CAFFEINE 5MG/ML SOLUTION FOR INJECTION
PL 20346/0002

UKPAR

TABLE OF CONTENTS

Lay Summary ................................................. Page 2
Scientific discussion ............................... Page 3
Steps taken for assessment ....................... Page 17
Steps taken after authorisation – summary .... Page 18
Summary of Product Characteristics ....... Page 19
Patient Information Leaflet ....................... Page 28
Labelling .................................................... Page 31
LAY SUMMARY

The MHRA granted Viridian Pharma Ltd a Marketing Authorisation (licence) for the medicinal product Caffeine 5mg/ml Solution for Injection (PL 20346/0002). This product is a prescription only medicine (POM) used to stimulate breathing and for the treatment of breathing difficulties as a result of being born prematurely.

Caffeine 5mg/ml Solution for Injection contains the active ingredient caffeine. Caffeine is a central nervous system stimulant.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Caffeine 5mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 7
Clinical assessment (including statistical assessment) Page 12
Overall conclusion and risk benefit assessment Page 16
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Caffeine 5mg/ml Solution for Injection (PL 20346/0002) to Viridian Pharma Ltd on 08 February 2008.

This application was submitted as an abridged application according to Article 10a of Directive 2001/83/EC, as amended.

The product contains the active ingredient caffeine and is indicated for the treatment of apnoea of prematurity.

Caffeine is a methylxanthine and acts as a nonspecific adenosine receptor antagonist.

The application for Caffeine 5mg/ml Solution for Injection has provided bibliographic published literature on the availability, efficacy and safety of this product.
PHARMACEUTICAL ASSESSMENT

COMPOSITION
The product is formulated as a solution for injection containing the active pharmaceutical ingredient caffeine at a strength of 5mg/ml. The excipients present are water for injections, sodium hydroxide, dilute hydrochloric acid, sodium chloride and citric acid.

Caffeine 5mg/ml Solution for Injection is presented in clear type I glass ampoules containing 1ml or 2ml, in packs of 10 ampoules.

DRUG SUBSTANCE
Caffeine
All aspects of the manufacture and control of caffeine are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of caffeine for inclusion in this medicinal product.

Stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT
Other ingredients
All excipients used in the manufacture of the solution for injection are routinely tested for compliance with their respective European Pharmacopoeial monograph.

Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

Manufacture
A full description and a basic flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of both vial sizes. The results are satisfactory.

Finished product specification
The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification. Suitable reference standards were used.

Container Closure System
Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food. The filter straw is CE marked for use as a medical
device for parenteral solutions. The filter straws were incorporated into the packaging to ensure that any glass particles which may be present after opening the ampoules are removed from the solution prior to administration.

**Stability**
Finished product stability data support the proposed shelf-life of 3 years with no special storage conditions.

**SPC, PIL, Labels**
The SPC, PIL and labels are pharmaceutically acceptable.

The marketing authorisation holder has provided a commitment to update the Marketing Authorisation with a patient information leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1 July 2008.

**CONCLUSION**
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

INTRODUCTION
This is a national application. The active ingredient is caffeine citrate which is intended for the treatment of apnoea of prematurity. The application is submitted under Article 10a of Directive 2001/83/EC, for a new indication and is supported by bibliographic data. The recommended daily dose is 2.5-5 mg/kg following a loading dose of 10 mg/kg (doses are expressed as caffeine base).

No preclinical studies have been conducted by the applicant and the preclinical dossier is purely supported by bibliographic data. Information is provided on the extent and type of bibliographic search that has been employed.

PHARMACODYNAMICS
As the Expert points out there is widespread dietary intake of caffeine and there is no restriction on the dietary intake even during pregnancy. It is apparent from the literature that caffeine and theophylline have been used in apnoea of prematurity as early as 1979. The literature would indicate that the desired plasma level for the treatment of apnoea is between 5-20 μg/ml.

In a study of 18 preterm infants (gestational age of 28-33 weeks) with idiopathic apnoea, 9 were treated with caffeine i.v., 10 mg/kg loading dose + 5 mg/kg/day maintenance dose for 4 weeks. Nine infants served as a control group. Serum caffeine levels ranged from 10-15 μg/ml. Caffeine treatment resulted in an increase in oxygen consumption and a decrease in weight gain in comparison to the controls. The prevalence of apnoea decreased from 20 to 8 episodes per day in the treated group.

In a 2001 review article on the use of caffeine citrate in apnoea of prematurity it was concluded that ‘Caffeine citrate was generally well tolerated by neonates in clinical trials and it decreased the incidence of apnoea of prematurity compared to placebo. It has demonstrated similar efficacy to theophylline, but is generally better tolerated and has a wider therapeutic index. Caffeine should be considered the drug of choice when pharmacological treatment of apnoea of prematurity is required.’

Although the exact mechanism of action of caffeine, relevant to the therapeutic indication, is not precisely defined, it seems likely that it is related to the CNS stimulant action of caffeine as a result of adenosine receptor antagonist. The majority of the data to indicate that caffeine is effective in the treatment of apnoea comes from numerous small clinical studies. It would appear that the dosing regimen as proposed by the applicant is the most commonly used, one could probably call it the ‘recognised standard’ amongst those using caffeine. It is also unknown whether there is likely to be any rebound effect following withdrawal of the caffeine. However, this seems unlikely given the very long T1/2. No information is provided on the likely duration of treatment of pre-term babies; one paper suggests that 14 days is sufficient.
Pharmacodynamics for the Proposed Indications

The primary mechanism of action relevant to the proposed indication is antagonist of adenosine at the A₁ and A₂A receptors in the CNS (inhibitory constants of 44 and 40 μmol/l, respectively). The exact mechanism by which caffeine alleviates neonatal apnoea is unknown, but may be via the effects caffeine has on respiratory function. Caffeine is known to increase mean respiratory rate and minute volume, stimulate respiratory centres, and increase pulmonary blood flow and increase central medullary areas to hypercapnia.

Secondary Pharmacology

The effects of caffeine on physiological systems, other that the respiratory system, are summarised in the dossier. The most common side effects with caffeine in preterm infants appear to be tachycardia and GI intolerance. It has been suggested that these effects are not due to the caffeine itself but due to theophylline levels. GI intolerance is certainly more common in infants treated with theophylline than with caffeine. Caffeine does not appear to affect cerebral blood flow of preterm infant as it does in adults.

