Part VI: Summary of the Risk management plan

SUMMARY OF THE RISK MANAGEMENT PLAN FOR PEYONA® (CAFFEINE CITRATE)

This is a summary of the risk management plan (RMP) for Peyona®. The RMP details important risks of Peyona®, how these risks can be minimised, and how more information will be obtained about Peyona® 's risks, and uncertainties (missing information).

The summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Peyona® should be used.

This summary of the RMP for Peyona® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Peyona®s RMP.

I. The medicine and what is it used for

Peyona® is authorised for treatment of primary apnoea of premature newborns. It contains caffeine citrate as the active substance, and it is given by intravenous infusion (loading dose) or by intravenous infusion orally (20 mg/ml -maintenance dose).
Further information about the evaluation of Peyona®'s benefits can be found in Peyona® 's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage ema.europa.eu/medicines/human/EPAR/peyona.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Peyona®, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and product information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute r*outine risk minimisation* measures.

In the case of Peyona®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse drug reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Peyona is not yet available, it is listed under 'missing information' below.

II.A List of important risks

Important risks of Peyona® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Peyona®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks

Important Identified risks:	• Toxicity due to maternal caffeine ingestion; • Increase in caffeine plasma levels in premature infants with cholestatic hepatitis; • Increase in caffeine plasma levels in premature infants with clinically relevant renal insufficiency; • Cardiac disorder in infants with pre-existing cardiac disease, including arrhythmias; • Treatment-related convulsions/seizures.
Important Potential risks:	• Decrease in weight gain / failure to thrive; • Caffeine withdrawal; • Necrotising enterocolitis; • Medication errors.
Missing information:	• Rare ADRs; • Drug interaction with the most commonly used drugs in the NICU; • Long-term effects of caffeine therapy.

II.B Summary of important risks

Important identified risk

Toxicity due to maternal caffeine ingestion	
Evidence for linking the risk to the medicine	Caffeine, derived from that ingested by the mother, crosses the placenta and caffeine concentrations that are close to therapeutic levels are often found in cord blood at birth. Studies conducted to determine caffeine present in cord blood samples from preterm infants showed that caffeine can be trans-placentally acquired from mothers who ingested caffeine McCulloch KM, 1989; Soyka LF, 1981).

	Caffeine is rapidly transferred to breast milk. Caffeine ingested by nursing mothers appears in breast milk within about 15 minutes in concentrations comparable to those in plasma and may comprise up to 4% of the maternal dose Even though the ingestion of one cup of coffee (approximately 100 mg of caffeine) by a lactating woman may not produce toxic effects in the infant, the consumption of greater amounts of caffeine at different times during the day may constitute a risk to the infant. Infants metabolise caffeine very slowly and could accumulate a significant level of caffeine in relation to weight, reaching toxic concentrations (Stavchansky S, 1988; Pyu JE, 1985). The mean volume of distribution of caffeine in infants is about 0.8-0.9 L/kg (Aranda JV, 1979; Gicoia GP, 1989), which is slightly higher than that in adults (0.6 L/kg) (Goodman, 1993).
Risk factors and risk groups	Neonates born or breastfed by mother heavy drinkers of caffeine.
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.2, 4.4, 4.6 and 5.2 - PL section 2. Legal status: Special medical prescription and reserved for NICUs use. Additional risk minimisation measures - DHPC - Laminated Card for NICUs.

Increase in Caffeine Plasma Levels in Premature Infants with Cholestatic Hepatitis	
Evidence for linking the risk to the medicine	In premature infants with cholestatic hepatitis a prolonged caffeine elimination half-life with an increase of plasma levels above the normal upper limit of variation has been observed. Neonatal hepatitis syndrome is defined as a state in the newborn period where, as a result of decreased bile flow, there is an accumulation of substances in the liver, blood and extrahepatic tissues which would normally be excreted in bile. Strictly speaking this implies elevated serum bile acids, but in practice it is usually defined by the presence of conjugated hyperbilirubinemia. The population incidence of the neonatal hepatitis syndrome is approximately 1:2500 – 1:5000 live births. The largest diagnostic groups are idiopathic neonatal cholestasis, biliary atresia and the multifactorial cholestasis seen in premature infants and those requiring neonatal surgery (McKiernan PJ, 2002; Fischler B, 2001; Roberts EA, 2003). The group of preterm babies with hepatis impairments in comparison with remaining newborns presented with higher number of ADRs What was 22.6 vs. 2.9%, respectively. The most common ADR was tachycardia (Lista G, 2016).
Risk factors and risk groups	Premature neonates with cholestatic hepatitis.
Risk minimisation measures	Routine risk minimisation measures:

