1 NAME OF THE MEDICINAL PRODUCT

Caffeine Citrate 10mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Caffeine Citrate 10mg/ml

Each 1ml of solution contains, 10mg Caffeine Citrate, equivalent to 5mg of Caffeine.

Each 2ml of solution contains, 20mg Caffeine Citrate, equivalent to 10mg of Caffeine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

Appearance: clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of apnoea of prematurity.

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 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 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 4.4 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.

	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 (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)

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 (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)
- 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 (see section 4.4)
- 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 (see section 5.2). 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 (see sections 4.4 and 4.8).

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 (see sections 4.4 and 5.2).

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.

Alternative dosage forms for oral administration are available on the market.

4.3 Contraindications

Caffeine Citrate 10mg/ml Solution for Injection is contraindicated in patients who have demonstrated hypersensitivity to any of its components.

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4.4 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.

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 5.2).

If there is inadequate clinical response to the first loading dose, a second dose may be given, but if there is continued inadequate response, the plasma levels should be confirmed before further doses are given, as the failure to respond could be an indication

of another cause of apnoea. Plasma levels should not normally exceed 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 (see sections 4.2 and 5.2).
Breast-feeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine-containing foods and beverages or medicinal products containing caffeine (see section 4.6), since caffeine is excreted into breast milk (see section 5.2).

Theophylline
In newborns previously treated with theophylline, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with 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 (see sections 4.2, 4.8 and 5.2). Doses should be adjusted by monitoring of caffeine plasma concentrations to avoid toxicity in this population.

Necrotising enterocolitis
Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for the development of necrotising enterocolitis (see section 4.8).
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.

Caffeine Citrate 10mg/ml Injection contains sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions between caffeine and other medications have been reported in premature infants. Nevertheless, certain clinical situations have a theoretical potential for interaction. If the child's mother has been treated with phenytoin or phenobarbitone during pregnancy, the child might have enhanced hepatic enzyme induction and thus require higher doses of caffeine to compensate for increased caffeine metabolism. Plasma caffeine levels should be monitored during treatment in such situations, to ensure that adequate caffeine has been administered.

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.

4.6 Pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Caffeine has been reported to cause a number of adverse effects in premature neonates. Effects described include CNS stimulation such as irritability, restlessness and jitteriness and cardiac effects such as tachycardia, hypertension and increased stroke volume. These effects are dose related and may necessitate dose reduction and measurement of plasma levels. They are generally, although not exclusively, associated with serum caffeine concentrations ≥50micrograms/ml.

On the available evidence, caffeine does not appear to aggravate cerebral hypoxia or to exacerbate any resulting damage, although the possibility cannot be ruled out.

Caffeine treatment may increase gastro-oesophageal reflux, induce intestinal stasis and increase enteral secretion and gastric aspirations. Caffeine treatment may also reduce splanchnic blood flow. These factors may increase the risk of necrotising enterocolitis, although the prevention of systemic hypoxia may offset this theoretical increased risk. No significantly increased incidence of necrotising enterocolitis has been reported in clinical trials.

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

Other adverse effects associated with caffeine are effects on blood glucose levels such as hypoglycemia and hyperglycemia, and renal effects including increased urine flow rate, increased sodium and calcium excretion.

Available evidence does not indicate any adverse long-term effects of neonatal caffeine therapy on neurodevelopmental outcome, failure to thrive, or on the cardiovascular, gastrointestinal or endocrine systems. However, the possibility of long-term adverse effects cannot be ruled out.

A withdrawal syndrome after discontinuation of caffeine treatment has not been reported in this age group.

4.9 Overdose

Caffeine overdose has been reported in a few cases in newborns and premature infants. There should normally be no concern with blood levels below 50micrograms/ml; based on limited data, toxicity seems to occur when levels over 100micrograms/ml are reached. Symptoms of overdosage from these reports include jitteriness, tachycardia, tachypnoea, tremor, opisthotonos, rigidity and tonic-clonic movements. 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.

Treatment of overdosage should include monitoring of blood levels of caffeine and supportive measures. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pharmacological actions of caffeine result from its effect as a nonspecific adenosine receptor antagonist. The desired respirogenic activity of caffeine is an expression of its central nervous system stimulation, although it may also increase the sensitivity of respiratory response to carbon dioxide levels. Caffeine increases both tidal volume and frequency of ventilation.

In the premature infant, caffeine produced increased minute ventilation, mainly due to an increase in inspiratory drive as shown by an increased mean respiratory flow (V_T/T_1). Caffeine regularises the breathing pattern, indicating that it stabilises the oscillation of the respiratory control system.

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

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

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

The stimulant effect may affect sleep patterns.

5.2 Pharmacokinetic properties

In neonates, orally administered caffeine has been shown to be rapidly and completely absorbed. Peak plasma levels and extent of absorption are comparable for oral administration and intravenous infusion. In premature infants, the volume of distribution is reported to be 0.8 to 0.9 L/kg. It is widely distributed throughout the body and passes readily into the central nervous system and into saliva.

Neonates, especially premature neonates, have a greatly reduced capacity to metabolise caffeine and it is largely excreted unchanged in the urine until hepatic metabolism

becomes significantly developed, a process which is completed by about 6 months of age. Elimination half-lives may be in excess of 52-96 hours in premature neonates.

Interconversion between caffeine and theophylline has been observed in premature infants. Approximately 3% to 8% of caffeine administered is Expected to be converted to theophylline. After theophylline administration, caffeine concentrations are approximately 25% of theophylline concentrations.

The predominant caffeine metabolic process in premature infants appears to be via N7-demethylation.

Low concentrations of caffeine may be present in breast milk of the mother, and it crosses the placenta.

5.3 Preclinical safety data

There is no preclinical data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

Sodium Hydroxide

Dilute Hydrochloric Acid

Sodium Chloride

Citric Acid

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Type I clear glass ampoule containing 1ml or 2ml in packs of 10 ampoules.

6.6 Special precautions for disposal and other handling

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

There was no detectable degradation of the solution when diluted 50/50 with commercial glucose 5%, glucose 4% saline 0.18%, and sodium chloride 0.9% infusions, when stored in disposable plastic syringes at room temperature for 4 hours.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 01883/0344

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/02/2008

10 DATE OF REVISION OF THE TEXT

06/05/2026