PATIENT LEAFLET: INFORMATION FOR THE USER

Caffeine Citrate 10mg/ml Solution for Injection

Equivalent to Caffeine 5mg/ml

Please read all of this leaflet carefully before your baby is given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask the hospital doctor who is looking after your baby. If your newborn gets any side effects, talk to your baby's doctor. This includes any possible side effects not listed in this leaflet. See section 4.

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What is in this leaflet:

1. What Caffeine Citrate 10mg/ml Solution for Injection is and what it is used for

- Caffeine belongs to a group of medicines known as methylxanthines
- It is used in the treatment of interrupted breathing in premature babies (primary apnoea of premature newborns).

These short periods when premature babies stop breathing are due to the baby's breathing centres not being fully developed. This medicine has been shown to reduce the number of episodes of interrupted breathing in premature newborns.

2. What you need to know before your baby is given Caffeine Citrate 10mg/ml Solution for Injection

Your baby should not be given Caffeine Citrate 10mg/ml Solution for Injection
- if allergic to caffeine citrate or to any of the other ingredients of this medicine listed in section 6

Warnings and precautions

Talk to your baby's doctor before your newborn is given Caffeine Citrate 10mg/ml Solution for Injection if your baby:
- has liver or kidney disease
- has had any unusual heart rhythms detected or heart disease
- suffers from seizures
- has frequent regurgitation
- produces more urine than usual
- has a reduced weight gain or food intake
- If you (the mother) consumed caffeine prior to delivery

Other medicines and Caffeine Citrate 10mg/ml solution for injection

Tell your baby's doctor if your newborn is taking, have recently taken or might take any other medicines.
- As with most medicines, Caffeine Citrate 10mg/ml Solution for Injection may interact with other medicines given at the same time. A premature baby may need many medicines, and any problems with caffeine are likely to be minor, but tell the doctor about any other medication they may not know about, particularly any other medicine (for example **theophylline**) given to your baby to help it breathe.
- Medications containing phenobarbitone or phenytoin, taken by the mother herself to treat epilepsy, may also have an effect on the way the baby reacts to caffeine therapy. If you have been taking treatment for epilepsy during pregnancy, please tell your baby's doctor about it.
- Doxapram (used to treat breathing difficulties)
- Cimetidine (used to treat gastric disease)
- Ketoconazole (used to treat fungal infections)
- This medicine may increase the risk for serious intestinal disease with bloody stools (necrotising enterocolitis) when administered with medicines used to treat gastric disease (such as antihistamine H2 receptor blockers or proton-pump inhibitors that reduces gastric acid secretion).

Pregnancy and breast-feeding

If you (the mother) are breast-feeding while your infant is treated with Caffeine Citrate 10mg/ml Solution for Injection, you should not drink coffee or take any other high caffeine product as caffeine passes into breast milk.

Caffeine Citrate 10mg/ml Solution for Injection contains sodium
- Caffeine Citrate 10mg/ml Solution for Injection contains 3.04mg sodium per 1 ml of the solution, which the doctor will need to consider if your baby is on a controlled sodium diet.
- Opening the ampoules may introduce glass particles into this solution. It is recommended that Caffeine Citrate 10mg/ml Solution for Injection be filtered before administration. Filters should **not** then be used to administer the dose from the syringe.

3. How Caffeine Citrate 10mg/ml Solution for Injection is used

Caffeine Citrate 10mg/ml solution for injection should only be used in a neonatal intensive care unit in which adequate facilities are available for patient surveillance and monitoring. Treatment should be initiated under supervision of a physician experienced in neonatal intensive care.

The doctor or nurse will administer Caffeine Citrate 10mg/ml Solution for Injection into a venous infusion (drip). It can also be equally effective when given by mouth, and all or some of the doses may be given this way when possible. **This medicine should not be given by intramuscular injection.**

The exact dose, to be determined by the doctor, depends on each baby's needs and response to the treatment, but will usually be:
- A starting dose of 20mg/kg of the baby's body weight calculated as caffeine citrate (equivalent to caffeine 10mg/kg or 2ml/kg of this solution) if by injection then infused over 30 minutes
- Followed after 24 hours by a lower daily maintenance dose of 5 to 10mg/kg of the baby's body weight calculated as caffeine citrate (equivalent to caffeine 2.5 to 5mg/kg or 0.5 to 1ml/kg of this solution) if by injection then infused over 10 minutes

If your baby fails to respond to the starting dose (after at least 4 hours), the doctor or nurse may give one more additional starter dose, before continuing to the lower maintenance doses.

Duration of treatment

Your baby's doctor will decide exactly how long your newborn must continue therapy with Caffeine Citrate 10mg/

Continued overleaf

TECHNICAL PRESCRIBING INFORMATION

Caffeine Citrate 10mg/ml Solution for Injection

Equivalent to Caffeine 5mg/ml

Composition

1. Each 1ml contains 10mg of caffeine citrate, equivalent to 5mg of caffeine.
   Each 2ml contains 20mg of caffeine citrate, equivalent to 10mg of caffeine.

