theophylline (versus expected value of 1.2 to 1.5 mmol/kg/day) and 4.5 to 5.8 mmol/kg/day for caffeine (versus expected value of 1.7 to 1.8 mmol/kg/day). Two theophylline treated infants developed necrotising enterocolitis, while no significant gastrointestinal effects were observed in caffeine treated

infants. Excitability and activity both increased in the theophylline group with only mild changes being observed in the caffeine group. No significant differences between groups were observed in arterial blood pressure or blood glucose concentrations. Overall, caffeine was better tolerated than theophylline.

In *Scanlon et al (1992)*, "standard dose" caffeine citrate (25/6 mg/kg), "higher dose" caffeine citrate (50/12 mg/kg), and theophylline (7.5 mg/kg load, 3 mg/kg tds maintenance) were administered for 10 days to infants with AOP.⁴ In the theophylline group, 5/12 (41.2%) infants required dosage adjustments or individual dose omissions on at least two occasions because of tachycardia (>195 bpm) compared with 1/24 (4.2%) infants in the "standard dose" caffeine group and no infants in the "higher dose" caffeine group. No "appreciable difference" among the three groups was observed in sodium intake, urinary sodium, or fractional sodium excretion over 10 days (no numerical results provided). No "jitteriness" or glucose intolerance was observed, and no serious adverse events attributable to the medications were seen. In *Larsen et al (1995)*, caffeine citrate 20.2 mg/kg load followed by 2.5 mg/kg bd maintenance (n=82) was compared with aminophylline 6.2 mg/kg load followed by 3.1 mg/kg bd maintenance (n=98) for 10 days for the prevention of AOP.⁷⁵ The caffeine citrate group had a lower mean heart rate on Day 3 and a smaller amount of gastric aspirate on Day 7 compared with the aminophylline group. The incidence of tachycardia (>160 bpm) was lower in the caffeine group than in the aminophylline group (17.9% [12/67] vs 41.3% [38/92]). There were no differences between the two groups in the incidence of respiratory distress syndrome or necrotising enterocolitis.

Other Studies

In *Davis et al (2000)*, theophylline for the treatment of clinically important apnoea administered to preterm infants with birth weights less than 1501 g and born between 1 October 1980 and 31 March 1982 was associated with a higher incidence of cerebral palsy at 14 years of age compared with a group of control children who had not been treated with theophylline.⁸¹ Of the 130 children assessed, 69 (53.1%) had been exposed to theophylline and 13.0% of these children had cerebral palsy which was significantly higher than the 1.6% of the 61 children who had not been exposed to theophylline (p<0.02). In this study, theophylline rather than caffeine was used to treat AOP. Concerns about a possible association between caffeine and development of cerebral palsy have been largely addressed by *Schmidt et al (2007)* which showed that cerebral palsy occurred significantly less frequently with caffeine compared with placebo in pre-term infants of corrected age 18 to 21 months (4.4% [40/909] vs 7.3% [66/901]; p=0.009).

In *Zanadro et al (1995)*, caffeine (10 mg/kg loading, 2.5 mg/kg/12h x 5 days) was associated with calciuria in 10 preterm infants with AOP.⁸² Mean calcium urinary excretion increased by about 7.5 fold after caffeine (formulation not specified) from a mean±SE value of 0.28±0.07 mmol/kg/24 hours before treatment to 2.1 mmol/kg/24 hours after treatment. This compared with an approximately 12-fold increase following theophylline (5 mg/kg loading, followed by 2.5 mg/kg/12h x 5 days). These calciuric effects were not seen in healthy,

⁸¹ Davis P.G et al. Callanan C. Methylxanthines and sensorineural outcome at 14 years in children < 1501 g birthweight. *J Paediatr Child Health* 2000; 36: 47-50.

⁸² Zanardo V et al. Methylxanthines increase renal calcium excretion in preterm infants. *Biology of the Neonate* 1995; 68: 169-174.

untreated control infants. The mean \pm SE serum creatinine also decreased significantly from baseline ($p < 0.05$) in both treatment groups: caffeine 75.8 \pm 10.6 to 50.6 \pm 3.7 $\mu\text{mol/L}$; theophylline 62.6 \pm 6.3 to 47.6 \pm 4.7 $\mu\text{mol/L}$. However, creatinine clearance increased following treatment with both drugs. There were no significant changes in serum calcium, sodium, potassium, or phosphate concentrations after treatment with either theophylline or caffeine. No diuresis or natriuresis was observed with either drug. The authors state that the calciuric effect of methylxanthines is well known in the adult population. The authors speculate on the reasons for the calciuric effect of methylxanthines in preterm infants (for example, changes in renal blood flow mediated by adenosine receptors, chelation of calcium by metabolite).

Van den Anker et al., 1992 reported a case of accidental caffeine overdose due to a pharmacy error in an infant treated for AOP.⁸³ Tachypnoea, tachycardia, compromised circulation, vomiting and convulsions were observed in association with a serum caffeine concentration of 346 mg/mL. There was rapid improvement in the infant's condition following cessation of caffeine, and at 18 months of age psychomotor development was reported to be "excellent".

