Summary of Product Characteristics
CAFFEJECT 10
(Caffeine Citrate 10 mg/ml Oral Solution)

1 Name of the medicinal product

Caffeject 10 – Caffeine Citrate 10 mg in 1 ml Oral Solution

2 Qualitative and quantitative composition

Each 1 ml of oral solution contains 10 mg caffeine citrate, equivalent to 5 mg caffeine (base).

Excipient(s) with known effect
Each 1 ml of solution contains 3.04 mg sodium (as sodium citrate).

For the full list of excipients, see section 6.1.

3 Pharmaceutical form

Oral solution.

Appearance: clear and colourless solution.

4 Clinical particulars

4.1 Therapeutic indications

Caffeject 10 is indicated in preterm neonates for:

- the treatment of apnoea in preterm neonates;
- the prevention of apnoea following extubation of preterm neonates of gestational age up to 37 weeks;
- the prevention of apnoea in preterm neonates of gestational age less than 34 weeks.

Treatment regimens should follow the most recent relevant treatment guidelines.

4.2 Posology and method of administration

Treatment with caffeine citrate should be initiated under the supervision of a physician experienced in neonatal intensive care. Treatment should be administered, where possible, in a neonatal intensive care unit in which adequate facilities are available for patient surveillance and monitoring.

Posology
Doses are expressed as caffeine citrate; 2 mg of caffeine citrate is equivalent to 1 mg caffeine (base). Please note that: (a) the dose expressed as caffeine citrate is twice the dose expressed as caffeine base; (b) caffeine is clinically effective within 4 hours, and if the patient fails to respond within this time a second loading dose may be given – if there is no clinical response to the second loading dose, caffeine blood levels should be measured (see section 4.4); (c) because of the slow elimination of caffeine in this patient population, there is no requirement for dose

tapering on cessation of treatment; and (d) infants must be of sufficient respiratory maturity not to require positive pressure ventilation.

Treatment of apnoea in preterm neonates
Initial (loading) dose: caffeine citrate 20 mg/kg by mouth as a single dose. Thereafter, beginning 24 hours after the loading dose, caffeine citrate 5 mg/kg once daily for 6 weeks or until there is an adequate clinical response. Where the response is insufficient, a maintenance dose of up to 10 mg/kg/day (expressed as caffeine citrate) may be considered, taking into account the potential for accumulation and, where clinically indicated, monitoring of caffeine plasma levels.

Extubation of preterm neonates born up to 37 weeks' gestation
Initial (loading) dose: caffeine citrate 20 mg/kg by mouth as a single dose. Thereafter, beginning 24 hours after the loading dose, caffeine citrate 5 mg/kg once daily for 6 days.

Prevention of apnoea in preterm neonates born before 34 weeks' gestation
Initial (loading) dose: caffeine citrate 20 mg/kg by mouth as a single dose. Thereafter, beginning 24 hours after the loading dose, caffeine citrate 5 mg/kg once daily for 6 weeks or according to clinical need.

Dosage, adjustments and monitoring
Plasma concentrations of caffeine may need to be monitored periodically throughout treatment in cases of incomplete clinical response or signs of toxicity. Doses may need to be adjusted according to medical judgement following routine monitoring of caffeine plasma concentrations in at-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 or renal impairment (see sections 4.4 and 5.2); 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 (see section 4.5); and infants whose mothers consume caffeine while providing breast milk for feeding.

Baseline caffeine levels should be measured in infants whose mothers may have ingested large quantities of caffeine prior to delivery (see section 4.4) and in infants previously treated with theophylline, which is metabolised to caffeine. Blood samples for monitoring should be taken just before the next dose in cases of therapeutic failure and 2 to 4 hours after the previous dose when toxicity is suspected. Although a therapeutic plasma concentration range has not been formally established, caffeine levels associated with clinical benefit ranged from 8 to 30 mg/litre, and no safety concerns have normally been raised with plasma levels below 50 mg/litre.

Duration of treatment
Treatment should be continued until the child has reached a gestational age of 37 weeks, by which time apnoea of prematurity usually resolves spontaneously. This

limit may, however, be revised according to clinical judgement in individual cases depending on response to treatment, the continuing presence of apnoeic episodes despite treatment, or other clinical considerations. It is recommended that caffeine citrate administration be stopped when the patient has had 5 to 7 days without a significant apnoeic attack. If the patient has recurrent apnoea, administration can be restarted with either a maintenance dose or a half loading dose, depending upon the interval from stopping treatment to recurrence of apnoea. As there is a risk of recurrence of apnoeas after cessation, monitoring of the patient should be continued for approximately one week.

