

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Caffeine 5mg/ml Solution for Injection

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Caffeine 5mg/ml

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

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

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**

The recommended doses of Caffeine 5mg/ml Solution for Injection are expressed below. Please note:

(a) the dose expressed as caffeine base is one half the dose when expressed as caffeine citrate.

(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 5mg/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.

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

\* In some cases maintenance doses higher than 5mg/kg/day (expressed as caffeine base) 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)

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.

Caffeine 5mg/ml Solution for 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.

Please see Section 4.4 below regarding use of the filter straws provided.

*Hepatic and Renal 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 reduce maintenance caffeine dose requirements.

### **Adults and Children**

Not applicable

### **Elderly**

Not applicable

## **4.3 Contraindications**

Caffeine 5mg/ml Solution for Injection is contraindicated in patients who have demonstrated hypersensitivity to any of its components.

## **4.4 Special warnings and precautions for use**

Care should be taken to exclude other causes of apnoea before initiation of treatment.

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 50mcg/ml (optimally 10-30mcg/ml).

There may be pre-existing caffeine in the blood of neonates

(a) whose mothers may have ingested large quantities of caffeine prior to delivery.

(b) who have previously been treated with theophylline, which is metabolised to caffeine.

There is evidence that caffeine causes tachyarrhythmias in susceptible individuals. In newborn babies this is usually a simple sinus tachycardia. If there have been any unusual rhythm disturbances on a CTG trace before the baby is born, caffeine should

be administered with caution. Caffeine should be used with caution in infants suffering gastro-oesophageal reflux, as the drug may exacerbate this condition.

Caffeine may increase cardiac output and heart rate in therapeutic doses. Caffeine should be used with caution in infants with cardiac disease.

Caffeine 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 may necessitate correction of fluid and electrolyte disturbances.

This medicinal product contains 7.7mg sodium per 1ml of the solution. To be taken into consideration by patients on a controlled sodium diet.

Opening the ampoules may introduce glass particles into this solution. It is recommended that the solution be filtered prior to use by means of the filter straws provided in the pack, to prevent administration of these particles.

**DIRECTIONS:** Use aseptic technique.

- Firmly attach syringe to filter straw hub.
- Remove device from package taking care not to touch the plastic tubing.
- Insert the filter straw tubing into the open glass ampoule.
- Withdraw fluid through the filter straw into the syringe.
- Remove filter straw from the syringe before using the solution.

#### **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  $\geq 50$ mcg/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 50mcg/ml; based on limited data, toxicity seems to occur when levels over 100mcg/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**

No special precautions for storage.

## **6.5 Nature and contents of container**

Type I clear glass ampoule containing 1ml or 2ml in packs of 10 ampoules. The pack also contains 10 filter straws.

## **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 20346/0002

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08/02/2008

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