Clinical Summary and Conclusions

It is considered that the pivotal study, *Schmidt et al 2006 & 2007*, has satisfactorily established the short and long-term efficacy and safety of caffeine citrate for the treatment and prevention of AOP, and to facilitate endotracheal removal in infants with a birth weight of 500 to 1250 g who were candidates for methylxanthine therapy in the first 10 days of life. In addition, it is considered that the supportive study, *Erenberg et al (2000)*, has satisfactorily established the short-term efficacy and safety of caffeine citrate for the treatment of AOP. Supportive evidence for the efficacy of caffeine is provided by the clinical studies comparing caffeine with theophylline or aminophylline, and the caffeine dose ranging studies. These studies did not include a placebo control group. The submitted clinical pharmacology studies are considered to have satisfactorily characterised the pharmacokinetics of caffeine and to provide relevant information on the cardiorespiratory effects of the drug. Overall, the submission is considered to support the registration of caffeine citrate for the treatment of AOP. However, there are several important issues relating to the indication, duration of treatment, and dosage and administration.

The pivotal efficacy and safety study is *Schmidt et al 2006 & 2007*. In this study, 40.2% ($n=377$) of the 937 caffeine treated infants had died or survived with a neurodevelopmental disability at a corrected age of 18 to 21 months (primary outcome) compared with 46.2% ($n=431$) of the 932 placebo treated infants: OR adjusted for centre = 0.77 [95% CI: 0.64-0.93], $p = 0.008$. This result indicates that the number of infants needed to be treated (NNT) with caffeine to prevent one event of death or neurodevelopmental disability is 16 [95% CI: 9-56]. In a *post-hoc* analysis, the most important explanatory variable for the difference between treatments in the primary outcome was earlier discontinuation of positive airway pressure in caffeine treated infants. On average, infants in the caffeine group receive positive airway pressure for one week less than placebo treated infants. The authors state that "ventilator induced lung injury in preterm infants promotes the development of bronchopulmonary dysplasia, which in turn is an important risk factor for neurodevelopmental disability in early childhood". However, even after accounting for six possible explanatory factors, 45% of the effect of caffeine on the primary outcome remained unexplained.

⁸³ van den Anker JN et al. Severe caffeine intoxication in a preterm neonate. *Eur J Pediatr* 1992; 151: 466-467.

Of the individual components of neurodevelopmental disability, compared with placebo caffeine statistically significantly reduced the incidence of cerebral palsy (4.4% vs 7.3%; OR adjusted for centre = 0.58 [95% CI: 0.39-0.87], $p = 0.009$), and cognitive delay (33.8% vs. 38.3%; OR adjusted for center = 0.81 [95% CI: 0.66-0.99], $p = 0.04$). However, the differences between caffeine and placebo were statistically non-significant as regards the remaining individual components of the composite primary endpoint (that is, death, severe hearing loss, bilateral blindness). Reassuringly, the differences between caffeine and placebo were statistically non-significant at a corrected age of 18-21 months as regards mean percentiles for height, weight, and head circumference. As regards the secondary short-term outcomes occurring before discharge home reported in *Schmidt et al., 2006*, bronchodysplasia was reported in 36.3% (350/1006) of caffeine treated infants compared with 46.9% (447/1000) of placebo treated infants; $p < 0.001$. However, the differences between treatments in the secondary short-term outcomes of death, brain injury, retinopathy, and necrotizing enterocolitis were statistically non-significant.

The submitted data satisfactorily established the safety of caffeine citrate at the proposed dose and at doses up to 60/30 mg/kg and 80/20 mg/kg in preterm infants. The primary and secondary outcomes in *Schmidt et al (2006 & 2007)* were fundamentally long and short-term safety outcomes which showed that treatment with caffeine was generally "safer" than treatment with placebo. Weight gain was reduced in the first three weeks of life in caffeine treated infants compared with placebo but by the end of the fourth week weight gain was similar in both treatment groups [Schmidt et al., 2006]. The safety data in the supportive study [Erenberg et al., 2000] showed that the short-term safety of caffeine was similar to that of placebo. Satisfactory clinical laboratory test data (haematological and biochemical) are limited and only *Zanadro et al (1995)* adequately reported numerical results for biochemical data. In this small ($n=10$), short-term (5 day) study caffeine increased the urinary excretion of calcium and reduced serum creatinine, but there were no significant effects on serum calcium concentration while creatinine clearance increased following treatment. In *Bairam et al (1986)* natriuresis was reported to be two-three fold higher following caffeine compared with expected values, while serum and urine sodium concentrations were unchanged as was creatinine clearance. Two other studies reported no abnormalities in laboratory tests following caffeine but no details were provided [Scanlon et al., 1992; Erenberg et al., 2000].

Extent of the Indication (Limited or Broad)

The first issue for consideration as regards the indication is whether it should be expanded to include other subgroups in addition to AOP. In *Schmidt et al 2006 & 2007*, the study population included not only infants with AOP (43%), but also infants treated to prevent AOP (23%) and to facilitate extubation (34%). Infants with a birth weight of 500 to 1250 g were eligible for enrollment if considered to be candidates for methylxanthine therapy during the first 10 days of life to "prevent apnoea, to treat apnoea, or to facilitate the removal of an endotracheal tube". The diverse study population raises the possibility that outcomes might vary depending on the subgroup. However, the study population was analyzed as a single unit and the results apply to the study population as a whole rather than to the individual subgroups. Consequently, it is considered that the study should be interpreted as supporting the study group as a whole. Therefore, it is recommended that the indications be "the treatment of apnoea of prematurity; the prevention of apnoea of prematurity; and the facilitation of endotracheal tube removal in preterm infants". *Erenberg et al (2000)*, supports short-term (10 days) treatment with caffeine of preterm infants with AOP. The three submitted Cochrane Reviews, written before publication of the results of the pivotal study, are considered to provide supportive evidence for the use of caffeine to treat AOP, and to facilitate extubation in preterm infants. In addition, the two large Australian dose-ranging

studies are considered to provide evidence supporting the use of caffeine to facilitate extubation in preterm infants and the prevention of apnoea [Steer et al., 2003; Steer et al., 2004]. Similarly, three of the caffeine versus theophylline or aminophylline comparative studies are considered to provide evidence supporting the use of caffeine for the treatment AOP [Brouard et al., 1985; Bairam et al., 1987; Scanlon et al., 1992], and one of these studies is considered to provide evidence supporting the use of caffeine for the prevention of AOP [Larsen et al., 1995].

