ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gencebok 10 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg caffeine citrate (equivalent to 5 mg caffeine).
Each 1 ml ampoule contains 10 mg caffeine citrate (equivalent to 5 mg caffeine).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless, aqueous solution, with a pH of 4.8 and an osmolality of 65 to 95 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of primary apnoea of premature newborns.

4.2 Posology and method of administration

Treatment with caffeine citrate should be initiated under the supervision of a physician experienced in neonatal intensive care. Treatment should be administered only in a neonatal intensive care unit in which adequate facilities are available for patient surveillance and monitoring.

Posology

The recommended dose regimen in previously untreated infants is a loading dose of 20 mg caffeine citrate per kg body weight administered by slow intravenous infusion over 30 minutes, using a syringe infusion pump or other metered infusion device. After an interval of 24 hours, maintenance doses of 5 mg per kg body weight may be administered by slow intravenous infusion over 10 minutes every 24 hours. Alternatively, maintenance doses of 5 mg per kg body weight may be administered by oral administration, such as through a nasogastric tube every 24 hours.
The recommended loading dose and maintenance doses of caffeine citrate are provided in the following table which clarifies the relationship between injection volumes and administered doses expressed as caffeine citrate.
The dose expressed as caffeine base is one-half the dose when expressed as caffeine citrate (10 mg caffeine citrate are equivalent to 5 mg caffeine base).

	Dose of caffeine citrate (Volume)	Dose of caffeine citrate (mg/kg body weight)	Route	Frequency
Loading dose	2.0 ml/kg body weight	20 mg/kg body weight	Intravenous infusion (over 30 minutes)	Once
Maintenance dose*	0.5 ml/kg body weight	5 mg/kg body weight	Intravenous infusion (over 10 minutes) or by oral administration	Every 24 hours*

* Beginning 24 hours after the loading dose

In preterm newborn infants with insufficient clinical response to the recommended loading dose, a second loading dose of 10-20 mg/kg maximum may be given after 24 hours.
Higher maintenance doses of 10 mg/kg body weight could be considered in case of insufficient response, taking into account the potential for accumulation of caffeine due to the long half-life in preterm newborn infants and the progressively increasing capacity to metabolise caffeine in relation to post-menstrual age (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 do not respond adequately to a second loading dose or maintenance dose of 10 mg/kg/day (see section 4.4).

Dosage adjustments and monitoring
Plasma concentrations of caffeine may need to be monitored periodically throughout treatment in cases of incomplete clinical response or signs of toxicity.
Additionally, doses may need to be adjusted according to medical judgment following routine monitoring of caffeine plasma concentrations in at risk situations such as:

- very premature infants (< 28 weeks gestational age and/or body weight <1000 g) particularly when receiving parenteral nutrition
- infants with hepatic and renal impairment (see sections 4.4 and 5.2)
- infants with seizure disorders
- infants with known and clinically significant cardiac disease
- infants receiving co-administration of medicinal products known to interfere with caffeine metabolism (see section 4.5)
- infants whose mothers consume caffeine while providing breast milk for feeding.

It is advisable to measure baseline caffeine levels in:

- infants whose mothers may have ingested large quantities of caffeine prior to delivery (see section 4.4)
- infants who have previously been treated with theophylline, which is metabolized to caffeine.

Caffeine has a prolonged half-life in premature newborn infants and there is potential for accumulation which may necessitate monitoring infants treated for an extended period (see section 5.2).
Blood samples for monitoring should be taken just before the next dose in the case of therapeutic failure and 2 to 4 hours after the previous dose when suspecting toxicity.

Although a therapeutic plasma concentration range of caffeine has not been determined in the literature, caffeine levels in studies associated with clinical benefit ranged from 8 to 30 mg/l and no safety concerns have normally been raised with plasma levels below 50 mg/l.

Duration of treatment
The optimal duration of treatment has not been established. In a recent large multicentre study on preterm newborn infants a median treatment period of 37 days was reported.
In clinical practice, treatment is usually continued until the infant has reached a post-menstrual age of 37 weeks, by which time apnoea of prematurity usually resolves spontaneously. This limit may however be revised according to clinical judgment in individual cases depending on the response to treatment, the continuing presence of apnoeic episodes despite treatment, or other clinical considerations. It is recommended that caffeine citrate administration should be stopped when the patient has 5-7 days without a significant apnoeic attack.
If the patient has recurrent apnoea, caffeine citrate administration can be restarted with either a maintenance dose or a half loading dose, depending upon the time interval from stopping caffeine citrate to recurrence of apnoea.
Because of the slow elimination of caffeine in this patient population, there is no requirement for dose tapering on cessation of treatment.

As there is a risk for recurrence of apnoeas after cessation of caffeine citrate treatment monitoring of the patient should be continued for approximately one week.

