Information on the safe use of Peyona (caffeine citrate)
20mg/ml solution for infusion and oral solution

Dear Healthcare Professional,

Chiesi Limited in Agreement with the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) wishes to provide you with relevant information concerning the safe use of Peyona (caffeine citrate).

Summary

- Peyona (caffeine citrate) is authorised only for the treatment of primary apnoea of premature newborns. Treatment must be initiated under the supervision of a physician experienced in neonatal intensive care. Peyona is for use in Neonatal Intensive Care Units only.
- Measurement of baseline caffeine levels, monitoring of plasma concentrations as well as dose adjustments during therapy is advisable.
- Healthcare professionals should pay special attention to dosage recommendations, contraindications, warnings and precautions for use.

Further information on dosage

- Peyona (caffeine citrate) is available as ampoules containing 20mg/ml of caffeine citrate solution for infusion or oral administration.
- There are two authorised presentations which differ in the fill-volume: 3ml (equivalent to 60mg of caffeine citrate) and 1ml (equivalent to 20mg of caffeine citrate).
- Each ampoule is for single and immediate use only.
- Doses specified on prescriptions should always be expressed as caffeine citrate in order to avoid medication errors, as the dose expressed as caffeine base is one-half the dose expressed as caffeine citrate (e.g. 20mg caffeine citrate is equivalent to 10mg caffeine base).
- Another formulation of caffeine citrate solution for treatment of apnoea in newborns is also available, which contains a different dose strength of caffeine citrate to Peyona. Care should be taken not to confuse the two products, as this may result in medication errors.
• **A second loading dose** of 10-20mg/kg may be given in preterm infants with insufficient clinical response to the recommended loading dose after 24 hours.

• **Higher maintenance doses** of 10mg/kg body weight could be considered in case of insufficient response taking into account the potential for accumulation of caffeine in premature neonates and the progressively increasing capacity to metabolise caffeine in relation to post-menstrual age (where clinically indicated, caffeine plasma levels should be monitored).

• **The diagnosis of apnoea of prematurity may need to be reconsidered** in patients who do not respond adequately to a second loading dose or higher maintenance dose.

**Further information on monitoring of plasma concentrations**

• **It is advisable to measure baseline caffeine levels** in infants whose mothers have ingested large quantities of caffeine prior to delivery or infants who previously have been treated with theophylline (caffeine citrate and theophylline should not be used together!).

• **Plasma concentrations of caffeine may need to be monitored and doses be adjusted** in cases of insufficient clinical response or signs of toxic effects and in patients with underlying conditions increasing the risk for elevated plasma concentrations (e.g. very premature infants particularly when receiving parenteral nutrition, infants with hepatic or renal impairment, co-medication known to interfere with caffeine metabolism) or clinical conditions with increased risk for adverse reactions (e.g. clinically significant cardiac disease, seizure disorders).

For detailed information on the administration, special warnings and precautions for use of Peyona, please refer to the attached Summary of Product Characteristics.

**Call for reporting**

Please be alerted to the known risks associated with the administration of Peyona as specified in the Summary of Product Characteristics. In addition please look out for any other suspected adverse drug reactions that might occur during caffeine therapy such as:

• Necrotising Enterocolitis (NEC)
• Symptoms of caffeine withdrawal
• Abnormal slow increase infantile weight gain
• Drug interactions with other medicines
Please report suspected adverse reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme online at www.yellowcard.gov.uk.

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines (CHM) free phone line: 0800-731-6789
- Or by electronic download through the MHRA website (http://yellowcard.mhra.gov.uk/downloads/)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Adverse reactions to Peyona may also be reported to Chiesi Limited at the following address:
Medical Services
Chiesi Limited
Cheadle Royal Business Park,
Highfield,
Cheadle
SK8 3GY
Tel: 0161 488 5555

**Communication information**

Should you have any further questions or require additional information regarding the use of Peyona please feel free to contact us under the below address:

Chiesi Limited
Cheadle Royal Business Park,
Highfield,
Cheadle,
SK8 3GY
Tel: 0161 488 5555
Name  Helen Phillips

Signature

Title  Medical Director

Date  4th May 2012

Annex

Summary of Product Characteristics
Duration of treatment

Caffeine citrate can be administered by intravenous infusion and by the oral route. The product must not be administered by intramuscular, subcutaneous, intrathecal, or by intraperitoneal injection.