PHARMACOKINETICS

The data presented are limited and some of the data that are presented may not be relevant to the proposed use. It is apparent that metabolism and excretion of caffeine is greatly different from adults. Metabolism by the liver is virtually nil in neonates and excretion is much slower than in adults.

Absorption

Summary of some of the pharmacokinetic data for caffeine
(Values are expressed as caffeine base):

<table>
<thead>
<tr>
<th>Species, sex (M,F)</th>
<th>Dose (mg/kg/day) x n days treatment, Route</th>
<th>Cmax μg/ml</th>
<th>Tmax hr</th>
<th>t½ hr</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm infants</td>
<td>10.2 x 1, i.v. 10 x 1, p.o.</td>
<td>11.5</td>
<td>-</td>
<td>102.9</td>
<td>Bioavailability almost complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-10</td>
<td>0.5-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm infants</td>
<td>11.2 x 9, p.o. 2.5 x 19, p.o.</td>
<td>45.3 (ss)</td>
<td>13.7 (ss)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ss = steady state

Caffeine is rapidly and almost completely absorbed following oral administration (>95%) with a Tmax of 0.5-2 hours. The volume of distribution is about 0.9 l/kg in preterm infants.

Plasma levels of caffeine were similar in newborn babies following a loading dose of 15 mg/kg and subsequent maintenance doses of 2 mg/kg/day whether given orally or intramuscularly.

Feeding appears to have no effect on the absorption of caffeine in preterm infants.
Distribution
Plasma protein binding of caffeine is reported to be 35% in humans. Caffeine crossed the placenta and is also excreted in milk. In paired maternal-fetal samples, the concentration of caffeine was slightly higher in maternal plasma (0.3-2.0 μg/ml) compared to fetal amniotic fluid (0.1-1.6 μg/ml).

Metabolism
During the first month of life, there is little metabolism of caffeine and more than 85% is excreted unchanged in the urine. Caffeine remains the predominant component for the first 3 months, but its percentage decreased gradually to adult values of <2% by the age of 7-9 months. The 4 day plasma T1/2 of caffeine characteristic of the newborn depends largely on slow urinary excretion of unchanged drug since there is little or no metabolism. The subsequent decrease in the T1/2 to about 4 hours by 8 months correlates closely with the rise in metabolic capability.

Literature data are provided on the metabolism of caffeine in rats and man and there appear to be differences in their metabolism. However, this information is probably of little relevance considering the proposed indication, although it is useful in determining exposure in toxicological studies.

Enzyme Induction/Inhibition
Caffeine is metabolised by CYP1A2 in adults and there is the potential for drug interactions that are substrates, inhibitors, or inducers of CYP1A2. However, as there is virtually no metabolism of caffeine in the proposed patient population, interactions at the CYP level are very unlikely. A number of caffeine interactions have been reported in the literature as a result of altered plasma clearance. These are probably the result of interaction at CYP level and are unlikely to be relevant (e.g. cimetidine, fluconazole). Some pharmacological interactions reported may be relevant to neonates (e.g. caffeine counteracts diazepam and antagonises pentobarbital).

TOXICOLOGY
Information in the literature would indicate that the per-capita consumption of caffeine from all sources is about 3-7 mg/kg/day. Consumption by pregnant women is estimated at 1-2.4 mg/kg/day.

There do not appear to be any concerns arising from the impurity profile or the excipients in the product. Studies in animals are very limited and would normally be considered inadequate to support the proposed indication. However, the extensive use of caffeine in the form of beverages and the clinical data base in preterm infants is considered to give adequate reassurance on the safety of caffeine. Nearly all the published studies recommend plasma concentration between about 5-20 μg/ml for the therapeutic treatment of apnoea. Plasma levels of caffeine > 50 μg/ml have been associated with clinical signs of overdose. There appears to be large intra-individual variation in plasma levels in neonates and most publications recommend the monitoring of plasma levels.

In general overdose with caffeine in premature infants has resolved slowly. In one case this was greatly speeded up by exchange transfusion.
Single Dose Toxicity Studies

Side effects in infants are generally first evident by jitteriness at plasma concentrations of > 50 μg/ml. There have been a number of reports in the literature of caffeine overdose in neonates at dose ranging from 36-160 mg/kg. Clinical signs at these doses are tachypnea, fine tremor of the extremities, opisthotonus, tonic-clonic movements, and nonpurposeful jaw and lip movements.

Oral LD_{50} values for mice, rats, hamsters and rabbits range from 127 to 335 mg/kg.

Repeated Dose Toxicity Studies

In a 90 day study in Syrian golden hamsters (Kamino et al. 1992), the only effect observed was morphological signs of follicular activation of the thyroid. However, when this study was later repeated (1995) using an identical study design and comparable dose ranges (caffeine administered in the drinking water), this observation could not be reproduced. The only effect in this latter study was a transient increase in T3 (tri-iodothyronine) after 3 days. Caffeine plasma levels in this latter study were up to 2.9 and 7.2 μg/ml for females and males respectively.

One publication found no difference in growth and development of 21 caffeine treated low-birth weight infants with neonatal apnoea compared to 21 matched control infants.

REPRODUCTION STUDIES

There have been various reviews of epidemiological studies in humans, many of which give conflicting information. The general consensus appears to be that adverse effects with caffeine on reproductive outcome are only seen at very large doses and that in general, caffeine is considered safe. However, pregnant women are still advised to moderate their caffeine consumption, particularly as caffeine elimination is reduced in the last trimester of pregnancy. Caffeine is not considered to be a teratogen. The lack of animal studies is not considered to be a problem bearing in mind the human experience of caffeine ingestion during pregnancy.

A number of studies were provided on the teratogenic or enhancement of teratogenic potential of other drugs by caffeine, however, these are not considered to be relevant to the proposed indication. For example, caffeine (50 mg/kg) has been shown to enhance the teratogenic effect (frequency and severity of ectrodactyly) of acetazolamide (200 and 1000 mg/kg) administered at gestation day 9 in C57BL/6J mice. The combination of paracetamol and caffeine at dose up to 350 mg/kg/day 70 mg/kg/day, respectively, administered to Wistar rats from GD 8-14 showed no evidence of a teratogenic effect. Fetal weight, length and placental weight were decreased.