Hepatic and renal impairment

There is limited experience in patients with renal and hepatic impairment. In a post authorisation safety study, the frequency of adverse reactions in a small number of very premature infants with renal/hepatic impairment appeared to be higher as compared to premature infants without organ impairment (see sections 4.4 and 4.8).
In the presence of renal impairment, there is increased potential for accumulation. A reduced daily maintenance dose of caffeine citrate is required and the dose should be guided by plasma caffeine measurements.
In very premature infants, clearance of caffeine does not depend on hepatic function. Hepatic caffeine metabolism develops progressively in the weeks following birth and for the older infants, hepatic disease may indicate a need for monitoring caffeine plasma levels and may require dose adjustments (see sections 4.4 and 5.2).

Method of administration

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

When given intravenously, caffeine citrate should be administered by controlled intravenous infusion, using a syringe infusion pump or other metered infusion device only. 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%) or calcium gluconate 100 mg/ml (10%) immediately after withdrawal from the ampoule (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Apnoea

Apnoea of prematurity is a diagnosis of exclusion. Other causes of apnoea (e.g., central nervous system disorders, primary lung disease, anaemia, sepsis, metabolic disturbances, cardiovascular abnormalities, or obstructive apnoea) should be ruled out or properly treated prior to initiation of treatment with caffeine citrate. Failure to respond to caffeine treatment (confirmed if necessary by measurement of plasma levels) could be an indication of another cause of apnoea.

Caffeine consumption

In newborn infants born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate, since caffeine readily crosses the placenta into the foetal circulation (see sections 4.2 and 5.2).

Breast-feeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine-containing foods and beverages or medicinal products containing caffeine (see section 4.6), since caffeine is excreted into breast milk (see section 5.2).

Theophylline

In newborns previously treated with theophylline, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate because preterm infants metabolise theophylline to caffeine.

Seizures

Caffeine is a central nervous system stimulant and seizures have been reported in cases of caffeine overdose. Extreme caution must be exercised if caffeine citrate is used in newborns with seizure disorders.

Cardiovascular reactions

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 newborns with known cardiovascular disease. There is evidence that caffeine causes tachyarrhythmias in susceptible individuals. In newborns this is usually a simple sinus tachycardia. If there have been any unusual rhythm disturbances on a cardiotocograph (CTG) trace before the baby is born, caffeine citrate should be administered with caution.

Renal and hepatic impairment

Caffeine citrate should be administered with caution in preterm newborn infants with impaired renal or hepatic function. In a post-authorisation safety study, the frequency of adverse reactions in a small number of very premature infants with renal/hepatic impairment appeared to be higher as compared to premature infants without organ impairment (see sections 4.2, 4.8 and 5.2). Doses should be adjusted by monitoring of caffeine plasma concentrations to avoid toxicity in this population.

Necrotising enterocolitis

Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for the development of necrotising enterocolitis (see section 4.8).

Caffeine citrate should be used with caution in infants suffering gastro-oesophageal reflux, as the treatment may exacerbate this condition.

Caffeine citrate 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 citrate may necessitate correction of fluid and electrolyte disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Inter-conversion between caffeine and theophylline occurs in preterm newborn infants. These active substances should not be used concurrently.

Cytochrome P450 1A2 (CYP1A2) is the major enzyme involved in the metabolism of caffeine in humans. Therefore, caffeine has the potential to interact with active substances that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2. However, caffeine metabolism in preterm newborn infants is limited due to their immature hepatic enzyme systems.

Although few data exist on interactions of caffeine with other active substances in preterm newborn infants, lower doses of caffeine citrate may be needed following co-administration of active substances which are reported to decrease caffeine elimination in adults (e.g., cimetidine and ketoconazole) and higher caffeine citrate doses may be needed following co-administration of active substances that increase caffeine elimination (e.g., phenobarbital and phenytoin). Where doubt exists about possible interactions, plasma caffeine concentrations should be measured.
As bacterial overgrowth in the gut is associated with the development of necrotising enterocolitis, co-administration of caffeine citrate with medicinal products that suppress gastric acid secretion

(antihistamine H2 receptor blockers or proton-pump inhibitors) may in theory increase the risk of necrotising enterocolitis (see section 4.4 and 4.8).
Concurrent use of caffeine and doxapram might potentiate their stimulatory effects on the cardio-respiratory and central nervous system. If concurrent use is indicated, cardiac rhythm and blood pressure must be carefully monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Caffeine in animal studies, at high doses, was shown to be embryotoxic and teratogenic. These effects are not relevant with regard to short term administration in the preterm infant population (see section 5.3).

Breast-feeding

Caffeine is excreted into breast milk and readily crosses the placenta into the foetal circulation (see section 5.2).
Breast-feeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine-containing foods, beverages or medicinal products containing caffeine.
In newborn infants born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate (see section 4.4).