Qualification of the Indication (Age and/or Weight)

The next issue for consideration as regards the indication is whether it should be qualified by age and/or weight. The indication proposed by the sponsor qualifies the indication (AOP) by gestational age (28 to less than 33 weeks). This age qualification appears to be primarily derived from *Erenberg et al (2000)*. However, in *Schmidt et al 2006 & 2007* enrollment was based on weight (500-1250 g) rather than gestational age. Data from the four caffeine vs theophylline/aminophylline studies indicate that mean gestational ages were about 28-31 weeks and mean birth weights were about 1200 to 1500 g. Data from the two large dose ranging studies included infants randomized to caffeine of gestational age < 30 weeks [Steer et al., 2004] and < 32 weeks [Steer et al., 2004]. Based on the totality of the submitted studies it is suggested that the indication not be qualified by specific age or weight limits. In practice, it is likely that caffeine will be used predominantly in the youngest group of preterm infants with the lowest birth weights.

Duration of Dosing (Prescriptive or Not Prescriptive)

The duration of the treatment recommended in the proposed PI is 7 to 10 days or until apnoea ceases. This treatment duration appears to be primarily based on that in the supportive study of *Erenberg et al (2000)*. Treatment duration in the four caffeine vs theophylline/aminophylline studies was also short at 5 to 10 days. In addition, treatment duration was 7 days in one of the two, large, Australian dose ranging studies [Steer et al., 2003]. However, in the other large Australian dose ranging study the mean treatment duration of both standard and high dose caffeine treatment regimens was about 33 days [Steer et al., 2004]. Furthermore, in the pivotal study *Schmidt et al (2006 & 2007)* infants treated with caffeine received their first dose at a median age of 28.1 weeks [interquartile range 26.6, 29.3] and their last dose at a median age of 34.4 weeks [interquartile range 33.0-35.9], with the median duration of treatment being 37 days [interquartile range 24-36]. In this study, treatment discontinuation was at the discretion of individual clinicians, but it was recommended that treatment be continued until the infant had tolerated at least five consecutive days without the use of positive airway pressure. There were no data on differences in treatment duration among the three subgroups included in the study population. Based on the pivotal study, it is recommended that treatment with caffeine be continued until apnoea ceases, or until treatment is considered to be no longer required. The option to stop treatment when considered to be no longer required is consistent with the procedure in the pivotal study in which treatment discontinuation was at the discretion of the clinician. The upper limit of the interquartile range of age at last dose (35.9 weeks) in the pivotal study indicates that for 25% of infants the last dose was after 35.9 weeks postmenstrual age.

Dosage and Administration Recommendations

The caffeine citrate dosing regimen used in *Schmidt et al 2006 & 2007* and *Erenberg et al 2000* is that proposed for registration (that is, 20 mg/kg IV loading followed by 5 mg/kg/day). In the pivotal study, the maintenance dose could be increased to a maximum of 10 mg/kg/day if apnoea persisted and it is suggested that this dosing option be included in the PI. Data from the two large Australian dose-ranging studies indicate that no additional

significant safety concerns are likely with this higher maintenance dose [Steer et al., 2003; Steer et al., 2004]. In the pivotal study, the maintenance dose was held or reduced for symptoms suggestive of caffeine toxicity, and it is suggested that this recommendation also be included in the proposed PI. No plasma caffeine monitoring was undertaken in the pivotal study with all dosage adjustments being made on clinical grounds.

Dose Ranging

There are no satisfactory dose ranging efficacy data in the submission. The dose ranging data in the two large Australian studies raise the possibility that a caffeine dosing regimen higher than that proposed might be more efficacious [Steer et al., 2003; Steer et al., 2004]. In *Steer et al (2004)*, extubation failure rates within 7 days from start of treatment were statistically significantly lower with a high dose regimen (80/20 mg/kg) compared with a standard dose regimen (20/5 mg/kg), while the standard dose regimen was marginally better tolerated than the high dose regimen. Similarly, in *Steer et al (2003)* extubation failure rates within 7 days from the start of treatment were lower with mid-range (30/15 mg/kg) and high dose (60/30 mg/kg) regimens than a low dose (6/3 mg/kg) regimen. However, in the absence of data from a formal dose ranging efficacy and safety study involving the recommended indications it is considered that the approved dosing regimen should be 20 mg/kg loading followed by 5 mg/kg/day maintenance.

Recommendation of the Evaluator

It was recommended that caffeine citrate be approved for the treatment of apnoea of prematurity; the prevention of apnoea of prematurity; and the facilitation of endotracheal tube removal in preterm infants.

It was recommended that the treatment regimen be a loading dose of 20 mg/kg administered by IV infusion over 30 minutes followed by a maintenance dose of 5 mg/kg daily administered IV or orally over 10 minutes. Maintenance doses should be adjusted weekly for changes in body weight.