There is evidence from an epidemiological study (2000) that caffeine may increase the risk of an early spontaneous abortion among non-smoking women. An earlier review (1993) concluded that ingestion of caffeine >300 mg/day is associated with an increased risk of intrauterine growth retardation but there was conflicting evidence on the effect on spontaneous abortions. A meta-analysis (1998) of 42,988 pregnancies revealed a small but statistically significant increase in the risk for spontaneous
abortions and low birth weight babies in pregnant women consuming >150 mg caffeine per day.

The only study considered to be of relevance to the proposed patient population would be a peri/post natal study. However, there do not appear to be specific studies of this nature published. One study investigates the effect of caffeine on development when given to premature infants; it was concluded that caffeine had no effect.

A study by Palm et al. (1978) investigated the effect of diluted coffee as the sole beverage at doses equivalent to 9, 19 and 38 mg/kg/day of caffeine from 5 weeks prior to mating to day 27 post partum. Other groups received caffeine (30 mg/kg/day) by gavage or in the drinking water. Group sizes were 25 females per group but only 5 per group were allowed to deliver spontaneously and were followed to determine the effect of treatment on post-natal development and reproductive function of the F1 generation. This study did not indicate a teratogenic effect. There was some indication of a delay in development as evidenced by reduced ossification in caffeine treated groups. In the F1 animals permitted to mature, no gross anomalies were observed and no treatment-related differences in body weigh, food or water consumption or reproductive performance.

MUTAGENIC POTENTIAL
Overall, caffeine is not generally regarded as mutagenic or clastogenic.

ONCOGENIC/CARCINOGENIC POTENTIAL
The very limited data presented would indicate that caffeine is tumorigenic in mice but not in rats. Normally for treatment periods of less than 6 months, carcinogenicity studies would not be required. The treatment times proposed are unlikely to warrant carcinogenicity studies. Even though the patient population will be at a very vulnerable age, the assessor is of the opinion that there is no carcinogenic risk.

ENVIRONMENTAL RISK ASSESSMENT (ERA)
An Environmental Risk Assessment has not been provided. However, considering the global ingestion of caffeine products, the contribution from the treatment of premature infants is likely to negligible.

THE PHARMACO-TOXICOLOGICAL EXPERT REPORT
The Expert Report was written by an appropriately qualified medical doctor. It is an adequate overview of the product based on data from the literature.

OVERALL CONCLUSIONS ON PRODUCT SAFETY
Even though the preclinical dossier would not normally be considered adequate, the lack of preclinical data is justified by the extensive experience of caffeine as a beverage and the clinical experience to date in the proposed patient population. There are no preclinical objections to the grant of a Marketing Authorisation for this product.
CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

This is a National application for an injectable Caffeine Citrate preparation for the treatment of apnoea of prematurity. No injectable caffeine product is currently licensed in the UK, nor is any caffeine product approved for the requested indication.

The application was submitted under the provisions of Directive 2001/83/EC Article 10a which requires that detailed references to published scientific literature are presented to show that the constituents of the proposed medicinal product have a well-established medicinal use, with recognised efficacy and an acceptable level of safety.

The initial application submitted was considered to be inadequate. Following advice from the Commission on Human Medicines (CHM), the applicant submitted a detailed written summary of the relevant bibliographic data including a tabulated summary for each of the submitted publications in addition to a more thorough clinical expert report. These data fulfil the requirements of an application of this type and are satisfactory.

INDICATION

The following indication has been approved:

Treatment of apnoea of prematurity.

DOSE AND DOSE SCHEDULE

The following dose and dose schedule have been approved:

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).

(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.

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Dose of Caffeine 5mg/ml Solution for Injection</th>
<th>Dose Expressed as Caffeine Citrate</th>
<th>Dose Expressed as Caffeine Base</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Se (b) Above</td>
<td>2ml/kg</td>
<td>20 mg/kg</td>
<td>10mg/kg</td>
<td>Intravenous** (over 30 min) or oral</td>
<td>Once</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance Dose</th>
<th>Dose of Caffeine 5mg/ml Solution for Injection</th>
<th>Dose Expressed as Caffeine Citrate</th>
<th>Dose Expressed as Caffeine Base</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-1ml/kg*</td>
<td>5-10mg/kg*</td>
<td>2.5-5.0mg/kg*</td>
<td>Intravenous** (over 10 min) or oral</td>
<td>Every 24 hours***</td>
<td></td>
</tr>
</tbody>
</table>

* 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.

**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

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**
A review of the relevant publications and the clinical expert report confirm that the content of section 5.2 of the SPC is a reasonable summary of the pharmacokinetics of caffeine in this population. It is notable that caffeine penetrates into the cerebrospinal fluid (CSF) more readily than theophylline as it is more lipophilic.

**Pharmacodynamics**
A review of the relevant publications confirms that the content of section 5.1 of the SPC is a reasonable summary of the primary and key secondary pharmacodynamic activities of caffeine in this patient population.

**CLINICAL EFFICACY**
There are only a small number of randomised controlled efficacy trials in the literature and only a single randomised placebo-controlled trial. The clinical expert argues that this is because a placebo-controlled trial of caffeine for apnoea of prematurity treatment would be unethical because there is a wide agreement and experience supporting caffeine’s efficacy. Therefore, other than the mentioned study, comparative studies have compared caffeine with historical controls or other treatment groups. It is accepted that there would now be major difficulties in performing adequate placebo-controlled trials in this clinical situation.

The total body of evidence from controlled and uncontrolled studies is sufficient to establish that caffeine citrate at the dose proposed in the SPC has highly clinically significant efficacy in the treatment of apnoea of prematurity.

**CLINICAL SAFETY**
The clinical expert report provides a review of safety issues identified in the bibliographic dossier which have been presented in the SPC.

**CLINICAL EXPERT REPORT**
The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the published literature as well as at the search methodology used and the reasons for omission of articles.
SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

Overall, there is no clinical objection to grant a Marketing Authorisation for this application. No new or unexpected safety concerns arose from the application.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Caffeine 5mg/ml Solution for Injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
Previous clinical experience with caffeine and the data published in the literature are considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
CAFFEINE 5MG/ML SOLUTION FOR INJECTION
PL 20346/0002

STEPS TAKEN FOR ASSESSMENT

1  The MHRA received the marketing authorisation application on 14 October 2003.

2  Following standard checks and communication with the applicant the MHRA considered the application valid on 17 November 2003.

