Rx Caffeine Citrate Injection USP

AMERICAN BARISTA 1 Injection

AMERICAN BARISTA 2 Injection

AMERICAN BARISTA 3 Injection

Composition:
Each ml contains:
Caffeine Citrate 20 mg
Water for Injections IP q.s.

1. CLINICAL PARTICULARS

1.1 Therapeutic indications
Treatment of primary apnoea of premature newborns.

1.2 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 only in a neonatal intensive care unit in which adequate facilities are available for patient surveillance and monitoring.

Posology
The recommended dose regimen in previously untreated infants is a loading dose of 20 mg caffeine citrate 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.
The recommended loading dose and maintenance doses of caffeine citrate 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 one-half the dose when expressed as caffeine citrate (20 mg caffeine citrate are equivalent to 10 mg caffeine base).

	Dose of caffeine citrate (Volume)	Dose of caffeine citrate (mg/kg body weight)	Route	Frequency
Loading dose	1.0 mL/kg body weight	20 mg/kg body weight	Intravenous infusion (over 30 minutes)	Once
Maintenance dose*	0.25 mL/kg body weight	5 mg/kg body weight	Intravenous infusion (over 10 minutes) or by oral administration	Every 24 hours*

* Beginning 24 hours after the loading dose

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. Additionally, doses may need to be adjusted according to medical judgment 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 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 metabolized to caffeine.

Caffeine 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.

Duration of treatment
The optimal duration of treatment has not been established. In a recent large multicentre study on preterm 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 clinical judgment in individual cases depending on the response to treatment, the continuing presence of apnoeic episodes despite treatment, or other clinical considerations. It is recommended that caffeine citrate administration should be stopped when the patient has 5-7 days without a significant apnoeic attack.
If the patient has recurrent apnoea, caffeine citrate administration can be restarted with either a maintenance dose or a half loading dose, depending upon the time interval from stopping caffeine citrate 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 caffeine citrate treatment monitoring of the patient should be continued for approximately one week.

Hepatic and renal impairment
There is limited experience in patients with renal and hepatic impairment. In a post authorisation safety study, the frequency of adverse reactions in a small number of very premature infants with renal/hepatic imparment appeared to be higher as compared to premature infants without organ impairment.
In the presence of renal impairment, there is increased potential for accumulation. A reduced daily maintenance dose of caffeine citrate 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
Caffeine citrate can be administered by intravenous infusion and by the oral route. The medicinal product must not be administered by intramuscular, subcutaneous, intrathecal or intraperitoneal injection.
When given intravenously, caffeine citrate should be administered by controlled intravenous infusion, using a syringe infusion pump or other metered infusion device only. Caffeine citrate can be either used without dilution or diluted in sterile solutions for infusion such as glucose 50 mg/mL (5%), or sodium chloride 9 mg/mL (0.9%) or calcium gluconate 100 mg/mL (10%) immediately after withdrawal from the ampoule.

1.3 Contraindications
Hypersensitivity to the active substance.

1.4 Special warnings and precautions for use
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 caffeine citrate. Failure to respond to caffeine treatment (confirmed if necessary by measurement of plasma levels) could be an indication of another cause of apnoea.

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 caffeine citrate, since caffeine readily crosses the placenta into the foetal circulation.

Breast-feeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine- containing foods and beverages or medicinal products containing caffeine, 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. Seizures
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 newborns with seizure disorders.

Cardiovascular reactions
Caffeine has been shown to increase heart rate, left ventricular output, and stroke volume in published studies. Therefore, caffeine citrate should be used with caution in newborns with known cardiovascular disease. There is evidence that caffeine causes tachyarrhythmias 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, caffeine citrate should be administered with caution.

