PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CAFCIT (caffeine citrate 10 mg/ml equivalent to 5 mg caffeine)

Solution for infusion or Oral administration.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg caffeine citrate equivalent to 5 mg caffeine.

Excipient(s) with known effect:

Sodium: each 1 ml of solution contains 3,04 mg sodium.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for IV infusion or Oral administration.

A clear, colourless solution.

pH: 2,0 – 3,0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of primary apnoea of premature newborns.

4.2 Posology and method of administration

Treatment with CAFCIT should be initiated under the supervision of a medical practitioner experienced in neonatal intensive care. Treatment should be administered only in a neonatal intensive care unit in which adequate facilities

are available for patient surveillance and monitoring.

Posology

Intravenous infusion

The recommended dose regimen in previously untreated infants is a loading dose of 20 mg CAFCIT per kg body weight administered by slow intravenous infusion over 30 minutes, using a syringe infusion pump or other metered infusion device. After an interval of 24 hours, maintenance doses of 5 mg per kg body weight may be administered by slow intravenous infusion over 10 minutes every 24 hours.

Alternatively, maintenance doses of 5 mg per kg body weight may be administered by oral administration, such as through a nasogastric tube every 24 hours.

Oral administration

The recommended loading dose and maintenance doses of CAFCIT are provided in the following table which clarifies the relationship between injection volumes and administered doses expressed as caffeine citrate. The dose expressed as caffeine base is half the dose when expressed as caffeine citrate (10 mg CAFCIT is equivalent to 5 mg caffeine base).

	Dose of CAFCIT (Volume)	**Dose of CAFCIT (mg/kg body weight)**	**Route**	**Frequency**
Loading dose	2,0 ml/kg body weight	20 mg/kg body weight	Intravenous infusion (over 30 minutes)	Once
Maintenance dose*	0,5 ml/kg body weight	5 mg/kg body weight	Intravenous infusion (over 10 minutes) or by oral administration	Every 24 hours*
Maintenance dose*	0,5 ml/kg body weight	5 mg/kg body weight	Oral administration	Every 24 hours*

* Beginning 24 hours after the loading dose.

In preterm infants with insufficient clinical response to the recommended loading dose, a second loading dose of 10-20 mg/kg maximum may be given after 24 hours.

Higher maintenance doses of 10 mg/kg body weight could be considered in case of insufficient response, taking into account the potential for accumulation of caffeine due to the long half- life in premature neonates and the progressively increasing capacity to metabolise caffeine in relation to post-menstrual age.

Where clinically indicated, caffeine plasma levels should be monitored. The diagnosis of apnoea of prematurity may need to be reconsidered if patients do not respond adequately to a second loading dose or maintenance dose 10 mg/kg/day.

When given intravenously, CAFCIT should be administered by controlled intravenous infusion, using a syringe infusion pump or other metered infusion device only.

Routine monitoring of plasma caffeine levels is not necessary in the majority of preterm infants. However, plasma concentrations of caffeine may need to be monitored periodically throughout treatment in cases of incomplete clinical response or signs of toxicity. Additionally, doses may need to be adjusted following routine monitoring of caffeine plasma concentrations in risk situations such as:

- very premature infants (< 28 weeks gestational age and/or body weight <1000 g) particularly when receiving parenteral nutrition.
- infants with hepatic and renal impairment.
- infants with seizure disorders.
- infants with known and clinically significant cardiac disease.
- infants receiving co-administration of medicinal products known to interfere with caffeine metabolism.
- infants whose mothers consume caffeine while providing breast milk for feeding.

It is advisable to measure baseline caffeine levels in:

- infants whose mothers may have ingested large quantities of caffeine prior to delivery.
- infants who have previously been treated with theophylline, which is metabolised to caffeine.

Caffeine as contained in CAFCIT has a prolonged half-life in premature newborn infants and there is potential for accumulation which may necessitate monitoring infants treated for an extended period.

Blood samples for monitoring should be taken just before the next dose in the case of therapeutic failure and 2 to 4 hours after the previous dose when suspecting toxicity.