It was recommended that there be an option to increase the maintenance dose to a maximum of 10 mg/kg daily if apnoea persists.

It was recommended that caffeine treatment be continued until apnoea ceases or until treatment is considered to be no longer required.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

All chemistry and quality control issues were resolved. Stability data support a shelf life of three years when stored below 30⁰C.

The sponsor has provided a justification for not providing bioavailability data based on the grounds that the absolute bioavailability of the oral solution is 100%. Several papers were submitted to support this; and that food (special care baby formula) did not affect the bioavailability. The justification also centred on the fact that caffeine was granted a waiver in the US FDA; 100% bioavailability is seen in the clinical studies submitted. The

Pharmaceutical Subcommittee (PSC) of ADEC stated that the submitted published papers adequately established bioavailability and showed no food effects. Overall, the quality evaluator recommended approval from a chemistry and quality control perspective

Nonclinical

The search strategy was considered restrictive and contained some errors. It was stated that caffeine citrate was primarily an adenosine receptor antagonist. In rats there was an acceleration of the development of the adenosinergic system in the brain associated with respiratory control and there was an increased respiratory response to hypercapnia. In preterm baboons there was an improvement in lung function.

CNS safety pharmacology studies were conducted in rats. Clinically equivalent levels at neonatal period resulted in affecting the neurological development in juvenile and adult stages of development. Anxiety, sensitivity to pain, activity, learning and memory were altered. Chronic treatment (up to 88 days of age) affected cardiac function and development in rats.

Caffeine is 100% bioavailable by the oral route and is widely distributed. In neonates hepatic metabolism is limited resulting in a long plasma half life (100 hours in human neonates vs 4 hours in adults).

The evaluator noted that there were no acute toxicity data submitted. Similarly, repeat dose studies (all conducted in rats) lacked sufficient detail to ascertain NOAEL.

Caffeine was not carcinogenic in a 2 year study in rats; tests for bacterial and mammalian mutagenicity and clastogenicity *in vitro* and *in vivo* returned negative results. Fertility was not affected in rats (exposed during late gestation and early postnatal period).

The evaluator recommended against registration based on the deficiencies in the nonclinical dataset. Specifically, the lack of repeat dose toxicity studies involving the IV route was identified as deficiencies. In addition the lack of well documented studies in very young animals, chronic studies in a second non-rodent species were also identified as significant deficiencies.

Clinical

Pharmacodynamic studies

There were six pharmacodynamic studies submitted and discussed. The evaluator noted conflicting results that may have partly been due to different dosing and treatment regimens in these studies. These studies examined the effects in the following systems:

Respiratory system: Three published studies using loading (up to 20mg/kg) and maintenance (10mg/kg) dose regimens in term and preterm infants did not reveal significant changes in respiratory rates or partial pressure of carbon dioxide. However, one study on 9 infants with AOP (apnoea of preterm) compared with 9 controls, showed increased oxygen consumption, increased carbon dioxide production and energy expenditure. Mean apnoeic spells also significantly reduced in the caffeine treated group.

Cardiovascular system: One study (*Hoecker et al*) on 16 infants using two loading doses (12.5mg/kg) of caffeine citrate 4 hours apart showed reduction in blood flow velocity in the internal carotid and anterior cerebral artery.⁵⁰ However, a second study (*Saliba et al*) showed no significant difference in mesenteric blood flow.⁴⁷ There were conflicting results in relation to left ventricular output, also. *Hoecker et al* also reports no difference with two loading doses of caffeine citrate in 16 infants; however, *Walther et al* found a significant increase in left ventricular output and stroke volume in 10 infants after loading and maintenance doses.⁴⁸

Similarly, there was an increased heart rate reported in one study (*Hoecker et al*) whilst the second study (*Saliba et al*) did not report an increase.

Central nervous system: One study examined 15 neurologically and clinically stable preterm infants: 10 received caffeine citrate (and 5 were controls). There was no significant difference between sleep –wake variables and transition between main and quiet sleep states. Habituation appears not to be assessed.

Pharmacokinetics

These were based on conventional studies on preterm infants given caffeine citrate and were also based on population pharmacokinetic studies. Though most studies were conducted on Caucasian neonates, the evaluator noted one good quality study on Singaporean Chinese and Malays.

Bioavailability: The oral bioavailability was estimated at 100% (in infants of gestational age 24 to 29 weeks). Food did not significantly affect C_{max} , AUC_(0-120h) indicating that oral caffeine could be administered either with or without food. The evaluator noted that Vd was consistent across several studies and was large, suggesting distribution in tissues. No information was submitted on protein binding or blood-plasma partitioning in preterm infants.

Metabolism: Caffeine is metabolised in the liver by CYP1A2. The metabolic pathways varied in the time to maturation (up to 4 months to 6 months postnatal age). The primary metabolites are paraxanthines, theobromine and theophylline. In one study on 23 infants with AOP given a loading dose (10mg/kg) followed by a maintenance dose (5mg/kg), there was an increase in theophylline concentration during maintenance treatment. The authors speculate that a higher caffeine maintenance dose might stimulate more rapid metabolism of caffeine to theophylline and to other xanthines. One study (*De Carolis et al*) examined the urine for caffeine and theophylline after loading dose (10mg/kg IV) followed by maintenance dose (2.5mg/kg/day) for 15 days in 10 infants with AOP.⁶⁴ There was a gradual increase in the total theophylline and caffeine collected in the urine over the treatment period and 24% of this was collected 24 hours after treatment. There was an elevation of caffeine and theophylline in serum after cessation and this may have the potential to cause side effects for some time after cessation of treatment.