Renal and hepatic impairment
Caffeine citrate should be administered with caution in preterm newborn infants 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 to be higher as compared to premature infants without organ impairment. 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 caffeine citrate should be carefully monitored for the development of necrotising enterocolitis.
Caffeine citrate should be used with caution in infants suffering gastro-oesophageal reflux, as the treatment may exacerbate this condition.
Caffeine citrate causes a generalised increase in metabolism, which may result in higher energy and nutrition requirements during therapy.
The diuresis and electrolyte loss induced by caffeine citrate may necessitate correction of fluid and electrolyte disturbances.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

1.5 Interaction with other medicinal products and other forms of interaction
Inter-conversion between caffeine and theophylline occurs in preterm newborn infants. These active substances should not be used concurrently.
Cytochrome P450 1A2 (CYP1A2) is the major enzyme involved in the metabolism of caffeine in humans. Therefore, caffeine has the potential to interact with active substances 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.Although few data exist on interactions of caffeine with other active substances in preterm newborn infants, lower doses of caffeine citrate may be needed following co-administration of active substances which are reported to decrease caffeine elimination in adults (e.g., cimetidine and ketoconazole) and higher caffeine citrate doses may be needed following co-administration of active substances 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 caffeine citrate with medicinal products that suppress gastric acid secretion (antihistamine H2 receptor blockers or proton-pump inhibitors) may in theory increase the risk of necrotising enterocolitis
Concurrent use of caffeine 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.

1.6 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.
Breast-feeding
Caffeine is excreted into breast milk and readily crosses the placenta into the foetal circulation.
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 with caffeine citrate.
Fertility
Effects on reproductive performance observed in animals are not relevant to its indication in the preterm newborn infants.

1.7 Effects on ability to drive and use machines
Not relevant.

Other special populations
In a post-authorisation safety study on 506 preterm infants treated with Peyona, safety data have been collected in 31 very premature infants with renal/hepatic impairment. Adverse reactions appeared to be more frequent in this subgroup with organ impairment than in other observed infants without organ impairment. Cardiac disorders (tachycardia, including one single case of arrhythmia) were mostly reported.

1.8 Overdose
Following overdose, published plasma caffeine levels have ranged from approximately 50 mg/L to 350 mg/L.
Symptoms
Signs and symptoms reported in the literature after caffeine overdose in preterm infants include hyperglycaemia, hypokalaemia, fine tremor of the extremities, restlessness, hypertonia, opisthotonus, tonic clonic movements, seizures, tachypnoea, tachycardia, vomiting, gastric irritation, gastro- intestinal haemorrhage, pyrexia, jitteriness, increased blood urea and 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. No deaths associated with caffeine overdose have been reported in preterm infants.
Management
Treatment of caffeine overdose is primarily symptomatic and supportive. Plasma potassium and glucose concentrations should be monitored and hypokalaemia and hyperglycaemia corrected. Plasma caffeine concentrations have been shown to decrease after exchange transfusion. Convulsions may be treated with intravenous administration of anticonvulsants (diazepam or a barbiturate such as pentobarbital sodium or phenobarbital).

2. PHARMACOLOGICAL PROPERTIES

2.1 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 A_{2A} subtypes, demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically in this indication.
Pharmacodynamic effects
Caffeine's main action is as a CNS stimulant. This is the basis of caffeine's effect in apnoea of prematurity, for which several mechanisms have been proposed for its actions including: (1) respiratory centre stimulation, (2) increased minute ventilation, (3) decreased threshold to hypercapnia, (4) increased response to hypercapnia, (5) increased skeletal muscle tone, (6) decreased diaphragmatic fatigue, (7) increased metabolic rate, and (8) increased oxygen consumption.

2.2 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. 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 (V_d) of caffeine in infants (0.8-0.9 L/kg) is slightly higherthan 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 fetal 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.

Storage: Store at a temperature between 15°C to 30°C.

Marketed by:
AMERICAN REMEDIES©
Care & Cure with Research
American Remedies Healthcare Pvt. Ltd.
(An ISO 9001-2015 Certified Company)
Gala No. 105 to 111, 1st Flr., Bldg. No. E-15/A,
Harihar Complex, Bhiwandi, Mumbai - 421302
E-mail: info@americanremedies.in
ICO: American Remedies LLC, DE, USA
© Copyright