Although a therapeutic plasma concentration range of caffeine has not been determined in the literature, caffeine levels in studies associated with clinical benefit ranged from 8 to 30 mg/l and no safety concerns have normally been raised with plasma levels below 50 mg/l. CAFCIT can be administered by intravenous infusion and by the oral route. CAFCIT must not be administered by intramuscular, subcutaneous, intrathecal or intraperitoneal injection.

Duration of treatment

The optimal duration of treatment has not been established. In a study on premature newborn infants a median treatment period of 37 days was reported. In clinical practice, treatment is usually continued until the infant has reached a post-menstrual age of 37 weeks, by which time apnoea of prematurity usually resolves spontaneously. This limit may however be revised according to the response to treatment, the continuing presence of apnoeic episodes despite treatment, or other clinical considerations. It is recommended that CAFCIT administration should be stopped when the patient has 5-7 days without a significant apnoeic attack.

If the patient has recurrent apnoea, CAFCIT administration can be restarted with either a maintenance dose or half a loading dose, depending upon the time interval from stopping CAFCIT to recurrence of apnoea.

Because of the slow elimination of caffeine in this patient population, there is no requirement for dose tapering on cessation of treatment. As there is a risk for recurrence of apnoeas after cessation of CAFCIT treatment monitoring of the patient should be continued for approximately one week.

Special populations

Hepatic and renal impairment

The safety of CAFCIT in patients with renal insufficiency has not been established.

In the presence of renal impairment, there is increased potential for accumulation. A reduced daily maintenance dose of CAFCIT is required and the dose should be guided by plasma caffeine measurements. In very premature infants, clearance of caffeine does not depend on hepatic function. Hepatic caffeine metabolism develops

progressively in the weeks following birth and for the older infants, hepatic disease may indicate a need for monitoring caffeine plasma levels and may require dose adjustments.

Method of administration

CAFCIT should be administered either:

- by slow intravenous infusion over 30 minutes, using a syringe infusion pump or other metered infusion device
- oral administration, such as through a nasogastric tube

4.3 Contraindications

Hypersensitivity to caffeine citrate or to any of the excipients listed under section 6.1.

4.4 Special warnings and precautions for use

Treatment with CAFCIT should be initiated under the supervision of a medical practitioner experienced in neonatal intensive care. Treatment should be administered only in a neonatal intensive care unit in which adequate facilities are available for patient surveillance and monitoring.

In neonates born to-mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with CAFCIT, since caffeine readily crosses-the placenta into the foetal circulation.

Apnoea

Apnoea of prematurity is a diagnosis of exclusion. Other causes of apnoea (e.g., central nervous system disorders, primary lung disease, anaemia, sepsis, metabolic disturbances, cardiovascular abnormalities, or obstructive apnoea) should be ruled out or properly treated prior to initiation of treatment with CAFCIT.

It is advisable to monitor plasma levels of caffeine periodically. However, at the recommended doses, frequent (more than weekly) monitoring of plasma levels is not normally necessary unless there are concerns regarding lack of efficacy or possible toxicity. In premature neonates, caffeine has a prolonged half-life. If higher maintenance

dosages are used, the medical practitioner should recognise this potential for accumulation and monitor plasma caffeine levels (see also Section 5.2).

If there is inadequate clinical response to the first loading dose, a second dose may be given, but if there is continued inadequate response, the plasma levels should be confirmed before further doses are given, as the failure to respond could be an indication of another cause of apnoea. Plasma levels should not normally exceed 50 micrograms/ml (optimally 10-30 micrograms/ml).

Caffeine consumption

In newborn infants born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with CAFCIT, since caffeine readily crosses the placenta into the foetal circulation (see sections 4.2 and 5.2).

Breastfeeding mothers of newborn infants treated with CAFCIT should not ingest caffeine-containing foods and beverages or medicinal products containing caffeine (see section 4.6), since caffeine is excreted into breast milk (see section 5.2).

Theophylline

In newborns previously treated with theophylline, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with CAFCIT because preterm infants metabolise theophylline to caffeine.

Seizures

Caffeine is a central nervous system stimulant and seizures have been reported in cases of caffeine overdose. Extreme caution must be exercised if CAFCIT is used in newborns with seizure disorders.