3  Following assessment of the application the MHRA requested further information relating to the quality dossier on 12 July 2007 and 18 October 2007.

4  The applications were discussed at a Commission on Human Medicines (CHM) (known as the Committee on Safety of Medicines (CSM) at the time) on 28 October 2004 when it was determined that the applicant had not provided sufficient safety, quality and efficacy data to allow for the grant of a Marketing Authorisation. The applicant provided responses on 20 May 2006 to the request for further information that was sent on 04 November 2004. The applications were reviewed again at CHM on 14 September 2006.

5  The applicant responded to the MHRA’s requests, providing further information on 25 July 2007 and 24 October 2007 for the quality section.

6  The application was determined on 08 February 2008.
# STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-12-2010</td>
<td>II</td>
<td>To remove the filter straws from packs, to correct the amount of sodium from 7.7mg/ml to 3.04mg/ml, and to replace the term ‘mcg’ with ‘micrograms’. Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), 4.9 (Overdose) and 6.5 (Nature and contents of container) of the Summary of Product Characteristics (SmPC) have been updated. The leaflet and labelling were updated consequentially.</td>
<td>Granted 18-04-2011</td>
</tr>
</tbody>
</table>
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.

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

* 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 ≥50mcg/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, opisthotonus, 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 \( V_{T1}/T_i \). 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
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

Viridian Pharma Ltd
Yew Tree House,
Hendrew Lane,
Llandevaud,
Newport,
Gwent
NP18 2AB

Distributed in the UK by
Macarthys Laboratories Ltd t/a Cardinal Health, Romford, Essex RM3 8UG

8 MARKETING AUTHORISATION NUMBER(S)

PL 20346/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/02/2008

10 DATE OF REVISION OF THE TEXT

08/02/2008
UKPAR Caffeine 5mg/ml Solution for Injection
PL 20346/0002

PATIENT INFORMATION LEAFLET

Caffeine 5mg/ml Solution for Injection
Equivalent to CAFFEINE CITRATE 10mg/ml

Please read all of this leaflet carefully before you give this medicine to your baby. If you have any questions, please ask your doctor or pharmacist who is looking after your baby.

This medicine is for infants aged 3 months and over, weighing at least 10 kg.

In this leaflet:
1. What Caffeine 5mg/ml Solution for Injection is and what it is used for
2. Before you give this medicine
3. How Caffeine 5mg/ml Solution for Injection is used
4. Possible side effects
5. Storing Caffeine 5mg/ml Solution for Injection

The name of this medicine is Caffeine 5mg/ml Solution for Injection and:
- the active ingredient is caffeine, as caffeine citrate
- other ingredients are:
  - water for injections
  - citric acid
  - sodium chloride
  - sodium hydroxide
  - dilute hydrochloric acid

Marketing authorisation holder:
Unicas Pharmaceuticals Ltd, New Tree House, Hendre Lane, Landaunder, Newport, Gwent NP18 3AB

Manufacturer:
Cardinal Health, Bampton Road, Harold Hill, Romford, Essex RM3 8UG

1. What Caffeine 5mg/ml Solution for Injection is and what it is used for

A 1ml ampoule of Caffeine 5mg/ml Solution for Injection contains 5mg of caffeine, equivalent to 10mg of caffeine citrate.

2. Before you give Caffeine 5mg/ml Solution for Injection

Your baby should not be given Caffeine 5mg/ml Solution for Injection if:
- there is known hypersensitivity (allergy) to any of the ingredients listed above.

Special care is needed with Caffeine 5mg/ml Solution for Injection when your baby:
- has had an unusual heart rhythm detected
- has had other medical problems that may affect his heart
- has had an allergic reaction to a medicine

As with most medicines, Caffeine 5mg/ml Solution for Injection may interact with other medicines given at the same time. A premature baby may need many medicines, and any problem with caffeine may be more noticeable, particularly any problem with caffeine medicines (for example theophylline) used for your baby’s breathing difficulties. Tell the doctor about this.

3. How Caffeine 5mg/ml Solution for Injection is used

The doctor or nurse will administer Caffeine 5mg/ml Solution for Injection into a venous infusion (drop). It can also be given by mouth or by intramuscular (into muscle) injection. The exact dose depends on each baby’s needs and response to the treatment. The doctor or nurse will usually give:
- A starting dose of 10mg/kg bodyweight calculated as caffeine, or
- 2.5mg/kg calculated as caffeine citrate (0.5ml/kg of this solution) if by injection then infused over 30 minutes

- Followed after 24 hours by a lower daily maintenance dose of
- 2.5mg/kg calculated as caffeine, or
- 5mg/kg calculated as caffeine citrate (1.5ml/kg of this solution) again if by injection 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 higher dose, before continuing to the lower maintenance doses.

4. Possible side effects

Caffeine acts as a stimulant to the nervous system. Side effects from this action may include restlessness or irritability. Caffeine may aggravate any tendency to vomiting.

Other side effects are not usually detected, but will be noted by the monitoring equipment used in the special care baby unit:
- your baby may produce more urine than usual, and as a consequence blood levels of certain chemicals (sodium, calcium and glucose) may be affected.
- increased blood pressure or heart rate

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.

Accidental overdose: 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 overdose, this can also occur. If signs of over-dosage are noticed, please tell the baby’s doctor immediately.

5. Storing Caffeine 5mg/ml Solution for Injection

Caffeine 5mg/ml Solution for Injection needs to be kept out of the reach and sight of children. There are no other special conditions of storage.

Use by date: Do not use Caffeine 5mg/ml Solution for Injection after the expiry date on the label, or if there are any signs of discoloration or clouding of the solution.

This leaflet was approved: 

Marketing Authorisation Number: 20346/0002

Distributed in the UK by:
Maccarrthy Laboratories Ltd, Cardinal Health, Romford RM3 8UG

Cardinal Health
Bampton Road, Harold Hill, Romford, Essex RM3 8UG
UKPAR Caffeine 5mg/ml Solution for Injection

PL 20346/0002

**TECHNICAL PRESCRIBING INFORMATION**

**Caffeine 5mg/ml Solution for Injection**

**Composition**

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

It also contains Water for Injections, Sodium Hydroxide, Dibasic Hydrogen Phosphate, Sodium Chloride and Citric Acid.