Elimination: The published studies revealed a consistent pattern of low caffeine clearance and long elimination half-life in preterm infants. Adult values were reached at approximately 6 months of age. Half-life and clearance tended to be consistent across the studies.

No drug interaction studies were submitted despite the fact that CYP 1A2 is the major enzyme metabolising this drug. No studies on sex differences, hepatic or renal impairment was submitted. Apart from a small study (n=18) examining the pharmacokinetics in Singaporean Chinese and Malay AOP infants, no other racial groups except for Caucasians was submitted. The values were consistent with those from the Caucasian population.

Several population pharmacokinetic studies were submitted. Of note, one by *Charles et al* included 110 infants of gestational age less than 30 weeks admitted to the neonatal intensive care nursery in Mater Maternity Hospital, Brisbane.⁵³ This was a subset of 234 preterm infants, who were enrolled in a large multicentre study examining the effect of two doses of caffeine citrate in the facilitation of extubation. Inclusion criterion was 24 hours before a planned extubation or within 6 hours of an unplanned extubation. There were two treatment regimens employed 1) a high dose regimen of 80 mg/kg followed by a maintenance dose of 20mg/kg or 2) a standard regimen of 20mg/kg followed by 5mg/kg. The analyses and assumptions employed were considered acceptable by the evaluator. The median (range)

estimates for CL and Vd were 0.116 (0.0268-0.376) mL /min/kg and 851 (36-1761) mL/kg. Mean (range) elimination half-life was 101 (24.5-371) hours. Apart from weight, post natal age improved the fit for CL. This was deemed a good quality population pharmacokinetic study due to the large number of subjects and samples.

Three other population pharmacokinetic studies were discussed and CL and Vd were consistent across these studies.

Dose ranging studies: The study by *Romagnoli et al* examined two doses of caffeine- 10mg/kg IV followed by an oral dose of 5mg/kg (n=13) or 2.5mg/kg (n=10). There was a dose response seen in reduction of apnoeic spells; the numbers involved were small, however.⁶³

The second study by *Steer et al* examined three doses of caffeine citrate loading/maintenance dosing regimens: 6/3 mg/kg (n=42), 30/15 mg/kg (n=40), and 60/30mg/kg (n=45).⁷⁷ Loading doses were given IV over 15 minutes and the maintenance dose intravenously or by nasogastric tube. There was no statistical difference in response between groups in term of the primary outcome (that is, failure to extubate); however, the failure rate was numerically higher in the low dose group. Tolerability was better with the lower dose group.

The third study also by *Steer et al* was a double blind randomised multicentre study conducted in Australia on 234 preterm infants; this study examined two dosing regimens of caffeine citrate loading /maintenance regimen: 80/20mg/kg (high dose) (n=113) vs 20/5 mg/kg (standard dose), n=121.⁷³ Though the higher dose performed better in terms of the primary outcome, failure of extubation rates (15% vs 29.8%), the short term adverse events tended to suggest that the standard dosing regimen was better.

The Delegate noted that there is a lack of adequate efficacy data from dose ranging studies. The third study by Steer et al suggests that the higher dose may be more efficacious; a wider range of dosing would be required to determine the optimum dose. The loading dose appears unnecessary; it is also not known whether multiple doses over 7-10 days are necessary. These questions are not addressed in the data. The use of the initial intravenous dose (unless the infant cannot take oral fluids) is not justified.

Efficacy

The “pivotal” study, by *Schmidt et al* was a large multicentre placebo controlled double blind study conducted to assess short term and long term efficacy of caffeine therapy for the treatment of AOP in infants of weights 500 g to 1250 g requiring methyl xanthine therapy during the first 10 days of life. Indications for treatment were: prevention or treatment of apnoea and facilitation of the removal of the endotracheal tube.

2006 infants were randomised on a 1:1 basis to active and placebo treatment group. The evaluator noted that the maternal and infant characteristics were well balanced in both groups; 43% in the active treatment group and 40% in the placebo group were recruited for the treatment of apnoea. Infants received a loading dose of 20 mg/kg of caffeine citrate (or saline) intravenously; it was followed by a maintenance dose of 5 mg/ kg or placebo equivalent. The dose could be increased to 10mg/kg if apnoea persisted.

The primary outcome was a composite of death or neurodevelopmental disability occurring before a corrected age of 18 to 21 months. The evaluator noted that a sample size of 1000 infants in each group gave the study a statistical power of 80% to detect a 25% relative risk reduction in death or disability attributable to caffeine compared to placebo.

The secondary outcomes were short term end points: bronchopulmonary dysplasia, ultrasonographic signs of brain injury, necrotising enterocolitis, retinopathy of prematurity and growth.

There was a statistically significant difference favouring caffeine in terms of the reduction in death or disability at a corrected age of 18 to 21 months (Table 7). There was no statistical significance in relation to the individual components of death before 18 months, severe hearing loss or bilateral blindness. There was a statistically significant difference in terms of cerebral palsy and cognitive delay.

In terms of the secondary end points, there was a statistically significant reduction in bronchopulmonary dysplasia (before the first discharge home) in the caffeine treated group (Table 8).