Cardiovascular reactions

Caffeine has been shown to increase heart rate, left ventricular output, and stroke volume in published studies. Therefore, CAFCIT should be used with caution in newborns with known cardiovascular disease. There is evidence that caffeine causes tachydysrhythmias in susceptible individuals. In newborns this is usually a simple sinus tachycardia. If there have been any unusual rhythm disturbances on a cardiotocograph (CTG) trace before

the baby is born, CAFCIT should be administered with caution.

Renal and hepatic impairment

CAFCIT should be administered with caution in preterm newborn infants with impaired renal or hepatic function. The frequency of adverse reactions in a small number of very premature infants with renal/hepatic impairment appeared to be higher as compared to premature infants without organ impairment (see sections 4.2, 4.8 and 5.2). Doses should be adjusted by monitoring of caffeine plasma concentrations to avoid toxicity in this population.

Necrotising enterocolitis

Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established.

As for all preterm infants, those treated with CAFCIT should be carefully monitored for the development of necrotising enterocolitis (see section 4.8).

CAFCIT should be used with caution in infants suffering gastro-oesophageal reflux, as the treatment may exacerbate this condition.

CAFCIT causes a generalised increase in metabolism, which may result in higher energy and nutrition requirements during therapy.

The diuresis and electrolyte loss induced by CAFCIT may necessitate correction of fluid and electrolyte disturbances.

Use of filter straws

Opening the ampoules may introduce glass particles into this solution. It is recommended that the solution be filtered prior to use by means of a suitable filter device.

Caffeine Citrate 10mg/ml Injection contains sodium

CAFCIT contains 3,04 mg sodium per 1 ml of the solution. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P450 1A2 (CYP1A2) is the major enzyme involved in the metabolism of caffeine in humans. Therefore, caffeine has the potential to interact with medicines that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2. However, caffeine metabolism in preterm newborn infants is limited due to their immature hepatic enzyme systems.

Interconversion between caffeine and other xanthines such as theophylline has been reported in premature neonates. Therefore the concurrent use of these medicines should be avoided. Baseline serum levels of caffeine should be measured in patients previously treated with theophylline.

Although few data exist on interactions of caffeine with other medicines in preterm newborn infants, lower doses of CAFCIT may be needed following co-administration of medicines which are reported to decrease caffeine elimination in adults (e.g., cimetidine and ketoconazole) and higher CAFCIT doses may be needed following co-administration of medicines that increase caffeine elimination (e.g., phenobarbital and phenytoin).
Where doubt exists about possible interactions, plasma caffeine concentrations should be measured.

As bacterial overgrowth in the gut is associated with the development of necrotising enterocolitis, co-administration of CAFCIT with medicines that suppress gastric acid secretion (antihistamine H2 receptor blockers or proton-pump inhibitors) may in theory increase the risk of necrotising enterocolitis (see section 4.4 and 4.8).

Concurrent use of CAFCIT and doxapram might potentiate their stimulatory effects on the cardio-respiratory and central nervous system. If concurrent use is indicated, cardiac rhythm and blood pressure must be carefully monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Caffeine in animal studies, at high doses, was shown to be embryotoxic and teratogenic. These effects are not relevant with regard to short term administration in the preterm infant population.

Breastfeeding

Caffeine is excreted into breast milk and readily crosses the placenta into the foetal circulation (see section 5.2). Breastfeeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine-containing foods, beverages or medicinal products containing caffeine.

In newborn infants born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate (see section 4.4).

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

a. Summary of the safety profile

The known pharmacology and toxicology of caffeine and other methylxanthines predict the likely adverse reactions to CAFCIT. Effects described include central nervous system (CNS) stimulation such as convulsion, irritability, restlessness and jitteriness, cardiac effects such as tachycardia, dysrhythmia, hypertension and increased stroke volume, metabolism and nutrition disorders such as hyperglycaemia. These effects are dose related and may necessitate measurement of plasma levels and dose reduction.

