SCHEDULING STATUS

S3

PROPRIETARY NAME (and dosage form)

CAYONA solution for infusion and oral solution

COMPOSITION

Each 1 ml ampoule contains 20 mg caffeine citrate (equivalent to 10 mg caffeine).

List of excipients:

Citric acid monohydrate

Sodium Citrate

Water for injection

PHARMACOLOGICAL CLASSIFICATION

A 1.4 Respiratory stimulants

PHARMACOLOGICAL ACTION

PHARMACODYNAMIC PROPERTIES

Caffeine is structurally related to methylxanthines theophylline and theobromine. Most of the effects of caffeine 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.

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.

In a study investigating the clinical efficacy of caffeine citrate, caffeine citrate was compared to placebo in preterm infants (gestational age 28 to < 33 weeks) with apnoea of prematurity. There were more days without any apnoea under caffeine citrate treatment (3,0 days, versus 1,2 days for placebo; p = 0,005); also, there was a higher percentage of patients with no apnoea's for ≥ 8 days (caffeine 22 % versus placebo 0 %). A study investigated short-term and long-term (18 - 21 months) outcomes of premature infants treated with caffeine citrate. Caffeine therapy reduced the rate of bronchopulmonary dysplasia [odds ratio (95 % CI) 0,63 (0,52 to 0,76)] and improved the rate of survival without neurodevelopmental disability [odds ratio (95 % CI) 0,77 (0,64 to 0,93)]. The effect of caffeine on death and disability differed depending on the degree of respiratory support infants needed at randomisation, indicating more benefit for the supported infants [odds ratio (95 % CI) for death and disability, see table below].

Death or disability according to subgroup of respiratory support at entry to study.

Subgroups	Odds ratio (95 % CI)
No support	1,32 (0,81 to 2,14)
Non invasive support	0,73 (0,52 to 1,03)
Endotracheal tube	0,73 (0,57 to 0,94)

PHARMACOKINETICS

Solubility:

Caffeine citrate readily dissociates in aqueous solution. The citrate moiety is rapidly metabolised 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 neonates, the peak plasma caffeine concentration (C_{max}) ranged from 6 to10 mg/l and the mean time to reach peak concentration (t_{max}) ranged from 30 min to 2 hours. 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 neonates approximate to their plasma levels. The mean volume of distribution (V_d) 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 is not available for neonates or infants. Caffeine readily crosses the placenta into the fetal circulation and is excreted into breast milk.

Metabolism:

Caffeine metabolism in preterm neonates is very limited due to their immature hepatic enzyme systems and most of the active substance is eliminated in urine. Inter-conversion between caffeine and theophylline has been reported in preterm neonates; 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 neonates, 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 neonates, 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 neonates 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.

INDICATIONS

Treatment of primary apnoea of premature newborns.

CONTRA-INDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS and SPECIAL PRECAUTIONS

Treatment with **CAYONA** 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.

In neonates 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 **CAYONA**, since caffeine readily crosses the placenta into the foetal circulation.

Breast-feeding mothers of neonates treated with **CAYONA** should not ingest caffeine-containing foods and beverages or medicinal products containing caffeine since caffeine is excreted into breast milk. (See PREGNANCY AND LACTATION.)

In newborns previously treated with theophylline, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with **CAYONA** because preterm infants metabolise theophylline to caffeine. Caffeine is a central nervous system stimulant and seizures have been reported in cases of caffeine overdose. Extreme caution must be exercised if **CAYONA** is used in newborns with

seizure disorders. Caffeine has been shown to increase heart rate, left ventricular

output, and stroke volume in published studies. Therefore, **CAYONA** 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, **CAYONA** should be administered with caution.

CAYONA should be administered with caution in preterm neonates with impaired renal or hepatic function .Doses should be adjusted by monitoring of caffeine plasma concentrations to avoid toxicity in this population.

Necrotising enterocolitis is a common cause of morbidity and mortality in premature neonates. 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 **CAYONA** should be carefully monitored for the development of necrotising enterocolitis.

CAYONA should be used with caution in infants suffering gastro-oesophageal reflux, as the treatment may exacerbate this condition. **CAYONA** causes a generalised increase in metabolism, which may result in higher energy and nutrition requirements during therapy. The diuresis and electrolyte loss induced by **CAYONA** may necessitate correction of fluid and electrolyte disturbances.

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 **CAYONA.** Failure to respond to caffeine treatment (confirmed if necessary by measurement of plasma levels) could be an indication of another cause of apnoea.

INTERACTIONS

Inter-conversion between caffeine and theophylline occurs in preterm neonates. These active substances should not be used concurrently. Cytochrome P450 $_1A_2$ (CYP_1A_2) 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 CYP_1A_2, inhibit CYP_1A_2, or induce CYP_1A_2.

However, caffeine metabolism in preterm neonates is limited due to their immature hepatic enzyme systems. Lower doses of **CAYONA** 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 **CAYONA** 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 **CAYONA** with medicinal products that suppress gastric acid secretion (antihistamine H_2 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.

PREGNANCY AND LACTATION

Caffeine is excreted into breast milk and readily crosses the placenta into the foetal circulation. Breast-feeding mothers of neonates treated with **CAYONA** should not ingest caffeine-containing foods, beverages or medicinal products containing caffeine. (See WARNINGS and SPECIAL PRECAUTIONS).In neonates 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 **CAYONA.**

DOSAGE AND DIRECTIONS FOR USE

Treatment with **CAYONA** 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.