The evaluator noted that the outcome at 18 months to 21 months may not accurately predict function later on in childhood. The study is being followed up to a corrected age of 5 years. There was also a lack of individual detail in the three treatment subgroups (treated for AOP; treated to prevent AOP; and treated to facilitate extubation). The efficacy outcomes for the three subgroups were not stated. This clearly is a deficiency. The evaluator noted that no details were provided on the definition of AOP, criteria used for initiating preventative treatment and time between treatment initiation and extubation.

The Delegate noted that this study examined long term outcomes as primary efficacy endpoints. Thus, this does not provide evidence of efficacy for the short term treatment of AOP, the indication that is being sought by the sponsor.

The evaluator discussed a “supportive” study (Erenberg et al).⁴⁴ This was a randomised, double blind, placebo controlled study with an open label caffeine rescue arm. The infants of 28 -32 weeks (post-conceptual age) \geq 24 hour post-gestational age with \geq 6 apnoeic episodes in a 24 hour period were eligible. Of the 87 infants recruited, 46 were randomised to caffeine and 41 to placebo. The evaluator noted that pharmacokinetic characteristics were ‘reasonably balanced’. The dosing regimen was as per the previous study. Treatment duration was 10 days. The primary outcome was a 50% reduction in apnoeic episodes. The \geq 50% reduction rate in apnoea episodes for an aggregate of 7-10 days treatment was statistically significantly greater in caffeine treated infants compared with placebo: 68.9 % vs 43.2% ($p=0.02$). The incidence of “no apnoea” also favoured caffeine.

The evaluator noted that this small study supported the findings of the previous study.

The Delegate noted that in relation to the indication sought by the sponsor, this study provides the pivotal evidence of efficacy. However, it is a small study, showing superiority of Cafnea versus placebo.

There were four comparative studies. The first two studies were small studies that used caffeine at the proposed dose comparing it with theophylline. The first study by *Brouard et al* recruited 16 infants and examined severe apnoeic attacks on Days 1 and 5 in the caffeine treated group ($n=8$) compared with theophylline ($n=8$).⁷⁶ There was no significant difference. The second study was also a small study ($n=20$) by *Bairam et al*.⁷⁴ The dose of caffeine used is different to that proposed for marketing and is of limited benefit. The third study was a larger study ($n=44$); this study used a different, higher doses of caffeine with aminophylline as the comparator. This was also considered a supportive study. The fourth study by *Larsen et al* was a large, double blind randomised study comparing caffeine citrate ($n=82$) with aminophylline ($n=98$).⁷⁵ The regimen used was similar to that proposed in Australia; aminophylline regimen was similar to that recommended in Australian guidelines. The number of apnoea episodes was similar in both groups in the 10 day period of treatment. Overall, the studies do not discuss the power calculations and whether these were non-inferiority studies. They provide supportive evidence of efficacy of caffeine in AOP.

The Delegate noted that additional evidence of efficacy is provided in the active comparator studies discussed above. Especially in the study by Larsen et al which had reasonable numbers in the caffeine and aminophylline groups, the number of apnoea episodes was similar. But no details are provided on whether this study was a non-inferiority study. In conclusion, the efficacy data are minimal and rests on the findings of the study by Erenberg et al.

Safety

There was no integrated safety summary provided; this was perhaps due to the fact that this was a literature based submission. The evaluator noted that they were mostly predictable as they related to the known pharmacological effects of caffeine. There were, however, limited data on haematological and biochemical parameters.

The primary endpoint from the *Schmidt* study was in essence a safety outcome. The primary composite outcome of death or survival with neurodevelopmental disability at corrected age of 18 to 21 months was better in the caffeine treated group. All five components of the primary outcome (cerebral palsy, cognitive delay, death before 18 months, severe hearing loss and bilateral blindness) were reported at a lower incidence in the caffeine treated group. The evaluator noted that overall, there were no short term or long term concerns identified in relation to safety.

In the supportive study (Erenberg et al) the adverse events were not significantly different from the placebo group. It was also stated in the paper that vital signs, laboratory investigations and body weight were not significantly different. However, the individual values were not given.

In relation to dose ranging studies, the high dose regimen (80/20mg/ kg) had more tachycardia (> 200 bpm) = 4% vs 1%); caffeine being withheld due to tachycardia was also higher (3% vs 0%). In the comparative studies, caffeine appeared better tolerated than theophylline.

In the active comparator studies, two studies were discussed. *Brouard et al* showed no significant difference between groups relating to mean weight, fluid load, diuresis, plasma and urine sodium concentration or creatine clearance.⁷⁷ Overall, caffeine was better tolerated. There was no significant difference between the caffeine treated group and the theophylline treated group.

Overall recommendation by the evaluator

The evaluator recommended approval for the proposed indication.

The evaluator noted that the pivotal study by *Schmidt et al* supports the short term and long term efficacy of caffeine citrate for treatment and prevention of AOP and the facilitation of endotracheal removal. Thus, the evaluator recommended that caffeine citrate be approved for the treatment of apnoea of prematurity; the prevention of apnoea of prematurity; and the facilitation of endotracheal tube removal in preterm infants.

In terms of qualifying the indication by age and/or by weight, the evaluator noted that some studies included subjects by gestational age and some studies by weight (500 – 1250 g). It is likely that in practice, to be used in the “youngest group of preterm infants with the lowest weight”.

The evaluator also recommended in the draft PI, that treatment be continued until apnoea ceases (based on the “pivotal” study). The evaluator noted that there was no satisfactory dose ranging study. There have been no formal dose ranging studies; however the pivotal study (*Schmidt et al*) supports the proposed dosing regimen.