	- SmPC section 4.2, 4.4, 4.8 and 5.2 - PL section 2. Legal status: Special medical prescription and reserved for NICUs use. <u>Additional risk minimisation measures</u> - DHPC - Laminated Card for NICUs.

Increase in Caffeine Plasma Levels in Premature Infants with clinically relevant renal insufficiency	
Evidence for linking the risk to the medicine	Peyona PASS confirmed (Lista G, 2016) the frequency of ADRs in very premature infants with renal/hepatic impairment resulted in higher occurrence of at least one ADR compared to premature infants without organ impairment. Cardiac disorders, specifically tachycardia, were the most common ADRs and SAEs. Since in the clinical practice a monitoring of the drug levels was not routinely performed, in line with the literature evidence (Walther FJ, 1990), it appears anyway difficult to clarify a possible correlation between elevated plasma levels and the above-described increase in ADRs.
Risk factors and risk groups	Premature neonates with renal impairment. (Defined as plasma creatinine concentration higher than 25µmol/l daily increase up to day 4 of life, or on the absence of physiologic decrease of creatinine normally observed after the 4th day of life)
Risk minimisation measures	<u>Routine risk minimisation measures:</u> - SmPC section 4.2, 4.4, 4.8 and 5.2 - PL section 2. Legal status: Special medical prescription and reserved for NICUs use. <u>Additional risk minimisation measures</u> - DHPC - Laminated Card for NICUs.

Cardiac Disorders in Infants with Pre-existing Cardiac Disease, Including Arrhythmias	
Evidence for linking the risk to the medicine	Theophylline therapy increases left ventricular output in preterm infants by a combination of positive inotropic and chronotropic effects. The cardiovascular effects of caffeine were evaluated in 20 clinically stable preterm infants (Roberts EA, 2003). Ten infants received intravenous caffeine citrate with a loading dose of 20 mg/kg and a maintenance dose of 5 mg/kg every 24 hours, and 10 infants were control subjects. Compared with controls, left ventricular output and stroke volume were significantly increased on days 1 to 7 of caffeine therapy. Caffeine led to an increase in the mean arterial blood pressure on the first 3 days of therapy, but the heart rate did not change. These data indicated that caffeine administration leads to a significant increase in left ventricular output in preterm infants and that this inotropic effect is accompanied by a pressor effect. Other studies have shown that the use of caffeine in neonates is associated with tachycardia (Brouard C, 1985; Scanlon JE, 1985; Romagnoli C, 1992; Larsen PB, 1995; Davis JM, 1986; Lista g, 2016). In contrast, the study on 21 premature neonates did not shown any changes in heart rate, blood pressure or the autonomic nervous system tone following administration

	of caffeine, nor were the nonlinear dynamical properties of the system altered by caffeine (Shoen K, 2014).
Risk factors and risk groups	Premature neonates with existing cardiovascular disease.
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.2, 4.4 and 4.8 - PL section 2 and 4 Legal status: Special medical prescription and reserved for NICUs use. Additional risk minimisation measures - DHPC - Laminated Card for NICUs.

