Caffeine Citrate Injection USP 10 mg/ml

SPLT-AFF10SI-CR10-01

10 x 1 ml

Prescription Only Medicine

Caffeine Citrate Injection USP 10 mg/ml

(For IV use only)

SWISS™

Non-UV/Varnish Zone For **Batch Details** Size : 25 x 19 mm

Caffeine Citrate Injection USP 10 mg/ml

Composition:
Each ml contains:

Caffeine Citrate	10 mg
equivalent to Caffeine BP	5 mg
Water for Injections BP	q.s.

Dosage:
As directed by the physician.

Storage: Store below 25°C.

KEEP OUT OF REACH OF CHILDREN

Sterile, nonpyrogenic, preservative free.

For single use only.
Discard unused portion.

Mfg. Lic. No. : G/28/1078

Batch No. :

Mfg. Date :

Exp. Date :

(01)18904180208517
(21)2H4LH4Z80XGCPR4

Manufactured by:
SWISS PARENTERALS LTD.
808, 809 & 810,
Kerala Industrial Estate,
GIDC, Nr. Bavla,
Dist.: Ahmedabad-382220,
Gujarat, INDIA.

Caffeine Citrate Injection USP 10 mg/ml

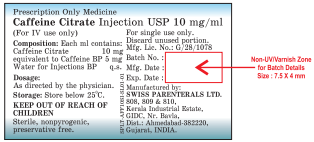
145 15 65

Caffeine Citrate Injection USP 10 mg/ml

PANTONE 3145 C

PANTONE 2985 C

BLACK



PANTONE 3145 C

PANTONE 2985 C

BLACK

Prescription Only Medicine

Caffeine Citrate Injection USP 10 mg/ml

(For IV use only)

Composition: Each ml contains:
Caffeine Citrate 10 mg
equivalent to Caffeine BP 5 mg
Water for Injections BP q.s.

Dosage:
As directed by the physician.

Storage: Store below 25°C.

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Discard unused portion.
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SPLT-AFF10SI-SL01-01

Non-UV/Varnish Zone for Batch Details Size : 7.5 X 4 mm

Enlarge Size

Prescription Only Medicine

Caffeine Citrate Injection USP 10mg/ml

(For IV use only)

Composition:
Each ml contains:

Caffeine Citrate	10mg
equivalent to Caffeine BP	5mg
Water for Injections BP	q.s.

Pharmacological properties
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 A1 and A2A subtypes, demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically in this indication.
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 (Cmax) ranged from 6 to 10 mg/l and the mean time to reach peak concentration (tmax) ranged from 30 min to 2 h. The extent of absorption is not affected by formula feeding but tmax 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 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 (t1/2) and fraction excreted unchanged in urine (Ae) of caffeine in infants are inversely related to gestational / postmenstrual age. In newborn infants, the t1/2 is approximately 3-4 days and the Ae is approximately 86% (within 6 days). By 9 months of age, the metabolism of caffeine approximates to that seen in adults (t1/2 = 5 hours and Ae = 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.
Therapeutic indications
Treatment of apnoea of prematurity.
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 doses of Caffeine Citrate Solution for Injection are expressed below. Please note:
(a) the dose expressed as caffeine citrate is twice the dose expressed as caffeine base.
(b) given orally or intravenously, caffeine is clinically effective within 4 hours. 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
(c) Caffeine Citrate 10mg/ml Solution for Injection is also effective when administered orally, and this route may be used alternatively without adjusting the dose.
(d) because of the slow elimination of caffeine in this patient population, there is no requirement for dose tapering on cessation of treatment.
(e) Infants must be of sufficient respiratory maturity not to require positive pressure ventilation.

	Dose of Caffeine Citrate 10mg/ml Solution for Injection	Dose Expressed as Caffeine Citrate	Dose Expressed as Caffeine Base	Route	Frequency
Loading Dose See (b) above	2ml/kg	20 mg/kg	10mg/kg	Intravenous** (over 30 min) or oral	Once
Maintenance Dose	0.5-1ml/kg*	5-10mg/kg*	2.5-5.0mg/kg*	Intravenous** (over 10 min) or oral	Every 24 hours***

* In some cases maintenance doses higher than 10mg/kg/day (expressed as caffeine citrate) may be required to achieve maximal efficacy (e.g.in continuing apnoeic episodes where plasma levels indicate the dose may be safely increased)
** By intravenous infusion
*** Beginning 24 hours after the loading dose(s)
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.
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 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 impairment appeared to be higher as compared to premature infants without organ impairment.
In the presence of renal impairment, a reduced daily maintenance dose of caffeine is required and the dose should be guided by blood caffeine measurements. There is increased potential for accumulation.
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 infant, hepatic disease may indicate a need for monitoring plasma levels and may require dose adjustments.
Adults and Children
Not applicable
Elderly
Not applicable
Method of administration
Caffeine Citrate Injection should not be given intramuscularly; being acidic, i.m. injection is likely to be painful. When given intravenously, it should be given as a slow infusion rather than a bolus injection; there is evidence that bolus administration may cause sudden changes in blood pressure.
Contraindications
Hypersensitivity to caffeine citrate or to any of the excipients.
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.
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 clinician should recognise this potential for accumulation and monitor plasma caffeine levels.

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 50micrograms/ml (optimally 10-30micrograms/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 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.

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.

For single use only. Any unused solution should be discarded.

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. 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.

Interconversion between caffeine and other xanthines such as theophylline has been reported in premature neonates. Therefore the concurrent use of these drugs 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 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.

Use in 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.

Undesirable effects

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:

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

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 include monitoring of blood levels of caffeine and supportive measures. Plasma potassium and glucose concentrations should be monitored and hypokalaemia and hyperglycaemia corrected.

Previous cases reported resolved satisfactorily.

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

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

Storage : Store below 25°C

Pack : Available in Glass ampule.

Pharmaceutical form: Solution for injection

Manufactured by:
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Ahmedabad, Gujarat, INDIA.

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