**Clinical PARTICULARS**

2.1. **Therapeutic Indications**

Treatment of apnoea of prematurity.

2.2. **Pharmacology and Method of Administration**

The recommended doses of Caffeine 5mg/ml Solution for injection are as follows. 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 frame, 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 5mg/ml Solution for injection is also effective when administered orally, and this route may be used particularly without adjusting the dose.
(d) because of the slow elimination of caffeine in this patient population, there is no requirement for dose tapering or vacuation of treatment.
(e) infants must be of sufficient respiratory maturity not to require positive pressure ventilation.

<table>
<thead>
<tr>
<th>Dose of Caffeine</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose as expressed as caffeine base</td>
<td>mg/kg</td>
<td></td>
</tr>
<tr>
<td>Dose as expressed as caffeine citrate</td>
<td>mg/kg</td>
<td></td>
</tr>
<tr>
<td>Loading Dose</td>
<td>20mg/kg</td>
<td>Once</td>
</tr>
<tr>
<td>Maintenance Dose</td>
<td>5-10mg/kg*</td>
<td>Every 24 hours***</td>
</tr>
</tbody>
</table>

* In some cases maintenance dose of caffeine citrate (20mg/kg/day) may be required to achieve maximal efficacy. 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 an approach to breathing usually resolves spontaneously. This limit may however be reduced 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 intravenously, as the volume of solution may exceed the available blood volume and cause hypovolaemic shock.

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.

**Adulthood and Children**

Not applicable

**Elderly**

Not applicable

2.3. **Contraindications**

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

2.4. **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. 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 60mg/ml (optimally 10-30mg/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 tachyphylaxis in susceptible individuals. In newborn babies this is usually a simple clinical reaction. If there have been any unusual respiratory disturbances or a CTS trace before the baby is born, caffeine should be administered with caution. Caffeine should be used with caution in infants suffering gastro-esophageal reflux, as the drug may exacerbate this condition.

Caffeine may decrease 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 77mg sodium per ml 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 screens provided in the pack, to prevent administration of these particles.

**DIRECTIONS**: Use aseptic technique.

- Familiarly attach syringe to filter straw hub.
- Remove filter 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 tubing.
- Remove filter straw from the syringe before using the solution.

2.5. **Interactions 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 history of the mother has been treated with phenytoin or phenobarbital 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.

Interactions between caffeine and other substances 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.

2.6. **Pregnancy and Lactation**

Not applicable.

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

Not applicable.
2.8 Undesirable Effects

Caffeine has been reported to cause a number of adverse effects in premature neonates. Effects include 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 ≥50mcg/ml.

On 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-esophageal reflux, induce intestinal bloating and increase retinal secretion and gastric aspirations. Caffeine treatment may also reduce splenic blood flow. These factors may increase the risk of necrotizing enterocolitis, although the prevention of systemic hypoxia may offset this theoretical concern. No significant incidence of necrotizing enterocolitis has been reported in clinical trials.

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

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

Available evidence does not indicate any adverse long-term effects of maternal 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.

2.9 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 overdose from these reports include jitteriness, tachypnoea, tachypnoea, tremor, opisthotonus, 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 incontinence, agitation, hyporeflexia, hypotonia, gastric ileus, disturbed sleep, metabolic acidosis, hyperglycaemia and elevated urea levels.

Treatment of overdose 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.

Pharmacological Properties

3.1 Pharmacodynamics Properties

The pharmacological actions of caffeine result from its effect as a nonselective adenosine receptor antagonist. The desired ergogenic 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 (Vt/T). Caffeine regularizes the breathing pattern, indicating that it stabilizes 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 bloodflow 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 splenic circulations. Elsewhere, it has a vasodilator effect due to an effect on vascular smooth muscle.

The stimulant effect may affect sleep patterns.

3.2 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 metabolize 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 20% of theophylline concentrations.

The predominant catabolic 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.

3.3 Preclinical Safety Data

There is no preclinical data of relevance to the prescriber.

Pharmaceutical Particulars

4.1 Incompatibilities

This medical product must not be mixed with other medicinal products except those mentioned in section 6.4.

4.2 Shelf Life

3 years

4.3 Special Precautions for Storage

No special precautions for storage.

4.4 Special Precautions for disposal and other handling.

Only clear solutions 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.

Marketing Authorization Number: 20346/0002

Marketing Authorization Holder: Vedan Pharma Ltd, Newport, Gwent NP10 2AB

Distributed in the UK by:

Macfarlanes Laboratories Ltd t/a Cardinal Health, Romford, Essex RM3 8UG

CardinalHealth

Bampton Road, Harold Hill, Romford, Essex RM3 8UG
Caffeine 5mg/ml Solution for Injection

For IV or oral use.
1ml contains 5mg caffeine/10mg caffeine citrate.
PL20346/0002

Lot: 1ml
Exp: POM
Caffeine 5mg/ml Solution for Injection

For IV or oral use.

2ml contains 10mg caffeine/20mg caffeine citrate.

PL20346/0002

Lot: 2ml
Exp: POM
Annex 1

Reference: PL 20346/0002 - 0011
Product: Caffeine 5mg/ml Solution for Injection
Marketing Authorisation Holder: Viridian Pharma Limited
Active Ingredient(s): Caffeine anhydrous

Reason
To remove the filter straws from packs, to correct the amount of sodium from 7.7mg/ml to 3.04mg/ml, and to replace the term ‘mcg’ with ‘micrograms’. Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), 4.9 (Overdose) and 6.5 (Nature and contents of container) of the Summary of Product Characteristics (SmPC) have been updated. The leaflet and labelling were updated consequentially.

Evaluation
This variation is a Type II C.I.4 change, i.e. variation related to significant modifications of the SmPC, due in particular to new quality, pre-clinical, clinical or pharmacovigilance plan data. It is noted that there is no appropriate change code in the new guideline for the proposed change, but as the change is a safety (medical) variation relating to change in product packaging (with consequent changes in product information that may affect patient use of the product and require both quality and clinical input), the submission type (Type II) is considered appropriate for this variation.