Renal impairment

In the presence of renal impairment there is an increased potential for accumulation; a reduced daily maintenance dose of caffeine is required and the dose should be guided by blood caffeine measurements.

Hepatic impairment

In very premature neonates, clearance of caffeine does not depend on hepatic function. Hepatic caffeine metabolism develops progressively in the weeks following birth; in the older infant, hepatic disease may impair caffeine metabolism and may indicate a need for plasma level monitoring and dose reduction.

Method of administration

Caffeject 10 should be given orally (for example, through a nasogastric tube) every 24 hours. The medicinal product must not be administered by the intramuscular, subcutaneous, intrathecal or intraperitoneal route.

4.3 Contraindications

- Hypersensitivity to caffeine citrate or to any of the excipients listed in section 6.1.
- Oral caffeine is contraindicated in neonates with tracheo-oesophageal fistula, necrotising enterocolitis and intestinal obstruction.

4.4 Special warnings and precautions for use

Apnoea

Apnoea of prematurity is a diagnosis of exclusion. Other causes of apnoea (for example, 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 caffeine citrate.

Inadequate response

If apnoea in the premature infant does not respond to adequate doses of caffeine citrate, other causes of apnoea should be considered. If there is inadequate clinical response to the first loading dose, a second dose may be given; if inadequate response continues, plasma levels should be confirmed before further

doses are given. Plasma levels should not normally exceed 50 micrograms/ml (optimally 10–30 micrograms/ml).

Plasma level monitoring
It is advisable to monitor plasma caffeine levels periodically. At the recommended doses, frequent (more than weekly) monitoring is not normally necessary unless there are concerns regarding lack of efficacy or possible toxicity. Caffeine has a prolonged half-life in premature neonates; if higher maintenance dosages are used, the potential for accumulation should be recognised and plasma levels monitored (see section 5.2).

Maternal 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, since caffeine readily crosses the placenta into the foetal circulation (see sections 4.2 and 5.2). Breast-feeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine-containing foods, beverages or medicinal products (see section 4.6), since caffeine is excreted into breast milk.

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

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

Cardiovascular disorders
Caffeine has been shown to increase heart rate, left ventricular output and stroke volume, and may cause tachyarrhythmias in susceptible individuals (in neonates usually a simple sinus tachycardia). Caffeine citrate should therefore be used with caution in neonates with known cardiovascular disease. If unusual rhythm disturbances were seen on a cardiotocograph before birth, caffeine citrate should be administered with caution.

Renal and hepatic impairment
Caffeine citrate should be administered with caution in preterm neonates with impaired renal or hepatic function. In a post-authorisation safety study, the frequency of adverse reactions in a small number of very premature infants with renal/hepatic impairment appeared higher than in those 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.

Necrotising enterocolitis and gastrointestinal disorders
There are reports of a possible association between the use of methylxanthines and the development of necrotising enterocolitis, although a causal relationship

with caffeine or other methylxanthine use has not been established. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for the development of necrotising enterocolitis. Reduced gastric acid secretion may promote bacterial overgrowth and increase this risk. Caffeine citrate should be used with caution in neonates suffering from gastro-oesophageal reflux, as treatment may exacerbate the condition.

Metabolic changes and diuresis
Caffeine citrate causes a generalised increase in metabolism, which may result in higher energy and nutritional requirements during therapy. The diuresis and electrolyte loss induced by caffeine citrate may necessitate correction of fluid and electrolyte disturbances.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 1A2 (CYP1A2) is the major enzyme involved in the metabolism of caffeine in humans; caffeine therefore has the potential to interact with active substances that are substrates for, inhibit, or induce CYP1A2. However, caffeine metabolism in preterm neonates is limited owing to their immature hepatic enzyme systems, and as these systems mature caffeine metabolism (mainly via CYP1A2) can be increasingly affected by such interactions in older infants.

Caffeine is a methylxanthine and inter-conversion between caffeine and other xanthines such as theophylline has been reported in premature neonates; concurrent use of these medicinal products should be avoided. Aminophylline and theophylline are metabolised to caffeine, and baseline serum caffeine levels should be measured in patients previously treated with theophylline. When switching treatment to Caffeject 10, it is important to consider that caffeine may already be present in the blood from previous treatment.

Although few data exist on interactions in preterm neonates, lower doses of caffeine citrate may be needed following co-administration of active substances reported to decrease caffeine elimination in adults (for example, cimetidine and ketoconazole), and higher doses may be needed following co-administration of active substances that increase caffeine elimination (for example, 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 caffeine citrate with medicinal products that suppress gastric acid secretion (H2-receptor blockers or proton-pump inhibitors) may, in theory, increase the risk of necrotising enterocolitis (see sections 4.4 and 4.8).