Risk-Benefit Analysis

Short term efficacy outcomes that support the proposed indication are assessed in the study by *Erenberg et al*. The pivotal study (*Schmidt et al*) had long term morbidity endpoints at 18-

21 months. Thus the pivotal study examined long term outcomes that do not support the “short term treatment of AOP”. Of the secondary endpoints which were short term endpoints, there was a statistically significant reduction in the caffeine treated group in bronchopulmonary dysplasia. The sponsor should state in its pre-ADEC response how this endpoint bears on “treatment of AOP”.

The study by *Erenberg et al* showed a statistical reduction in apnoea over the 12 day double blind period. Thus this study provides evidence of efficacy of caffeine for short term treatment of apnoea of prematurity in infants between 28 to 33 weeks gestational age. However, the numbers are small; approximately 40 in each group.

Thus, the concern of the Delegate was that the efficacy data is minimal to support the indication. The optimal dosing regimen has not been identified. The Delegate did not agree with the evaluator’s recommendation to grant a wider indication than what has been sought. The sponsor has sought the indication “for the short term treatment of AOP”; and in the opinion of the Delegate, the study by *Erenberg et al* provides the evidence of efficacy in the short term treatment of AOP; the so called “pivotal study” does not provide the necessary efficacy endpoints to support short term treatment of AOP. In this context, to approve wider indication as recommended by the evaluator would be inappropriate.

In terms of safety, based on the published data, there were no concerns identified to preclude registration.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, agreed with the Delegate’s proposal.

The ACPM recommended approval of the submission for the indication:

For the short term treatment of apnoea of prematurity (AOP) in infants between 28 and 33 weeks gestational age

In making this recommendation the ACPM noted that although the efficacy data were few, there were a number of comparator studies that do provide further evidence of the potential role in treating AOP with Cafnea. The Committee also agreed with the Delegate in restricting the indication to that sought by the sponsor.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cafnea Injection containing caffeine citrate injection 40 mg/2 mL and Cafnea Oral Solution containing caffeine citrate oral solution 25 mg/5 mL for the indication:

for the short-term treatment of apnoea of prematurity in infants of gestational age 28 to less than 33 weeks

Attachment 1. Product Information

PRODUCT INFORMATION
Cafnea™ Injection and
Cafnea™ Oral Solution



Cafnea™ Injection
caffeine citrate injection 40 mg / 2 mL
equivalent to caffeine 20 mg / 2 mL

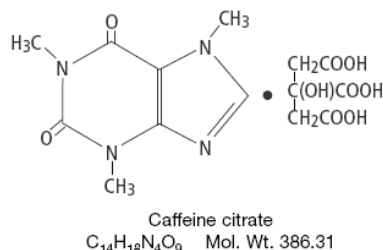
Cafnea™ Oral Solution
caffeine citrate oral solution 25 mg / 5 mL
equivalent to caffeine 12.5 mg / 5 mL

NAME OF THE MEDICINE

Caffeine Citrate

The molecular weight of the compound is 386.3 and the CAS registry number is 69-22-7. The molecular formula is $C_8H_{10}N_4O_2 \cdot C_6H_8O_7$.

Structural Formula:



DESCRIPTION

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.

CAFNEA INJECTION contains 20 mg/mL caffeine citrate (equivalent to 10 mg/mL of caffeine base). The excipients are citric acid monohydrate and sodium citrate in water for injections. It is a 2 mL solution contained in a 2 mL vial. The injection contains no preservatives.

CAFNEA ORAL SOLUTION contains 5 mg/mL caffeine citrate (equivalent to 2.5 mg/mL of caffeine base). The excipients are citric acid monohydrate and sodium citrate in water for injections. It is a 5 mL sterile solution contained in a 7 mL vial. The solution contains no preservatives.

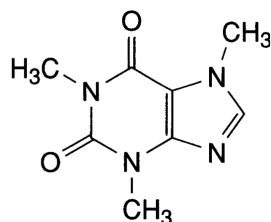
Caffeine in the presence of citric acid forms caffeine citrate in solution.

The chemical name for caffeine is 1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione.

The molecular weight of caffeine is 194.2 and the CAS registry number is 58-08-2.

The molecular formula is $C_8H_{10}N_4O_2$.

Structural Formula of caffeine:



PRODUCT INFORMATION

Cafnea™ Injection and Cafnea™ Oral Solution



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

PHARMACOLOGY

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

Pharmacodynamics

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, TcPO₂, TcPCO₂ are unchanged
- blood flow volume in the coeliac artery and superior mesenteric artery, LVO, PCO₂, do not change significantly
- caffeine increases cerebral blood flow in some studies but not in others.

Pharmacokinetics

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 regimen¹ (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 metabolized 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 catalyzes N1-, N3-, and N7- demethylation of caffeine. In addition, CYP2E1 also catalyses N1- and N7- demethylation, while CYP3A catalyses 8-hydroxylation. The N3- and N-7 metabolic pathways are not mature until a post natal age of about 4 months and explain the long half life and low clearance in infants younger than this age.

