Part VI: Summary of the risk management plan

Summary of risk management plan for Gencebok (Caffeine)

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

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

This summary of the RMP for Gencebok 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 Gencebok's RMP.

I. The medicine and what it is used for

Gencebok is authorised for the treatment of primary apnoea in premature newborns (see SmPC for the full indication). It contains caffeine as the active substance and it is given by intravenous infusion and orally.

Further information about the evaluation of Gencebok's benefits can be found in Gencebok's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/gencebok.

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

Important risks of Gencebok, together with measures to minimise such risks and the proposed studies for learning more about Gencebok's 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 SmPC 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 *routine risk minimisation* measures.

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

In addition to these measures, information about adverse 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*.

II.A List of important risks and missing information

Important risks of Gencebok 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 Gencebok. 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 and missing information	
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 adverse reactions; • 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 Risks**

Toxicity due to maternal caffeine ingestion	
Evidence for linking the risk to the medicine:	Caffeine intake by the pregnant mother is widespread and therefore a concomitant fetal exposure, as shown by significant concentrations of caffeine from most cord blood samples, no obvious deleterious effects on the neonate have been observed (Aranda 1979). Between November 2011 and September 2013, 506 preterm infants from 21 NICUs were enrolled into a PASS study (Lista 2016). Sixty-nine mothers (13.6%) confirmed caffeine consumption prior to delivery and 54 (10.7%) during breast-feeding, with a mean intake of 1.4 units/day (1 unit = a cup of coffee or a glass of drink containing caffeine). Despite the several stratifications performed in this study there was none for the caffeine consumption in the mother and the safety/efficacy results are not distinguished in this subgroup from that in the whole patients' sample.
Risk factors and risk groups:	Infants born or breastfed to mothers heavy drinkers of caffeine.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4 ,4.6 and 5.2 PL section 2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of long term effects of caffeine therapy

Increase in caffeine plasma levels in premature infants with cholestatic hepatitis	
Evidence for linking the risk to the medicine:	In a recent post approval safety study (Lista et al 2016), out of 506 preterm infants, a group of 31 infants with hepatic or renal impairment were included. In comparison to the remaining patients, they presented a higher number of ADRs (23% vs. 3%). Cardiac disorders, specifically tachycardia, were the most common ADRs and serious AEs. However, the percentages of severe and long-lasting ADRs were still low in this patient population. Furthermore, due to the low incidence of these conditions in the population analysed, it was difficult to identify a possible correlation between elevated plasma levels and the described increase in ADRs, and so, any conclusion regarding an eventual dose adjustment cannot be drawn any conclusion regarding an eventual dose adjustment cannot be drawn.
Risk factors and risk groups:	Premature infants with cholestatic hepatitis .
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4 , 4.8 and 5.2 PL section 2

	Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of increase in caffeine plasma levels in premature infants with cholestatic hepatitis

Increase in caffeine plasma levels in premature infants with clinically relevant renal insufficiency	
Evidence for linking the risk to the medicine:	In a recent post approval safety study (Lista et al 2016), out of 506 preterm infants, a group of 31 infants with hepatic or renal impairment were included. In comparison to the remaining patients, they presented a higher number of ADRs (23% vs. 3%). Cardiac disorders, specifically tachycardia, were the most common ADRs and serious AEs. However, the percentages of severe and long-lasting ADRs were still low in this patient population. Furthermore, due to the low incidence of these conditions in the population analysed, it was difficult to identify a possible correlation between elevated plasma levels and the described increase in ADRs, and so, any conclusion regarding an eventual dose adjustment cannot be drawn any conclusion regarding an eventual dose adjustment cannot be drawn.
Risk factors and risk groups:	Premature infants with renal insufficiency.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and 5.2 PL section 2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of increase in caffeine plasma levels in premature infants with clinically relevant renal insufficiency

Cardiac disorder in infants with pre-existing cardiac disease, including arrhythmias	
Evidence for linking the risk to the medicine:	The cardiovascular effects of caffeine were evaluated in 20 clinically stable preterm infants. 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. 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 (Walther 1990). There were no 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. Caffeine does not have detrimental effects on heart rate variability, heart rate or blood pressure in conventional doses given

	to premature newborns (Ulanovsky 2014). In a recent post approval safety study tachycardia was the most frequent AE "of special interest" (5.0 and 13.5%, AOP group vs. off-label group); in this prospective real-situation safety study however, only in 6 patients from both the AOP treatment group (2.3%) and the off-label group (2.5%) was tachycardia classified as an ADR by the investigators (Lista 2016).
Risk factors and risk groups:	Infants with pre-existing cardiac disease.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of cardiac disorder in infants with pre-existing cardiac disease, including arrhythmias