Intravenous Infusion

The recommended dose regimen in previously untreated infants is a loading dose of 20 mg **CAYONA** 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.

Oral administration

The recommended loading dose and maintenance doses of **CAYONA** 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 half the dose when expressed as caffeine citrate (20 mg **CAYONA** is equivalent to 10 mg caffeine base).

	Dose of **CAYONA** (Volume)	Dose of **CAYONA** (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*
Maintenance dose*	0,25 ml/kg body weight	5 mg/kg body weight	Oral administration	Every 24 hours*

*Beginning 24 hours after the loading dose

In preterm infants with insufficient clinical response to the recommended loading dose, a second loading dose of 10-20 mg/kg maximum may be given after 24 hours.

Higher maintenance doses of 10 mg/kg body weight could be considered in case of insufficient response, taking into account the potential for accumulation of caffeine due to the long half- life in premature neonates and the progressively increasing capacity to metabolise caffeine in relation to post-menstrual age.

Where clinically indicated, caffeine plasma levels should be monitored.

The diagnosis of apnoea of prematurity may need to be reconsidered if patients do not respond adequately to a second loading dose or maintenance dose of

10 mg/kg/day.

When given intravenously, **CAYONA** should be administered by controlled intravenous infusion, using a syringe infusion pump or other metered infusion device only. **CAYONA** can be either used without dilution or diluted in sterile solutions for infusion such as 5 % glucose or 0,9 % sodium chloride 10 % calcium gluconate immediately after withdrawal from the ampoule.

CAYONA must not be mixed or concomitantly administered in the same intravenous line with other medicinal products except those mentioned above.

Routine monitoring of plasma caffeine levels is not necessary in the majority of preterm infants. However, 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 following routine monitoring of caffeine plasma concentrations in 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 metabolised 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. **CAYONA** can be administered by intravenous infusion and by the oral route. The product must not be administered by intramuscular, subcutaneous, intrathecal or intraperitoneal injection.

Duration of treatment

The optimal duration of treatment has not been established. In a study on premature 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 the response to treatment, the continuing presence of apnoeic episodes despite treatment, or other clinical considerations. It is recommended that **CAYONA** administration should be stopped when the patient has 5-7 days without a significant apnoeic attack.

If the patient has recurrent apnoea, **CAYONA** administration can be restarted with either a maintenance dose or half a loading dose, depending upon the time interval from stopping

CAYONA 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 apnoea's after cessation of **CAYONA** treatment monitoring of the patient should be continued for approximately one week.

Patient with impaired hepatic or renal function

The safety of **CAYONA** in patients with renal insufficiency has not been established. In the presence of renal impairment, there is increased potential for accumulation. A reduced daily maintenance dose of **CAYONA** 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.

SIDE – EFFECTS

Effects described include central nervous system (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 measurement of plasma levels and dose reduction.

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Sepsis	Frequency not known
Immune system disorders	Hypersensitivity reaction	Less frequent
Metabolism and nutrition disorders	Hypoglycaemia, hyperglycaemia, failure to thrive, feeding intolerance	Frequency not known
Nervous system disorders	Irritability, jitteriness, restlessness, brain injury*, convulsion*	Frequency not known
Ear and labyrinth disorders	Deafness*	Frequency not known
Cardiac disorders	Tachycardia, also associated with increased left ventricular output and increased stroke volume	Frequency not known
Gastrointestinal disorders	Regurgitation, increased gastric aspirate, necrotising enterocolitis**	Frequency not known
General disorders and administration site conditions	Infusion site phlebitis, infusion site inflammation	Frequent
Investigations	Urine output increased, urine sodium and calcium increased, haemoglobin decreased, thyroxine decreased	Frequency not known

*Brain injury, convulsion and deafness were observed, but were more frequent in the placebo group.

**See below

Necrotising enterocolitis

Necrotising enterocolitis is a common cause of morbidity and mortality in premature neonates. 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 **CAYONA** should be carefully monitored for the development of necrotising enterocolitis. Caffeine may suppress erythropoietin synthesis and hence reduce haemoglobin concentration with prolonged treatment. Transient falls in thyroxine (T4) have been recorded in infants at the start of therapy but these are not sustained with maintained therapy. Available evidence does not indicate any adverse long-term reactions of neonatal caffeine therapy as regards neurodevelopmental outcome, failure to thrive or on the cardiovascular, gastrointestinal or endocrine systems. Caffeine does not appear to aggravate cerebral hypoxia or to exacerbate any resulting damage, although the possibility cannot be ruled out.

KNOWN SYMPTOMS OF OVERDOSAGE AND TREATMENT

Following overdose, published plasma caffeine levels have ranged from approximately 50 mg/l to 350 mg/l. 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.

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).

IDENTIFICATION

Clear, colourless solution free of visible particles.

PRESENTATION

CAYONA is supplied in a 1 ml clear, colourless Type 1 glass ampoule. Pack size of 10 ampoules.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep out of reach of children.

CAYONA should be inspected visually for particulate matter and discoloration prior to administration. Discard ampoules containing discoloured solution or visible particulate matter.

After opening the ampoule, the product should be used immediately.

For single use only.

Discard any unused portion left in the ampoule.

From a microbiological point of view, when administered with solutions for infusion the product should be used immediately after dilution by aseptic technique.

Chemical and physical compatibility of the diluted solution has been demonstrated for 24 hours at or below 25 °C and at or below 2 - 8 °C.

REGISTRATION NUMBER

48/1.4/0091

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