   It also contains Water for Injections, Sodium Hydroxide, Dilute Hydrochloric Acid, Sodium Chloride and Citric Acid

Clinical Particulars

2.1. **Therapeutic Indications**
Treatment of apnoea of prematurity.

2.2. **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. The recommended doses of Caffeine Citrate 10mg/ml 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 (see 'special warnings and precautions for use' section 2.4 below)
(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.

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.

	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*	2.5-5mg/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 (eg 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)

Please see Section 2.4 below regarding use of filter straws. 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 10mg/ml 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.

2.3 **Contraindications**
Hypersensitivity to caffeine citrate or to any of the excipients listed in section 6.1

2.4 **Special Warnings and Precautions for Use**
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 (see also section 3.2).

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 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.

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.

This medicinal product contains 3.04mg sodium per 1ml of the solution. To be taken into consideration by patients on a controlled sodium diet.

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2.5 **Interactions 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.

2.6 **Fertility, Pregnancy and Lactation**

Fertility
Effects on reproductive performance observed in animals are not relevant to its indication in the preterm newborn infants.

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.

Lactation
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.

2.7 **Effects on Ability to Drive and Use Machines**

Not applicable.

2.8 **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, metabolism and nutrition disorders such as hyperglycaemia. These effects are dose related and may necessitate measurement of plasma levels and dose reduction.

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).
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

Additional information can be found on the product SmPC.

2.9 **Overdose**

Following overdose, published plasma caffeine levels have ranged from approximately 50 mg/l to 350 mg/l. Signs and symptoms of overdosage from these reports include jitteriness, tachycardia, tachypnoea, tremor, opisthotonos, rigidity and tonic-clonic movements hypokalaemia, fine tremor of the extremities, restlessness, seizures, tachypnoea, vomiting, 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.

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).

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ml Solution for Injection. If your baby has 5 to 7 days without apnoea attacks, the doctor will stop treatment.
The doctor may decide to check the levels of caffeine in a blood sample as a precaution, or if your baby is not responding to treatment as expected.

If your baby is given more Caffeine Citrate 10mg/ml Solution for Injection than they should
If too much caffeine solution is accidentally given to your baby, the side effects described above may become more noticeable. In cases of very high overdosage, fits can also occur. If signs of over-dosage are noticed, please tell the baby's doctor immediately.
Treatment with Caffeine Citrate 10mg/ ml Solution for Injection should be stopped immediately and your baby's doctor should treat the overdose.
If you have any further questions on the use of this medicinal product, ask your baby's doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. However, it is difficult to distinguish them from frequent complications occurring in premature babies and complications due to the disease.
While under treatment with Caffeine Citrate 10 mg/ml Solution for Injection, your newborn may experience some of the following reactions:

Serious side effects
- serious intestinal disease with bloody stools (necrotising enterocolitis).
- serious intestinal disease with bloody stools (necrotising enterocolitis).
- convulsion
- allergic reactions
- bloodstream infection (sepsis)

Other side effects
Common (may affect up to 1 in 10 people)
- cardiac disorders such as fast heart beat (tachycardia)
- increased sugar in blood or serum (hyperglycaemia)

Uncommon (may affect up to 1 in 100 people)
- cardiac disorders such as irregular heart beat (arrhythmia)

Not known (frequency cannot be estimated from the available data)
- reduced sugar in blood or serum (hypoglycaemia)
- failure to grow
- feeding intolerance
- stimulation of central nervous system such as irritability
- nervousness and restlessness
- brain injury
- deafness
- regurgitation
- increase in stomach aspirate
- increase of urine flow
- increase of certain urine components (sodium and calcium)
- changes in blood tests (reduced levels of haemoglobin after prolonged treatment)
- reduced thyroid hormone at the start of treatment

Reporting of side effects
If your newborn gets any side effects, talk to your baby's doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Caffeine Citrate 10mg/ml Solution for Injection

Keep this medicine out of the sight and reach of children. Store below 25°C. After opening the ampoule, the medicinal product should be used immediately.
Do not use this medicine after the expiry date which is stated on the label, or if there are any signs of discolouration or clouding of the solution.
The expiry date refers to the last day of that month. Ampoules of all parenteral solutions must be inspected visually for particulate matter prior to administration. After opening the ampoules, the medicinal product should be used immediately.

6. Contents of the pack and other information

What Caffeine Citrate 10mg/ml Solution for Injection contains
The active ingredient is caffeine citrate 10mg/ml, equivalent to caffeine 5mg/ml.
Other ingredients are:
- water for injections
- citric acid
- sodium chloride
- sodium hydroxide
- dilute hydrochloric acid

What Caffeine Citrate 10mg/ml Solution for Injection looks like and contents of the pack
- Each 1ml ampoule of Caffeine Citrate 10mg/ml Solution for Injection contains 10mg of caffeine citrate, equivalent to 5mg caffeine.
- Each 2ml ampoule of Caffeine Citrate 10mg/ml Solution for Injection contains 20mg of caffeine citrate, equivalent to 10mg caffeine.
- Caffeine Citrate 10mg/ml Solution for Injection is available in ampoules of 1ml or 2ml, in packs of 10 ampoules

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