Concurrent use of caffeine and doxapram might potentiate their stimulatory effects on the cardio-respiratory and central nervous systems. If used concurrently, cardiac rhythm and blood pressure must be carefully monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Caffeine readily crosses the placenta into the foetal circulation. Consumption of large amounts of caffeine before delivery may mean that the neonate already has circulating caffeine before Caffeject 10 is given. In animal studies, caffeine at high doses was shown to be embryotoxic and teratogenic; these effects are not relevant with regard to the short-term administration of caffeine citrate in the preterm neonate population (see section 5.3).

Breast-feeding

Caffeine is excreted into breast milk and readily crosses the placenta into the foetal circulation (see section 5.2). Breast-feeding 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 (see section 4.4).

Fertility

Effects on reproductive performance observed in animals are not relevant to the use of caffeine citrate in the preterm neonate population (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant. The effect of Caffeject 10 on the performance of skilled tasks is not relevant to neonates.

4.8 Undesirable effects

Summary of the safety profile

The known pharmacology and toxicology of caffeine and other methylxanthines predict the likely adverse reactions to caffeine citrate. Effects described include central nervous system (CNS) stimulation such as convulsion, irritability, restlessness and jitteriness; cardiac effects such as tachycardia, arrhythmia, hypertension and increased stroke volume; and 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.

Tabulated list of adverse reactions

The adverse reactions described in the short- and long-term published literature and obtained from a post-authorisation safety study that can be associated with caffeine citrate are listed below by System Organ Class and Preferred Term (MedDRA). Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100

to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Not known	Sepsis
Immune system disorders	Rare	Hypersensitivity reaction
Metabolism and nutrition disorders	Common	Hyperglycaemia
	Not known	Hypoglycaemia, failure to thrive, feeding intolerance
Nervous system disorders	Uncommon	Convulsion
	Not known	Irritability, jitteriness, restlessness, brain injury
Ear and labyrinth disorders	Not known	Deafness
Cardiac disorders	Common	Tachycardia
	Uncommon	Arrhythmia
	Not known	Increased left ventricular output and increased stroke volume
Gastrointestinal disorders	Not known	Regurgitation, increased gastric aspirate, necrotising enterocolitis
Investigations	Not known	Urine output increased, urine sodium and calcium increased, haemoglobin decreased, thyroxine decreased

Description of selected adverse reactions

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 its development; however, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established. In a double-blind placebo-controlled study of caffeine citrate in 85 preterm infants, necrotising enterocolitis was diagnosed in the blinded phase in two infants on active treatment and one on placebo, and in three infants on caffeine during the open-label phase; three of the infants who developed necrotising enterocolitis died. A large multicentre study (n = 2006) investigating long-term outcome did not show an increased frequency of necrotising enterocolitis in the caffeine group when compared to placebo. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for its development (see section 4.4).

Brain injury, convulsion and deafness were observed in clinical study but 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 continued treatment. Available

evidence does not indicate any adverse long-term reactions of neonatal caffeine therapy with regard to neurodevelopmental outcome, failure to thrive, or the cardiovascular, gastrointestinal or endocrine systems; caffeine does not appear to aggravate cerebral hypoxia or to exacerbate any resulting damage. Adverse reactions may be more frequent in premature neonates with renal or hepatic impairment, mostly cardiac disorders (tachycardia, including one single report of arrhythmia).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

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

Signs and symptoms of overdose

Signs and symptoms of caffeine overdosage reported in neonates and premature infants include jitteriness, tachycardia, tachypnoea, opisthotonos, rigidity and tonic-clonic movements, hypokalaemia, fine tremor of the extremities, restlessness, gastric irritation, gastro-intestinal haemorrhage, increased white blood cell count, and non-purposeful jaw and lip movements. Effects of gross overdose include fever, agitation, hyperexcitability, hypertonia, gastric residues, distended abdomen, metabolic acidosis, hyperglycaemia and elevated urea levels. One case of caffeine overdose was complicated by intraventricular haemorrhage and long-term neurological sequelae; in another case, circulation was compromised and the neonate developed vomiting and seizures. No deaths from caffeine overdose have been reported in preterm neonates.

Management

Caffeine overdose in preterm neonates is managed by supportive measures. Blood caffeine levels should be monitored, and plasma potassium and glucose concentrations should be monitored and any hypokalaemia and hyperglycaemia corrected. Previous cases reported have resolved satisfactorily. Convulsions may be treated with intravenous administration of an anticonvulsant (such as phenobarbital, phenytoin or levetiracetam). In severe overdose, exchange transfusion should be considered; in one case, each transfusion reduced plasma caffeine concentration by 40 mg/litre.