The proposed changes are:

1. TO REMOVE FILTER STRAWS FROM PACK
The approved product is for treatment of apnoea in premature infants and has been approved for administration via the oral or the intravenous (IV) infusion route. The marketing authorisation was authorised on 08 February 2008.

IV filter straws (10 filter straws for the pack size of 10 ampoules) are included in the approved pack as a practical way of eliminating glass particles from the solution upon opening the ampoules. This issue was originally raised by the quality assessor (and endorsed by the MHRA’s Commission on Human Medicines) at initial assessment in relation to oral use only. It is stated that, at the time, the only straws available were designed for use with injectable products only, and the inclusion of the IV filter straws was a practical solution for both routes of administration, but was not based on any evidence that it would resolve the issue. The IV filter straws have connections that are only compatible with the IV syringes.

Since then the marketing authorisation holder states that suitable oral/enteral filter straws are now available on the market to fit onto the oral syringes, and hospitals in the UK have adopted a policy of using oral/ng syringes or IV syringes only for the respective route of administration (promulgated by National Patient Safety Agency). Therefore, the marketing authorisation holder proposes to remove the IV filter straws from the pack to allow the user to select the appropriate filter straw/syringe device from their own stock.

In this submission, the applicant justifies this change based on the following reasons and states that inclusion of filter straws does not necessarily ensure all doses are filtered because:
(1) The pack is too large, and ampoules and filter straws may be separated before being supplied to neonatal intensive care units (NICU’s), where storage space is often limited. This problem would be made worse if further oral filter straws are included in the pack, as they are packed in larger envelopes than the IV filter straws.
(2) Some hospitals have a specific policy on which straws to use (e.g. Beckton-Dickinson), so may reject the particular type of straws included (Braun).
(3) If the product is (unusually) being used by the oral route, then multiple transfers are required to use the straw provided and get the dose into an oral/ng syringe. This has been a matter of complaint to the company. Furthermore, the current pack may dissuade nurses from filtering oral doses, as the straws provided (a) indicate that filtration should be undertaken, but (b) are unsuitable unless multiple manipulation is used.
(4) The majority of NICU’s asked carry straws anyway, so did not see the inclusion in the finished product packaging as an advantage.
(5) Where NICU’s did not have a policy of filtering all products, inclusion in one of a number of products used only was regarded as confusing.
(6) At the Neonatal and Paediatric Pharmacists Group (NPPG) Conference, a fringe meeting was held to discuss the presentation of this product. The meeting was unanimous that the straws should not be included ($n=\sim20$).
(7) Whilst the practice of filtering ampoule products in the NICU would seem to be an obviously sensible precaution, there is no firm data known to the applicant that serious injury has resulted from the many ampoules still administered that do not include filter straws in the pack. Data presented herein firmly suggests that including IV filter straws in the pack of this one product only does not ensure this (probably) good practice takes place.
(8) The applicant is not aware of any data that shows the provision of filter straws in a pack has a significant effect on practice at ward level - there was no licensed product with filter straws supplied prior to the launch of this product.

A survey ($n = 20$) was carried out by the applicant at the NPPG conference in Nov 2010 to support the above statements.

The potential concerns if the straws are removed are discussed by the applicant. It is stated that, although there is no evidence that there is a serious safety issue in infants in the use of the product without filtering, there is an accepted risk for all ampoule products with glass particle shedding upon ampoule opening. However, the applicant has clarified that their product is packed in one-point cut (OPC) ampoules, which is claimed to reduce this risk.

The consequence of removing the IV filter straws from the pack was also discussed at the meeting. It was agreed that there is a concern that if the filter straws are removed when they should have normally been supplied in the pack, this change in packaging may give the user a wrong impression that the product no longer requires filtration prior to administration.

Therefore, the applicant has agreed to undertake the following means to inform the users of the change in the packaging and to encourage the practice of filtering ampoule products in NICU before administration:
1. Write a letter to all units advising that the straws are to be removed, but that the product should still be filtered using an appropriate filter straw, depending on route of administration.
2. Prepare and distribute a poster with this recommendation, and make it available online also.
3. Include a red warning film on the clear plastic lidding that seals the top of the ampoule trays of at least the first three batches sold without filter straw stating ‘Draw up solution through appropriate filter straw’. This will ensure that, as the user opens the tray, they will see the printed warning.
The applicant’s justifications, and their proposed measures to reduce confusion among users of the new packaging (without filter straws) and encourage filtering of ampoule products are acceptable. The revised outer label mock-up also includes a statement to advise the user to filter the product using a filtering device appropriate to the route (see below). The SmPC and patient information leaflet (PIL) still recommend to use a filter straw.

It is acknowledged that the recently centrally authorised product Nymusa (EMEA/H/C/001014; authorised on 02/07/09), which is a similar product containing caffeine 20 mg/ml solution packed in glass ampoules used for the same indication and dual routes of administration, contains no filter straws in the pack.

2. TO CORRECT CONTENT OF SODIUM STATEMENT IN THE SMPC
The sodium content was stated incorrectly in the SmPC, technical leaflet and PIL. This has been amended appropriately in this variation.

3. TO REPLACE THE ABBREVIATION MCG WITH MICROGRAMS
The abbreviation mcg in the SmPC and technical leaflet has been substituted with micrograms in line with current requirements. This is acceptable.

No change to the formulation has been made. The changes to the packaging being submitted in this variation have no effect on the pharmaceutical quality of the product. The product will be manufactured and testing to the same quality.

A satisfactory quality expert curriculum vitae is provided.
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.

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

* 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.

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 50micrograms/ml (optimally 10-30micrograms/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 3.04mg 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 a suitable filter device.

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 phenobarbital 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
overdose 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 overdose 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 respiriogenic 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 (VT/T1). 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 vasodilator in the cerebral and splanchnic circulations. Elsewhere, it has a vasoconstrictor 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.