Treatment-related convulsions/seizures	
Evidence for linking the risk to the medicine:	Compared with caffeine, theophylline therapy has been associated with increased adverse events in the neonatal population, including seizures and hypokalemia (Schoen 2014). Caffeine has less plasma concentration fluctuations, and greater CNS penetration without producing fluctuations in cerebral blood flow. Furthermore, theophylline therapy has been associated with seizures in the neonatal population (Abdel-Hady 2015). In a single report of a toxic over- dose of 160 mg/kg in a 31-week gestation 1,860-g infant, the serum concentration was 217.5 mg/L 36.5 hours after dosing. Toxic manifestations included hypertonia, sweating, tachycardia, cardiac failure, pulmonary oedema, metabolic acidosis, hyperglycemia, and creatine kinase elevation (Natarajan 2007). Case reports of accidental caffeine overdose in premature infants have described a variety of acute neurologic, cardiovascular, and metabolic abnormalities. Neurologic symptoms associated with an overdose included agitation, irritability, tremor, opisthotonus, and hypertonia, as well as tonic-clonic movements and nonpurposeful jaw and lip movements representative of seizure activity (Dobson 2013). However, the latter reference is to a 30-day-old 28-week preterm newborn who was exposed to 300 mg.kg-1 caffeine base by mouth accidentally. The patient exhibited agitations, irritability, tachycardia, tachypnoea, diuresis, electrolyte abnormalities, hyperglycaemia and metabolic acidosis, for which he received supportive treatment. No seizure activity was observed. The effects of intoxication lasted for 96 h and then completely resolved. (Ergenekon 2001)
Risk factors and risk groups:	Risk factors would be caffeine overdose. Infants with seizure disorders
Risk minimisation measures:	Routine risk minimisation measures:

	SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of treatment-related convulsions/seizures.

- **Important Potential Risks**

Decrease in weight gain / failure to thrive	
Evidence for linking the risk to the medicine:	Caffeine intake during pregnancy were analysed by the CARE Study Group and highlighted the association of foetal growth restriction to caffeine consumption during pregnancy. Foetal growth restriction secondary to high-dose maternal caffeine exposure is consistent across all trimesters. An incremental intake of caffeine during pregnancy was reported with LBW in 7% and small for gestational age (SGA) in 10%. 18–21-month follow-up of caffeine-exposed infants for the treatment of AOP did not show reduction in weight or head circumference, somatic effect of dose- and duration-specific exposure during the neonatal period. During a 15-year study period, a total of 457 ELBW and VLBW infants were exposed to caffeine citrate (Philip 2018). A higher rate of increase in MDWG was found for the lower dose group (5 mg/kg/day) compared with the higher dose group (10 mg/kg/day): the MDWG were 17.2 ± 12 g vs. 13.0 ± 10.2 g (p=0.04). The dose of caffeine seems to be responsible for the slower increase in MDWG.
Risk factors and risk groups:	Preterm infants (including those exposed to large quantities of caffeine prior delivery and during breast-feeding).
Risk minimisation measures:	Routine risk minimisation measures: SmPC section 4.8 PL sections 2 and 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of decrease in weight gain / failure to thrive