PRODUCT INFORMATION

Cafnea™ Injection and Cafnea™ Oral Solution

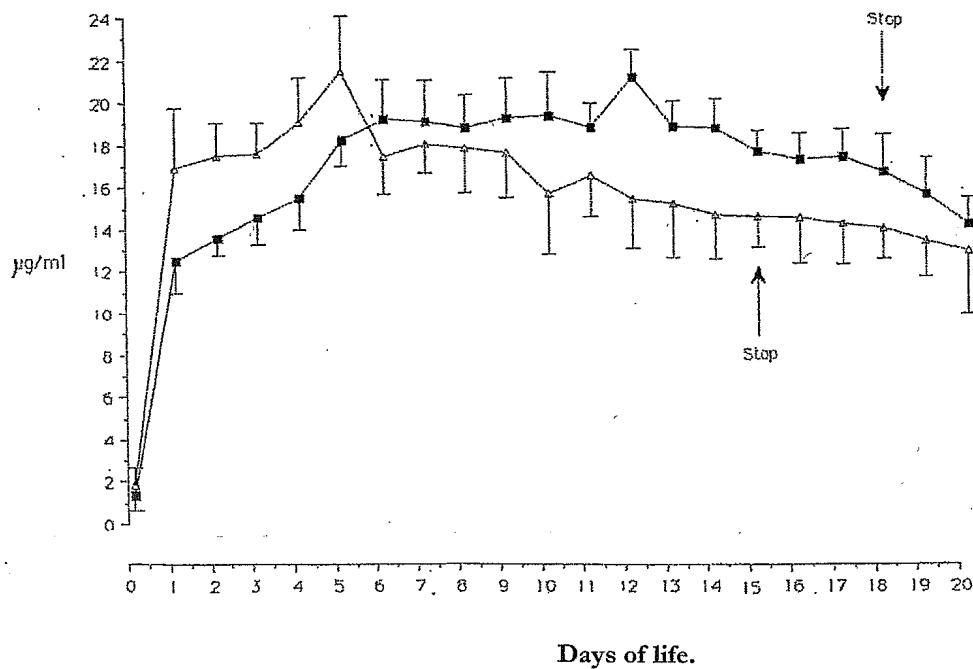


Figure 1: Mean±SD serum concentrations for caffeine following caffeine citrate 10/5 (loading/maintenance) mg/mL [■] to 13 premature neonates and caffeine citrate 10/2.5 (loading/maintenance) mg/mL [▲] to 10 premature neonates.²

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 the 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 tachycardia³.

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.

Clinical Trials

Efficacy study

The randomised double blinded placebo controlled trial by Erenberg et al⁶ 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-conceptual 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 ($p = 0.005$).

PRODUCT INFORMATION

Cafnea™ Injection and Cafnea™ Oral Solution



Safety Study

The long term safety study by Schmidt et al^{4,5} 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 1: Primary and secondary outcomes from Schmidt et al clinical study⁴

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 18mths	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 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		

INDICATIONS

CAFNEA INJECTION and CAFNEA ORAL SOLUTION are indicated for the short-term treatment of apnoea of prematurity in infants of gestational age 28 to less than 33 weeks.

CONTRAINDICATIONS

CAFNEA INJECTION and CAFNEA ORAL SOLUTION are contraindicated in patients who have demonstrated hypersensitivity to caffeine or citrate.

WARNINGS

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

PRECAUTIONS

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.

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.

PRODUCT INFORMATION

Cafnea™ Injection and Cafnea™ Oral Solution



Renal and Hepatic Impairment

CAFNEA INJECTION and CAFNEA ORAL SOLUTION should be administered with caution in infants with impaired renal or hepatic function. In such cases, serum caffeine should be monitored and dose administration should be adjusted to avoid potential toxicity.

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.

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.

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 tumor 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.

Interactions with other Medicines

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 coadministration of mexiletine, cimetidine, fluvoxamine, oral idroclamide, oral methoxsalen and 5-methoxypsoralen, enoxacin, tiabendazole, artemisinin, fluconazole and terbinafine, verapamil may decrease caffeine elimination. Coadministration of phenytoin may increase caffeine elimination. Caffeine antagonises the effects of benzodiazapines. 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 ofloxacin.

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

ADVERSE EFFECTS

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

PRODUCT INFORMATION

Cafnea™ Injection and Cafnea™ Oral Solution



Table 2: Percentages of most frequently reported adverse events from Erenberg et al⁶

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
Hyponatremia	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^{4, 5} controlled clinical trials have included tachycardia, tachypnea, jitteriness, tremors, unexplained seizures and vomiting. Caffeine reduced weight gain temporarily.

DOSAGE AND 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 (eg. 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 body weight. If symptoms suggestive of caffeine induced toxicity are observed such as tachycardia, tachypnea, 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.

PRODUCT INFORMATION

Cafnea™ Injection and Cafnea™ Oral Solution



OVERDOSAGE

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.

In Australia, contact the Poisons Information Centre on 13 11 26 for further advice on overdose management.

Treatment of withdrawal

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

PRESENTATION AND STORAGE CONDITIONS

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. The injection contains no preservatives. The product is for single use in one patient only. Discard any residue.

AUST R 153873

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. The solution contains no preservatives. The product is for single use in one patient only. Discard any residue.

AUST R 153874

Phebra product code- SOL026

Store below 30°C

POISONS SCHEDULE

Not scheduled

NAME AND ADDRESS OF SPONSOR

Phebra Pty Ltd, 332 Burns Bay Road, Lane Cove NSW 2066, Australia.
Telephone: 1800 720 020

Date of TGA Approval: 17th March 2010

PRODUCT INFORMATION

Cafnea™ Injection and Cafnea™ Oral Solution



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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au