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**
Viridian Pharma Ltd  
Yew Tree House,  
Hendrew Lane,  
Llandevaud,  
Newport,  
Gwent  
NP18 2AB

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 20346/0002

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
08/02/2008

10 **DATE OF REVISION OF THE TEXT**
18/04/2011
Caffeine 5mg/ml Solution for Injection
Caffeine Citrate 10mg/ml
For IV or oral use
1ml contains 5mg caffeine as 10mg caffeine citrate
PL20346/0002

1ml POM

Lot V
Exp. Vvvvv
Caffeine 5mg/ml Solution for Injection

For intravenous and oral administration

Each 2ml ampoule contains 10mg of Caffeine, equivalent to 20mg of caffeine citrate

This product also contains: Water for injections, Sodium Hydroxide, Sodium Chloride, Gluteraldehyde, Edetate Disodium, Hydroxypropyl Beta-Cyclodextrin. Use diluted by a medical practitioner. Keep out of reach of children.

No special conditions of storage. Do not use if there are any signs of decomposition or clouding of the solution. Use unopened and discard unopened and any remaining solution in appropriate manner.

Read enclosed leaflet prior to use.

Manufactured and distributed by Meneava Pharmaceuticals on behalf of the Marketing Authorisation holder: Meneava Pharmaceuticals, Newport, NP19 4AE. PL20346/0002
Caffeine 5mg/ml Solution for Injection
Caffeine Citrate 10mg/ml
For IV or oral use
2ml contains 10mg caffeine as 20mg caffeine citrate
PL20346/0002
2ml [POM]
Lot Vwww A1423
Exp. Vwww
Caffeine 5mg/ml Solution for Injection

Equivalent to Caffeine Citrate 10mg/ml

Composition

Each tube contains 5mg of caffeine, equivalent to 10mg of caffeine citrate. Each vial contains 5mg of caffeine, equivalent to 10mg of caffeine citrate. It also contains Water for Injections, Sodium Hydroxide, Citric Acid and/or Acetic Acid.

Clinical Particulars

2.1 Therapeutic indications

Treatment of apnoea of prematurity.

2.2.1 Pharmacology and method of administration

Therapeutically effective dose of caffeine citrate for preterm infants is approximately 20-24mg/kg/day divided into 3-4 doses. Higher doses may be required in patients with severe apnoea. The effective dose can be increased gradually.

2.2.2 Dosage and route of administration

Loading dose

<table>
<thead>
<tr>
<th>Route</th>
<th>Caffeine Citrate (mg)</th>
<th>Caffeine Solution (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>2 (0.4mg/kg)</td>
<td>1</td>
</tr>
</tbody>
</table>

Maintenance

<table>
<thead>
<tr>
<th>Route</th>
<th>Caffeine Citrate (mg)</th>
<th>Caffeine Solution (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1 (0.2mg/kg)</td>
<td>1/2</td>
</tr>
</tbody>
</table>

In some cases maintenance dose 2-4 times higher than loading dose. Increase caffeine dose by 1-2mg/kg/day, to a maximum of 15mg/kg/day. Do not exceed 6mg/kg/day. Do not exceed 10mg/kg/day. By intravenous infusion.

2.3 Contraindications

Caffeine citrate solution for injection should not be administered in cases of hyperthyroidism, hypercalcaemia, hyperparathyroidism, or acute renal failure.

2.4 Special warnings and precautions for use

Caffeine citrate solution for injection should not be used in cases of acute renal failure or liver failure.

---

UKPAR Caffeine 5mg/ml Solution for Injection

Equivalent to Caffeine Citrate 10mg/ml

Composition

Each tube contains 5mg of caffeine, equivalent to 10mg of caffeine citrate. Each vial contains 5mg of caffeine, equivalent to 10mg of caffeine citrate. It also contains Water for Injections, Sodium Hydroxide, Citric Acid and/or Acetic Acid.

Clinical Particulars

2.1 Therapeutic indications

Treatment of apnoea of prematurity.

2.2.1 Pharmacology and method of administration

Therapeutically effective dose of caffeine citrate for preterm infants is approximately 20-24mg/kg/day divided into 3-4 doses. Higher doses may be required in patients with severe apnoea. The effective dose can be increased gradually.

2.2.2 Dosage and route of administration

Loading dose

<table>
<thead>
<tr>
<th>Route</th>
<th>Caffeine Citrate (mg)</th>
<th>Caffeine Solution (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>2 (0.4mg/kg)</td>
<td>1</td>
</tr>
</tbody>
</table>

Maintenance

<table>
<thead>
<tr>
<th>Route</th>
<th>Caffeine Citrate (mg)</th>
<th>Caffeine Solution (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1 (0.2mg/kg)</td>
<td>1/2</td>
</tr>
</tbody>
</table>

In some cases maintenance dose 2-4 times higher than loading dose. Increase caffeine dose by 1-2mg/kg/day, to a maximum of 15mg/kg/day. Do not exceed 6mg/kg/day. Do not exceed 10mg/kg/day. By intravenous infusion.

2.3 Contraindications

Caffeine citrate solution for injection should not be administered in cases of hyperthyroidism, hypercalcaemia, hyperparathyroidism, or acute renal failure.

2.4 Special warnings and precautions for use

Caffeine citrate solution for injection should not be used in cases of acute renal failure or liver failure.

---

UKPAR Caffeine 5mg/ml Solution for Injection

Equivalent to Caffeine Citrate 10mg/ml

Composition

Each tube contains 5mg of caffeine, equivalent to 10mg of caffeine citrate. Each vial contains 5mg of caffeine, equivalent to 10mg of caffeine citrate. It also contains Water for Injections, Sodium Hydroxide, Citric Acid and/or Acetic Acid.

Clinical Particulars

2.1 Therapeutic indications

Treatment of apnoea of prematurity.

2.2.1 Pharmacology and method of administration

Therapeutically effective dose of caffeine citrate for preterm infants is approximately 20-24mg/kg/day divided into 3-4 doses. Higher doses may be required in patients with severe apnoea. The effective dose can be increased gradually.

2.2.2 Dosage and route of administration

Loading dose

<table>
<thead>
<tr>
<th>Route</th>
<th>Caffeine Citrate (mg)</th>
<th>Caffeine Solution (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>2 (0.4mg/kg)</td>
<td>1</td>
</tr>
</tbody>
</table>

Maintenance

<table>
<thead>
<tr>
<th>Route</th>
<th>Caffeine Citrate (mg)</th>
<th>Caffeine Solution (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1 (0.2mg/kg)</td>
<td>1/2</td>
</tr>
</tbody>
</table>

In some cases maintenance dose 2-4 times higher than loading dose. Increase caffeine dose by 1-2mg/kg/day, to a maximum of 15mg/kg/day. Do not exceed 6mg/kg/day. Do not exceed 10mg/kg/day. By intravenous infusion.