Caffeine withdrawal	
Evidence for linking the risk to the medicine:	A literature search had identified only 4 articles-describing infants born to mothers who consumed large quantities of caffeine during pregnancy (200 to 1800 mg daily) and who have developed symptoms attributed to caffeine withdrawal, such as irritability and vomiting. Apnea has also been reported in these infants. A total of 14 infants were described, with detailed case information provided for only 4 of the infants (Cafcit CDER evaluation 2000). ln the one preterm infant (31 weeks GA) among the complete case descriptions, a serum caffeine concentration of 40.3 mg/L was found on day 4 of life prior to a loading dose of caffeine administered for AOP (Khanna 1984). The extrapolated serum level at birth, assuming a half-life of 100 hours, was 80 mg/L. No clinical evidence of caffeine toxicity was noted at any time during the hospital stay. Measured caffeine levels ranged from 51.1 mg/l at day 23 of life, to 0.7 mg/l on day 37 of life; therapeutic caffeine was administered on at least 2 occasions during the infant's hospital stay. The authors postulated that the apnea could be a manifestation of methylxanthine withdrawal. ln the 3 remaining documented case reports with adequate detail, all infants were 2300 g and two were described as term infants. One infant had an episode of apnea; the other two did not. Symptoms attributed to withdrawal in these children included vomiting, tonic episodes, bradycardia and cyanosis, and a dilated bowel gas pattern on x-ray. For these 3 infants and an additional 5 others (McGowan 1988), tremulousness/jitteriness was noted in 6, and nonbilious vomiting that required discontinuation of feeding was noted in 5. Two infants each were described as having bradycardia (with heart rates as low as 70bpm) and tachypnea (>60 breaths/minute). Vasomotor instability was observed in one infant. Five infants whose mothers reported substantial caffeine intake were reported to manifest neonatal abstinence syndrome, with symptoms beginning at approximately 5 days of age; these included excessive crying, irritability, poor sleep patterns, and feeding difficulties and vomiting (Cafcit CDER report 2000). An extensive literature search on-caffeine withdrawal in neonates identified no articles on withdrawal symptoms following discontinuation of caffeine therapy in preterm infants or neonates. A Medline literature search by the FDA Medical reviewer in year 2000 confirmed the absence of literature on neonatal withdrawal from the therapeutic use of caffeine. A similar search in 2019 does not provide additional findings in preterm infants.
Risk factors and risk groups:	Infants born to mothers heavy drinkers of caffeine or exposed.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of decrease in weight gain / failure to thrive

Necrotising enterocolitis	
Evidence for linking the risk to the medicine:	From a FDA review in 2000 (Cafcit CDER 2000) the overall incidence of NEC showed variation from centre to centre, as well as within centre from one year to the next. The incidence of NEC observed in the Erenberg 2000 study (7.9% for caffeine exposed and 4.5% for placebo, p=1.0) is within the range reported by multiple sites and by the literature. The rate of NEC seen in association with caffeine use in this study does not exceed historical ranges and the observed variability between and within sites provides a potential explanation for the observed numeric difference from placebo treatment. For one investigational site, incidence data for NEC were described according to methylxanthine use. These crude data show year-to-year variation in the incidence of NEC, with a greater incidence among patients treated with methylxanthines during 1994 and 1997. Conversely, the incidence of NEC was lower among methylxanthine-treated patients in 1995 and 1996. These data provided reassurance that the rates of NEC seen among patients on methylxanthines ranged within historical limits described in the literature. However, since these data are not adjusted for differences in birth weight, other diagnoses (including AOP), and numerous other factors, they cannot provide any conclusive evidence about the potential association of NEC with methylxanthine use.
Risk factors and risk groups:	Preterm infants.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of necrotising enterocolitis

Medication errors	
Evidence for linking the risk to the medicine:	This risk is highlighted by the company based on the difference of concentration between the reference product Peyona and Gencebok (20 mg/ml of caffeine citrate for Peyona and 10 mg/ml of caffeine citrate for Gencebok). Considering the high-risk population treated, medication error may have a major impact.
Risk factors and risk groups:	Risk factors would be unclear labelling or misunderstanding inducing confusion in concentration and/or caffeine base/citrate content.
Risk minimisation measures:	Routine risk minimisation measures: SmPC section 4.2 Labelling about caffeine citrate/base Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of medication error.

Rare adverse reactions	
Evidence for linking the risk to the medicine:	It is not known the rare adverse drug reactions with caffeine
Risk minimisation measures:	Routine risk minimisation measures: SmPC section 4.8 PL section 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of rare adverse reactions.

Drug interaction with the most commonly used drugs in the NICU	
Evidence for linking the risk to the medicine:	Critically ill patients in neonatal intensive-care units (NICU) are exposed to a large number of drugs. Clinical trials for safety, dosing and efficacy are lacking although age- dependent alterations of pharmacokinetics (PK), drug-drug-interactions (DDIs), as well as intravenous admixture incompatibilities (IAI) may impact drug efficacy and trigger side- effects in this vulnerable population. There are limited data about the interaction between caffeine and drugs metabolised by CYP1A2 in premature newborn.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5 and 5.2 PL section 2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of drug interaction with the most commonly used drugs in the NICU.

Long-term effects of caffeine therapy	
Evidence for linking the risk to the medicine:	It is not known whether caffeine has long-term adverse effects on sleep architecture and ventilatory control, which could result in an increased prevalence of sleep disorders later in childhood, such as insomnia or obstructive sleep apnea syndrome (OSAS).
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: None

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 Gencebok.

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

There are no studies required for Gencebok.