Caffeine has a prolonged half-life in premature newborn infants and there is potential for accumulation which may necessitate monitoring infants treated for an extended period, e.g., very premature infants. Routine monitoring of plasma caffeine levels is not necessary in the majority of preterm infants. However, plasma concentrations of caffeine may need to be monitored to ensure safety in patients who do not respond adequately to a second loading dose or maintenance dose of 10 mg/kg/day (see section 4.4).

For the infant, clearance of caffeine does not depend on hepatic function. Hepatic caffeine metabolism develops progressively in the weeks following birth and for the older patient population, there is no requirement for dose tapering on cessation of treatment.

**Table: Dose of caffeine citrate**

<table>
<thead>
<tr>
<th>Dose of caffeine citrate</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose*</td>
<td>mg/kg body weight</td>
<td>once*</td>
</tr>
<tr>
<td>Maintenance dose*</td>
<td>mg/kg body weight</td>
<td>once*</td>
</tr>
</tbody>
</table>

**Maintenance dose**

- If, at any time during the treatment period, the infant does not respond adequately to a second loading dose or maintenance dose of 10 mg/kg/day, higher maintenance doses of 10 mg/kg body weight may be considered in case of insufficient response, taking into account the potential for accumulation over 10 minutes or by hours.

**Interactions**

Caffeine citrate should be administered with caution in preterm neonates with impaired renal or hepatic function (see sections 4.2 and 5.2). Doses should be adjusted according to renal function and the degree of hepatic impairment.

Caffeine citrate should be administered with caution in neonates with known cardiovascular disease. There is evidence that caffeine causes tachyarrhythmias in susceptible individuals. In newborns this is usually a transient phenomenon with resolution within days, but in some cases prolonged tachycardia and atrial fibrillation have been reported.

In newborns previously treated with theophylline, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate. Inter-conversion between caffeine and theophylline occurs in preterm neonates. These active substances should not be used concurrently.

Breast-feeding mothers of neonates treated with caffeine citrate should not ingest caffeine-containing foods and beverages or medicinal products containing caffeine. In the event of accidental ingestion, there is no available antidote for caffeine.

**Contra-indications**

Caffeine citrate should not be used in neonates with suspected or known intrauterine growth retardation or significant perinatal asphyxia, or for neonates with a history of significant intracranial hemorrhage in the first 24 hours of life, as the potential neurotoxicity of caffeine is not well characterized for these groups.

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Caffeine citrate can be administered by intravenous infusion and by the oral route. The product must not be administered by intramuscular, subcutaneous, or intrathecal routes.

Caffeine has a prolonged half-life in premature newborn infants and there is potential for accumulation which may necessitate monitoring infants treated for an extended period. Infants receiving co-administration of medicinal products known to interfere with caffeine metabolism (see section 4.5) may require increased monitoring.

Routine monitoring of plasma caffeine levels is not necessary in the majority of preterm infants. However, plasma concentrations of caffeine may need to be monitored during the treatment period, as signs of overstimulation may be noted.

Caffeine citrate can be either used without dilution or diluted in sterile solutions for infusion such as glucose 50 mg/ml (5%), or sodium chloride 9 mg/ml (0.9%) (see section 5.2). Where clinically indicated, caffeine plasma levels should be monitored. The diagnosis of apnoea of prematurity may need to be reconsidered if patients receive caffeine citrate treatment and continue to have apnoeaic episodes despite treatment, or other clinical considerations. It is recommended that caffeine citrate administration should be stopped when the patient is able to maintain normal spontaneous breathing for at least 1 hour without signs of apnoea (see section 2).

Absorption: The onset of action of caffeine from caffeine citrate is within minutes of commencement of infusion. After oral administration of 10 mg caffeine base/kg body weight, caffeine citrate causes a generalised increase in metabolism, which may result in higher energy and nutrition requirements during therapy. Caffeine citrate should be carefully monitored for the development of necrotising enterocolitis (see section 4.8).

Caffeine has been shown to increase heart rate, left ventricular output, and stroke volume in published studies. Therefore, caffeine citrate should be used with caution in premature infants where left ventricular output may be low.

In neonates born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to any dose and monitored during treatment.

Concurrent use of caffeine and doxapram might potentiate their stimulatory effects on the cardio-respiratory and central nervous system. If concurrent use is indicated, patients should be monitored closely for signs of overstimulation.

Metabolism and nutrition disorders

Hypoglycaemia, hyperglycaemia, failure to thrive, feeding intolerance

Not known

4.8 Undesirable effects

Adverse effects have been reported in preterm infants receiving caffeine citrate. These include vomiting, diarrhoea, and agitation.

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Investigations

Urine output increased, urine sodium and calcium increased, Not known

5.2 Pharmacokinetic properties

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