Treatment-related Convulsions/Seizures	
Evidence for linking the risk to the medicine	During repeat dose toxicity studies conducted mainly by the oral route effects on CNS were seen at high doses. Two publications (Davis JM, 1986; Van den Anker JN, 1992) have reported seizures in patients treated with caffeine. Davis reported 2 cases where the patients developed generalised seizures after the administration of caffeine. Both patients had received caffeine for the treatment of SIDS. The first case (a 2.5-month-old boy) had received a 20 mg/kg IV loading dose and had a caffeine level of 13.7 mg/L. After 2 years of treatment with phenobarbital, the patient's EEG normalised as did his neurological status. The second case (a 4-month-old girl) had received an oral loading dose of 20 mg/kg. She was treated with anticonvulsants and experienced developmental delay and neurological deficits over the next 2 years. The other report concerned a 33 week infant who received caffeine for treatment of apnoea of prematurity. On the second day of treatment, the patient presented with tachypnoea, tachycardia, compromised circulation, vomiting and convulsions. Serum caffeine level was 346 mg/L. Caffeine was discontinued and after 9 days the caffeine concentration was 32.9 mg/L. At 18 months of age the follow up psychomotor examination was normal. A systematically review of literature (Shoen K, 2014) confirmed that caffeine compared with theophylline therapy has been associated with less ADRs in neonatal population, including the seizures and hypokalaemia.
Risk factors and risk groups	Risk - overdose of caffeine. Premature with existing seizure disorder are at higher risk.
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.2, 4.4 and 4.8 - PL section 2 and 4. Legal status: Special medical prescription and reserved for NICUs use. Additional risk minimisation measures - DHPC - Laminated Card for NICUs.

Important potential risk

Decrease in weight gain / failure to thrive	
Evidence for linking the risk to the medicine	In the Schmidt study (Schmidt B, 2006), the percentage of children admitted to hospital for "failure to thrive" was 2.4%. Again, the frequency was greater than placebo, but not significantly so. No significant differences in weight gain were observed between four and six weeks after randomisation. Similarly, no significant differences in the mean weight, height and head circumference measures were detected in the five – years follow-up. In the Romagnoli study (Romagnoli C, 1992) vomiting and other feeding problems occurred in 20% (2/10) of infants treated with 2.5 mg/kg and at 84.6% (11/13) in infants treated with 5 mg/kg caffeine. However, treatment did not influence the weight curve. In the Steer study (Steer P, 2004), there was no significant difference in the incidence of feed intolerance between the groups given 5 mg/kg versus those given 20 mg/kg (30.6% versus 35.4%) but the percentages were relatively high and increased with increased dose. Although the time to regain birth weight was significantly longer for infants in the higher dose group (mean ± SD) 14.8 ± 5.3 days versus 12.9 ± 5.0 days in the lower dose group; ($p<0.01$), there was no difference in overall weight gain between the groups for the duration of caffeine treatment as measured by weight on cessation. In the other Steer study (Steer P, 2003), there was also an increase in the number of infants with feeding intolerance in the 15 mg (35.0%) and 30 mg groups (46.7%) compared with the 3 mg group (31.0%), although again this was not statistically significant, and there was no statistically significant difference in weight across the groups.
Risk factors and risk groups	Not known
Risk minimisation measures	<u>Routine risk minimisation measures:</u> - SmPC section 4.2 and 4.8 - PL section 2. Legal status: Special medical prescription and reserved for NICUs use. <u>Additional risk minimisation measures</u> - DHPC - Laminated Card for NICUs.

Caffeine withdrawal;	
Evidence for linking the risk to the medicine	In some of the studies in infants, subjects were noted to have irritability, excitability or other symptoms that are typical of methylxanthine treatment. To the extent that infants may become tolerant to such effects, it is conceivable that some of them might experience withdrawal effects when caffeine treatment is discontinued. The observation period in most trials, including the pivotal study, did not necessarily follow infants to the end of their caffeine treatment. In most trials, including the pivotal study, it is not clear how rigorously non-serious adverse events that might be markers for a withdrawal syndrome, such as irritability or insomnia, were assessed. In one publication (Khanna NN, 2004), eight infants born to mothers who were heavy users of caffeine during pregnancy were described. The infants exhibited

	irritability, jitteriness, and vomiting with no cause being identified. Caffeine was present in the serum of six infants, and three of the six infants had caffeine in their urine. The symptoms resolved spontaneously. It was hypothesised that these infants were exposed to high maternal levels of caffeine for the majority of the pregnancy, resulting in a withdrawal syndrome after delivery. Another report (Sankaran K, 2004) described a case of a premature infant with unusually high concentrations of transplacental acquired caffeine. The mother drank 24 cups of coffee per day during pregnancy. The infant developed apnoea and was started on caffeine therapy. Serum caffeine concentration was found to be 40.3 micrograms/ml prior to caffeine administration on the fifth day of age. It was suggested that manifestation of apnoea in this infant may have been related to caffeine withdrawal.
Risk factors and risk groups	Not known.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> - SmPC section 4.2 Legal status: Special medical prescription and reserved for NICUs use. <u>Additional risk minimisation measures:</u> - DHPC - Laminated Card for NICUs.