They are generally, although not exclusively, associated with serum caffeine concentrations ≥ 50 micrograms/ml.

b. Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Unknown
Infections and infestations			Sepsis
Immune system disorders		Hypersensitivity reaction	
Metabolism and nutrition disorders			Hypoglycaemia, hyperglycaemia, failure to thrive, feeding intolerance
Nervous system disorders			Irritability, jitteriness, restlessness, brain injury, convulsion
Ear and labyrinth disorders			Deafness
Cardiac disorders			Increased left ventricular output and increased stroke volume, tachycardia, dysrhythmia
Gastrointestinal disorders			Regurgitation, increased gastric aspirate, necrotising enterocolitis
General disorders and administration site conditions	Infusion site phlebitis, infusion site inflammation		
Investigations			Urine output increased, urine sodium and calcium increased, haemoglobin decreased, thyroxine

			decreased

c. Description of selected adverse reactions

Necrotising enterocolitis

Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established.

As for all preterm infants, those treated with CAFCIT should be carefully monitored for the development of necrotising enterocolitis (see section 4.4). Brain injury, convulsion and deafness were observed but they were more frequent in the placebo group.

Caffeine may suppress erythropoietin synthesis and hence reduce haemoglobin concentration with prolonged treatment.

Transient falls in thyroxine (T4) have been recorded in infants at the start of therapy but these are not sustained with maintained therapy.

Available evidence does not indicate any adverse long-term reactions of neonatal caffeine therapy as regards neurodevelopmental outcome, failure to thrive or on the cardiovascular, gastrointestinal or endocrine systems. Caffeine does not appear to aggravate cerebral hypoxia or to exacerbate any resulting damage, although the possibility cannot be ruled out.

Other special populations

Adverse reactions appeared to be more frequent in very premature infants with renal/hepatic impairment with organ impairment than in other observed infants without organ impairment. Cardiac disorders (tachycardia, including one single case of dysrhythmia) were mostly reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Following overdose, published plasma caffeine levels have ranged from approximately 50 mg/l to 350 mg/l.

Symptoms

Signs and symptoms of overdosage from these reports include jitteriness, tachycardia, tachypnoea, tremor, opisthotonos, rigidity and tonic-clonic movements, hypokalaemia, restlessness, gastric irritation, gastro-intestinal haemorrhage, increased white blood cell count, non-purposeful jaw and lip movements. One case of caffeine overdose complicated by development of intraventricular haemorrhage and long-term neurological sequelae has been reported. In one case of overdose the patient developed compromised circulation, vomiting and seizures. Other reported effects of gross overdose include fever, agitation, hyperexcitability, hypertonia, gastric residues, distended abdomen, metabolic acidosis, hyperglycaemia and elevated urea levels. No deaths associated with caffeine overdose have been reported in preterm infants.

Management

Treatment of overdosage should primarily be symptomatic and supportive measures, including monitoring of blood levels of caffeine.

Plasma potassium and glucose concentrations should be monitored, and hypokalaemia and hyperglycaemia corrected.

In severe cases of overdose, exchange transfusion should be considered. In one case, this was found to reduce plasma caffeine levels by 40 mg/l per transfusion.

Convulsions may be treated with intravenous administration of anticonvulsants (diazepam or a barbiturate such as pentobarbital sodium or phenobarbital).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics xanthine derivatives

ATC code: N06BC01

Mechanism of action

Caffeine is structurally related to the methylxanthines theophylline and theobromine. Most of its effects have been attributed to antagonism of adenosine receptors, both A_1 and $A2_A$ subtypes, demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically in this indication.

Pharmacodynamic effects

The desired respirogenic activity of caffeine is an expression of its central nervous system stimulation, although it may also increase the sensitivity of respiratory response to carbon dioxide levels. Caffeine increases both tidal volume and frequency of ventilation.

In the premature infant, caffeine produced increased minute ventilation, mainly due to an increase in inspiratory drive as shown by an increased mean respiratory flow (VT/T1). Caffeine regularises the breathing pattern, indicating that it stabilises the oscillation of the respiratory control system.

Caffeine also inhibits phosphodiesterase, but this effect only occurs at concentrations associated with toxicity, and not at therapeutic concentrations.