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 the A1 and A2A subtypes, demonstrated in receptor-binding assays at concentrations approximating those achieved therapeutically in this indication. As a CNS stimulant, caffeine increases inspiratory drive and regularises the breathing pattern; this blockade of adenosine receptors is thought to increase respiratory drive.

Pharmacodynamic effects

Caffeine's main action is as a CNS stimulant, which is the basis of its effect in apnoea of prematurity. Several mechanisms have been proposed, including respiratory-centre stimulation, increased minute ventilation, a decreased threshold to and increased response to hypercapnia, increased skeletal muscle tone, decreased diaphragmatic fatigue, increased metabolic rate, and increased oxygen consumption. Caffeine increases both tidal volume and frequency of ventilation and, in the premature infant, increases minute ventilation mainly through an increase in inspiratory drive; it regularises the breathing pattern, stabilising the oscillation of the respiratory control system. Caffeine also inhibits phosphodiesterase, but only at concentrations associated with toxicity, 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 reabsorption at the proximal tubules, which can lead to mild diuresis. Adenosine is a vasodilator, and caffeine, as its antagonist, can cause vasoconstriction; it is therefore a vasoconstrictor in the cerebral and splanchnic circulations, while elsewhere it has a vasodilator effect due to an action on vascular smooth muscle. The stimulant effect may affect sleep patterns.

Clinical efficacy and safety

Evidence on the benefit of caffeine citrate in preterm neonates includes a 2023 Cochrane review of 18 clinical studies involving a total of 2,705 neonates. Treatment with caffeine citrate reduces chronic lung disease and may reduce the risk of death and major neurodevelopmental disability at 18 to 24 months.

Efficacy for the treatment of apnoea: results from 6 clinical studies involving 959 preterm neonates (gestational age less than 37 weeks) treated for apnoea with a methylxanthine (including caffeine) showed moderate benefit and no evidence of harm.

Outcome	Study population	Relative risk (95% CI)
Decreased apnoeic episodes	1 study; 43 preterm neonates	RR 0.70 (0.30 to 1.62)
Decreased use of mechanical ventilation	5 studies; 192 preterm neonates	RR 0.34 (0.12 to 0.97)
Decreased bronchopulmonary dysplasia (supplemental oxygen at 36 weeks' GA)	1 study; 805 preterm neonates	RR 0.72 (0.58 to 0.89)

Outcome	Study population	Relative risk (95% CI)
Decreased death or major neurodevelopmental disability (up to 5 years)	1 study; 767 preterm neonates	RR 0.85 (0.71 to 1.01)

Efficacy after extubation: results from 7 clinical studies involving 870 preterm neonates (gestational age less than 34 weeks) treated with a methylxanthine (including caffeine) after extubation to prevent apnoea showed moderate benefit and no evidence of harm.

Outcome	Study population	Relative risk (95% CI)
Decreased failed extubation (need for re-intubation)	6 studies; 197 preterm neonates	RR 0.48 (0.32 to 0.71)
Decreased bronchopulmonary dysplasia (supplemental oxygen at 36 weeks' GA)	2 studies; 704 preterm neonates	RR 0.81 (0.70 to 0.92)
Decreased death or major neurodevelopmental disability (up to 5 years)	1 study; 676 preterm neonates	RR 0.85 (0.73 to 0.99)

Efficacy for the prevention of apnoea: results from 7 clinical studies involving 706 preterm neonates treated with a methylxanthine (including caffeine) for the prevention of apnoea showed small or moderate benefit in decreasing bronchopulmonary dysplasia and apnoeic episodes but little or no effect on reducing death, with uncertain evidence of harm (low-certainty evidence of an increase in the use of mechanical ventilation).

Outcome	Study population	Relative risk (95% CI)
Decreased apnoeic episodes by hospital discharge	2 studies; 104 preterm neonates	RR 0.19 (0.09 to 0.41)
Decreased use of mechanical ventilation	4 studies; 208 preterm neonates	RR 1.33 (0.48 to 3.72)
Decreased bronchopulmonary dysplasia (supplemental oxygen at 36 weeks' GA)	3 studies; 541 preterm neonates	RR 0.78 (0.63 to 0.97)
Decreased death or major neurodevelopmental disability (up to 5 years)	1 study; 423 preterm neonates	RR 1.00 (0.80 to 1.24)
Decreased death	3 studies; 129 preterm neonates	RR 2.19 (0.85 to 5.68)