Necrotising enterocolitis	
Evidence for linking the risk to the medicine	Several papers have been published about the use of xanthine therapies in infants at risk of NEC. The authors postulated that in these cases, NEC was related to bacterial overgrowth due to decreased GI motility which followed the use of xanthines. In pre-clinical studies, it was of particular interest that mucosal hypertrophy, mild hyperaemia and moderate inflammation were observed as dose-dependent phenomena in the stomach, small bowel and caecum. In the pivotal trial, two of the patients randomised to caffeine developed NEC. In addition, three patients who had been exposed to caffeine during the open label phase of the trial developed NEC. In the Schmidt trial (Schmidt B, 2006), however, the rate of NEC did not differ significantly between caffeine citrate (63/1006, 6.3%) and placebo (67/1000, 6.7%) [AOR 0.94, 95% CI (0.65 – 1.34), P=0.63]. This data has been more recently confirmed in Canadian study (Sankaran K, 2004), while the results of a retrospective study published in 2014 (Dobson NR, 2014) still suggested that the early use of caffeine, besides being associated with improved survival without BPD in preterm infants, was indeed associated with an increase in the risk of NEC (OR 1.41, 95% CI 1.04-1.91, p=0.027). Finally available results of a study aimed at prospectively comparing and documenting the safety profile of the use of extemporaneous caffeine citrate or Peyona in preterm infants with AOP have shown that the extemporaneous presentation was, associated with a higher risk of NEC (risk ratio (RR): 2.68, 95% CI: 1.01– 7.12, p = 0.047) that the registered product (Vatlach, 2014). The findings in the literature are not conclusive as to whether caffeine exposure is associated with an increased incidence of NEC, nor if there is a subset of patients at a higher risk of developing this disease if exposed to caffeine.

Risk factors and risk groups	Preterm neonates.
Risk minimisation measures	Routine risk minimisation measures: - SmPC 4.2, 4.4, 4.5 and 4.8 - PL section 2 and 4. Legal status: Special medical prescription and reserved for NICUs use. Additional risk minimisation measures - DHPC - Laminated Card for NICUs.

Medication errors	
Evidence for linking the risk to the medicine	Caffeine citrate solution for infusion or oral administration is authorised for the treatment of primary apnoea of premature newborns. There are 2 formulations available which contain 10 mg/mL caffeine citrate or 20 mg/mL of caffeine citrate. Care must be taken over which product is being used when dosing with caffeine citrate, as confusing the products may cause dosing errors (MRHA, 2013).
Risk factors and risk groups	Risk factor – unclear labelling. Risk group - Not known.
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.2 Legal status: Special medical prescription and reserved for NICUs use. Additional risk minimisation measures: - DHPC - Laminated Card for NICUs.

Missing information

Rare ADRs	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: - DHPC - Laminated Card for NICUs.

Drug interaction with the most commonly used drugs in the NICU	
Evidence for linking the risk to the medicine	Cytochrome P450 1A2 (CYP1A2) is known to be the major enzyme involved in the metabolism of caffeine. Therefore, caffeine has the potential to interact with drugs that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2.

	Few data exist on PK with caffeine in preterm neonates. Based on adult data, lower doses of caffeine may be needed following coadministration of drugs which are reported to decrease caffeine elimination (e.g., cimetidine and ketoconazole) and higher caffeine doses may be needed following coadministration of drugs that increase caffeine elimination (e.g., phenobarbital and phenytoin) (Wilson C, 2018).
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.2 and 4.5 - PL section 2. Legal status: Special medical prescription and reserved for NICUs use. Additional risk minimisation measures: - DHPC - Laminated Card for NICUs.

Long-term effects of caffeine therapy	
Risk minimisation measures	No risk minimisation measures.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Peyona®.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Peyona®.