Caffeine increases metabolic rate, heart rate, cardiac contractility and output. It also increases blood flow to the kidneys and prevents sodium and chloride from reabsorbing at the proximal tubules, so mild diuresis can occur.

Adenosine is a vasodilator and therefore caffeine, as its antagonist, can cause vasoconstriction. Hence it is a vasoconstrictor in the cerebral and splanchnic circulations. Elsewhere, it has a vasodilator effect due to an effect on vascular smooth muscle.

The stimulant effect may affect sleep patterns.

5.2 Pharmacokinetic properties

Caffeine citrate readily dissociates in aqueous solution. The citrate moiety is rapidly metabolized on infusion or ingestion.

Absorption

The onset of action of caffeine from caffeine citrate is within minutes of commencement of infusion. In neonates, orally administered caffeine has been shown to be rapidly and completely absorbed. After oral administration of 10 mg caffeine base/kg body weight to preterm newborn infants, the peak plasma caffeine concentration (C_{max}) ranged from 6 to 10 mg/l and the mean time to reach peak concentration (t_{max}) ranged from 30 min to 2 h. The extent of absorption is not affected by formula feeding but t_{max} may be prolonged.

Distribution

Caffeine is rapidly distributed into the brain following caffeine citrate administration. Caffeine concentrations in the cerebrospinal fluid of preterm newborn infants approximate to their plasma levels. The mean volume of distribution (Vd) of caffeine in infants (0,8 – 0,9 l/kg) is slightly higher than that in adults (0,6 l/kg). Plasma protein binding data are not available for newborn infants or infants. In adults, the mean plasma protein binding in vitro is reported to be approximately 36 %.

Caffeine readily crosses the placenta into the foetal circulation and is excreted into breast milk.

Biotransformation

Caffeine metabolism in preterm newborn infants is very limited due to their immature hepatic enzyme systems and most of the active substance is eliminated in urine. Hepatic cytochrome P450 1A2 (CYP1A2) is involved in caffeine biotransformation in older individuals.

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

Elimination

In young infants, the elimination of caffeine is much slower than that in adults due to immature hepatic and/or renal function. In newborn infants, caffeine clearance is almost entirely by renal excretion. Mean half-life ($t_{1/2}$) and fraction excreted unchanged in urine (A_e) of caffeine in infants are inversely related to gestational / postmenstrual age. In newborn infants, the $t_{1/2}$ is approximately 3-4 days, and the A_e is approximately 86 % (within 6 days). By 9 months of age, the metabolism of caffeine approximates to that seen in adults ($t_{1/2}$ = 5 hours and A_e = 1 %).

Studies examining the pharmacokinetics of caffeine in newborn infants with hepatic or renal insufficiency have not been conducted.

In the presence of significant renal impairment, considering the increased potential for accumulation, a reduced daily maintenance dose of caffeine is required and the doses should be guided by blood caffeine measurements. In premature infants with cholestatic hepatitis a prolonged caffeine elimination half-life with an increase of plasma levels above the normal limit of variation has been found suggesting a particular caution in the dosage of these patients (see sections 4.2 and 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid

Sodium chloride

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

3 years

After opening the ampoule, the medicinal product should be used immediately.

6.4 Special precautions for storage

Store below 30 °C.

CAFCIT diluted with 5 % glucose or 0,9 % sodium chloride or glucose 4 % with saline 0,18 % is stable for up to 4 hours when stored under ambient conditions.

6.5 Nature and contents of container

Type I clear, glass ampoule containing 1 ml in packs of 1 or 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Only clear solution without particulate matter should be used. For single use only. Any unused solution should be discarded.

CAFCIT can be either used without dilution or diluted in sterile solutions for infusion such as 5 % glucose or 0,9 % sodium chloride or glucose 4 % with saline 0,18 % immediately after withdrawal from the ampoule.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive, Route 21 Corporate Park

Nellmapius Drive, Irene

Pretoria

8. REGISTRATION NUMBER(S)

56/1.4/0312

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 October 2023

10. DATE OF REVISION OF THE TEXT