Pivotal clinical studies of caffeine citrate provide supporting evidence. In a multicentre, randomised, double-blind study comparing caffeine citrate with placebo in 85 preterm infants (gestational age 28 to < 33 weeks) with apnoea of prematurity, infants received a 20 mg/kg loading dose followed by a 5 mg/kg daily maintenance dose (intravenous or oral) for up to 10–12 days. There were more days without any apnoea under caffeine citrate treatment (3.0 days versus 1.2 days for placebo; $p = 0.005$), and a higher percentage of patients with no apnoeas for ≥ 8 days (caffeine 22% versus placebo 0%). A large placebo-controlled multicentre study (n = 2006) reported that caffeine therapy reduced the rate of bronchopulmonary dysplasia (odds ratio 0.63; 95% CI 0.52 to 0.76) and improved survival without neurodevelopmental disability (odds ratio 0.77; 95% CI 0.64 to

0.93). The size and direction of the effect on death or disability differed by the degree of respiratory support required at randomisation, indicating greater benefit for supported infants.

Respiratory support at entry to study	Odds ratio for death or disability (95% CI)
No support	1.32 (0.81 to 2.14)
Non-invasive support	0.73 (0.52 to 1.03)
Endotracheal tube	0.73 (0.57 to 0.94)

5.2 Pharmacokinetic properties

Caffeine citrate readily dissociates in aqueous solution; the citrate moiety is rapidly metabolised on ingestion.

Absorption

Caffeine citrate is rapidly and completely absorbed after oral administration; bioavailability is the same whether caffeine citrate is given orally or intravenously, so the route of administration does not affect the pharmacokinetics of caffeine citrate. After oral administration of caffeine base 10 mg/kg to preterm neonates, Cmax ranged from 6 to 10 mg/litre and tmax ranged from 30 minutes to 2 hours. The extent of absorption is not affected by formula feeding, but tmax may be prolonged.

Distribution

Caffeine distributes rapidly, including into the brain; caffeine concentrations in the cerebrospinal fluid of preterm neonates approximate to their plasma levels. The mean volume of distribution in infants (0.8–0.9 l/kg) is slightly higher than that in adults (0.6 l/kg). Plasma protein binding data are not available for neonates or infants; in adults, 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 neonates is very limited owing to their immature hepatic enzyme systems, and most of the active substance is eliminated in urine. In preterm neonates, caffeine mainly undergoes N7-demethylation via CYP1A2; there is almost no first-pass metabolism. Inter-conversion between caffeine and theophylline has been reported in preterm neonates: caffeine levels are approximately 25% of theophylline levels following theophylline administration, and approximately 3–8% of administered caffeine would be expected to convert to theophylline.

Elimination

In young infants, the elimination of caffeine is much slower than in adults owing to immature hepatic and/or renal function; in newborn infants, clearance is almost entirely by renal excretion. Mean half-life (t½) and the fraction excreted unchanged in urine are inversely related to gestational/postmenstrual age. In newborn infants, the t½ is approximately 3–4 days and about 86% of the dose is

excreted unchanged in urine within 6 days. By 9 months of age, caffeine metabolism approximates that of adults (t½ = 5 hours; approximately 1% excreted unchanged). Mean systemic clearance (Cl/F) is in the range of 2–17 ml/kg/hour, depending on gestational age. The metabolising enzymes involved are mainly CYP1A2 and, in part, xanthine oxidase.

Pharmacokinetics in special populations

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 dose should be guided by blood caffeine measurements. In premature neonates with cholestatic hepatitis, a prolonged caffeine elimination half-life with plasma levels raised above the normal limit of variation has been found, calling for particular caution in the dosage of these patients (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data revealed no major hazard for humans based on studies of repeated-dose toxicity of caffeine. However, at high doses, convulsions were induced in rodents. At therapeutic doses, some behavioural changes were induced in newborn rats, most likely as a consequence of increased adenosine-receptor expression that persisted into adulthood. Caffeine was shown to be devoid of mutagenic and oncogenic risk. Teratogenic potential and effects on reproductive performance observed in animals are not relevant to the use of caffeine citrate in the preterm neonate population.

6 Pharmaceutical particulars

6.1 List of excipients

- Citric acid
- Sodium citrate
- Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 2 years.

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

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Type I clear glass ampoule containing 1 ml of solution, in packs of 5 or 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Marketing authorisation holder

Tasa Pharma Limited

Unit C1-C3, Kay Complex

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Nairobi

Kenya

8 Marketing authorisation number

CTD13952

9 Date of first authorisation/renewal of the authorisation

21.07.2026

10 Date of revision of the text

21.07.2026