2.3 Contraindications

Caffeine citrate solution for injection should not be administered in cases of hyperthyroidism, hypercalcaemia, hyperparathyroidism, or acute renal failure.

2.4 Special warnings and precautions for use

Caffeine citrate solution for injection should not be used in cases of acute renal failure or liver failure.
UKPAR Caffeine 5mg/ml Solution for Injection

2.3.1. Interactions with other Medicinal Products and other Forms of Treatment

No clinically significant interactions between caffeine and other medicinal products have been reported in premature infants. However, certain clinical situations have a theoretical potential for interaction. If the mother has been treated with phenytoin or phenobarbital during pregnancy, the child might have increased hepatic enzyme induction and thus require higher doses of caffeine to compensate for increased caffeine metabolism. Plasma caffeine level should be monitored for such patients. In patients with chronic liver disease, it is recommended to administer a lower dose so that adequate caffeine has been administered.

Interactions between caffeine and other medicines such as theophylline has been reported in premature neonates. Therefore the concentration of one of these drugs should be adjusted; baseline serum levels of caffeine should be measured in patients previously treated with theophylline.

2.4. Pregnancy and lactation

Not applicable.

2.5. Effects on Ability to Drive and Use Machines

Not applicable.

2.6. Undesirable Effects

Caffeine has been reported to cause a number of adverse effects in premature neonates. Effects described include:
- Irritability
- Restlessness
- Fretfulness
- Increased motor activity
- Increased crying
- Increased apneas
- Increased apneas with bradycardia
- Increased jaundice
- Caffeine withdrawal

Caffeine should only be used when necessary and should only be administered if the risks of not using caffeine are higher than the risks of using caffeine.

2.7. Overdose

Caffeine overdose has been reported in a few cases in neonates and premature infants. There should normally be no concerns with blood levels below 100mg/L or organ damage of the newborns. However, toxicity symptoms occur when blood levels over 200mg/L are reached. Symptoms of overdosage from these reports include:
- Irritability
- Restlessness
- Fretfulness
- Increased motor activity
- Increased crying
- Increased apneas
- Increased crying with bradycardia
- Increased jaundice
- Increased respiratory rate
- Increased apneas with bradycardia
- Increased jaundice

In severe cases of overdose, exchange transfusion should be considered. In one case, it was found that a dose of caffeine similar to 100mg/L per kg of body weight.

2.8. Pharmacological Properties

The pharmacological actions of caffeine result in an increase in central nervous system stimulation, although it may also increase the sensitivity of respiratory response to carbon dioxide levels. Caffeine induces both tonic tension and frequency of ventilation. In the premature infant, caffeine produced increased irritability, especially due to an increase in respiratory rate and frequency by an increase in respiratory flow rate. Caffeine suppresses the breathing pattern, indicating that it suppresses the output of the respiratory control system. Caffeine also inhibits phosphodiesterase, but this effect occurs at concentrations associated with toxicity, and not at therapeutic concentrations.

Caffeine increases bone density, body weight, cardiac output and contractility. It also increases blood flow to the kidneys, and prevents sodium and fluid loss due to the subsequent renal vasodilation. Caffeine increases bone density, body weight, cardiac output and contractility. It also increases blood flow to the kidneys, and prevents sodium and fluid loss due to the subsequent renal vasodilation. Caffeine increases bone density, body weight, cardiac output and contractility. It also increases blood flow to the kidneys, and prevents sodium and fluid loss due to the subsequent renal vasodilation.

The stimulant effect may affect sleep patterns.

3.2. Pharmacokinetics

In two cases, orally administered caffeine has been shown to rapidly and completely absorbed. Peak plasma levels are attained, with the lowest levels occurring in premature infants. The elimination of caffeine is largely due to renal excretion, with a small amount eliminated in the feces. Caffeine is excreted in the urine as its free form and also as its conjugates with glucuronic acid. Caffeine is excreted in the urine as its free form and also as its conjugates with glucuronic acid. Caffeine is excreted in the urine as its free form and also as its conjugates with glucuronic acid.

3.3. Therapeutic Safety Data

There is no published data on safety in the neonatal period.

4. Possible side effects

Caffeine acts as a stimulant to the nervous system. Side effects from this action may include:

- Irritability
- Restlessness
- Fretfulness
- Increased motor activity
- Increased crying
- Increased apneas
- Increased jaundice
- Increased respiratory rate
- Increased apneas with bradycardia
- Increased jaundice

4.1. Incompatibilities

- Incompatible with:
- Phenothiazines
- Other medicinal products except those mentioned in section 4.4

4.2. Special Precautions for Storage

- Store at a temperature below 25°C

4.3. Special Precautions for Management

- Only available with such conditions that the drug is to be administered in a dosage form suitable for the intended use.
- Only administered in a dosage form suitable for the intended use.
- Only administered in a dosage form suitable for the intended use.

4.4. Special Precautions for Disposal

- Dispose of the drug in the most suitable way following the recommendations of the national medical authorities.

5. Storing Caffeine Solution for Injection

Caffeine solution for injection needs to be kept out of the reach of children. There are no special precautions for storage.

5.1. Marketing Information

- Marketing Authorisation Number: PL 20346/0002
- Marketing Authorisation Number: PL 20346/0002
- Marketing Authorisation Number: PL 20346/0002
- Marketing Authorisation Number: PL 20346/0002
- Marketing Authorisation Number: PL 20346/0002

5.2. Marketing Authorisation Number: PL 20346/0002

6. Further Information

When Caffeine Solution for Injection contains:

- The active ingredient in Caffeine Solution for Injection contains:
- Caffeine 5mg/ml Solution for Injection contains:
- Caffeine 5mg/ml Solution for Injection contains:
- Caffeine 5mg/ml Solution for Injection contains:
- Caffeine 5mg/ml Solution for Injection contains:
- Caffeine 5mg/ml Solution for Injection contains:
- Caffeine 5mg/ml Solution for Injection contains:

7. Contact Information

- For further information:
- For further information:
- For further information:
- For further information:
- For further information:
- For further information:
- For further information:
Conclusion
The removal of the filter straws from the pack can be accepted.

Decision - Granted
Date 18/04/11