Fertility

Effects on reproductive performance observed in animals are not relevant to its indication in the preterm newborn infants (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The known pharmacology and toxicology of caffeine and other methylxanthines predict the likely adverse reactions to caffeine citrate. Effects described include central nervous system (CNS) stimulation such as convulsion, irritability, restlessness and jitteriness, cardiac effects such as tachycardia, arrhythmia, hypertension and increased stroke volume, metabolism and nutrition disorders such as hyperglycaemia. These effects are dose related and may necessitate measurement of plasma levels and dose reduction.

Tabulated list of adverse reactions

The adverse reactions described in the short- and long-term published literature and obtained from a post-authorisation safety study that can be associated with caffeine citrate are listed below by System Organ Class and Preferred Term (MedDRA).
Frequency is defined as: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Sepsis	Not known

Immune system disorders	Hypersensitivity reaction	Rare
Metabolism and nutrition disorders	Hyperglycaemia	Common
	Hypoglycaemia, failure to thrive, feeding intolerance	Not known
Nervous system disorders	Convulsion	Uncommon
	Irritability, jitteriness, restlessness, brain injury	Not known
Ear and labyrinth disorders	Deafness	Not known
Cardiac disorders	Tachycardia	Common
	Arrhythmia	Uncommon
	Increased left ventricular output and increased stroke volume	Not known
Gastrointestinal disorders	Regurgitation, increased gastric aspirate, necrotising enterocolitis	Not known
General disorders and administration site conditions	Infusion site phlebitis, infusion site inflammation	Common
Investigations	Urine output increased, urine sodium and calcium increased, haemoglobin decreased, thyroxine decreased	Not known

Description of selected adverse reactions

Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established.
In a double-blind placebo-controlled study of caffeine citrate in 85 preterm infants (see section 5.1), necrotising enterocolitis was diagnosed in the blinded phase of the study in two infants on active treatment and one on placebo, and in three infants on caffeine during the open-label phase of the study. Three of the infants who developed necrotising enterocolitis during the study died. A large multicentre study (n=2006) investigating long-term outcome of premature infants treated with caffeine citrate (see section 5.1) did not show an increased frequency of necrotising enterocolitis in the caffeine group when compared to placebo. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for the development of necrotising enterocolitis (see section 4.4).
Brain injury, convulsion and deafness were observed but they were more frequent in the placebo group.

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

Other special populations

In a post-authorisation safety study on 506 preterm infants treated with caffeine citrate, safety data have been collected in 31 very premature infants with renal/hepatic impairment. Adverse reactions appeared to be more frequent in this subgroup with organ impairment than in other observed infants without organ impairment. Cardiac disorders (tachycardia, including one single case of arrhythmia) were mostly reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

Symptoms

Signs and symptoms reported in the literature after caffeine overdose in preterm infants include hyperglycaemia, hypokalaemia, fine tremor of the extremities, restlessness, hypertonia, opisthotonus, tonic clonic movements, seizures, tachypnoea, tachycardia, vomiting, gastric irritation, gastro-intestinal haemorrhage, pyrexia, jitteriness, increased blood urea and increased white blood cell count, non-purposeful jaw and lip movements. One case of caffeine overdose complicated by development of intraventricular haemorrhage and long-term neurological sequelae has been reported. No deaths associated with caffeine overdose have been reported in preterm infants.

Management

Treatment of caffeine overdose is primarily symptomatic and supportive. Plasma potassium and glucose concentrations should be monitored and hypokalaemia and hyperglycaemia corrected. Plasma caffeine concentrations have been shown to decrease after exchange transfusion. Convulsions may be treated with intravenous administration of anticonvulsants (diazepam or a barbiturate such as pentobarbital sodium or phenobarbital).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics, xanthine derivatives, ATC code: N06BC01

Mechanism of action

Caffeine is structurally related to the methylxanthines theophylline and theobromine.
Most of its effects have been attributed to antagonism of adenosine receptors, both A_1 and A_{2A} subtypes, demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically in this indication.

Pharmacodynamic effects

Caffeine's main action is as a CNS stimulant. This is the basis of caffeine's effect in apnoea of prematurity, for which several mechanisms have been proposed for its actions including: (1) respiratory centre stimulation, (2) increased minute ventilation, (3) decreased threshold to

hypercapnia, (4) increased response to hypercapnia, (5) increased skeletal muscle tone, (6) decreased diaphragmatic fatigue, (7) increased metabolic rate, and (8) increased oxygen consumption.

Clinical efficacy and safety

The clinical efficacy of caffeine citrate was assessed in a multicentre, randomised, double-blind study that compared caffeine citrate to placebo in 85 preterm infants (gestational age 28 to <33 weeks) with apnoea of prematurity. Infants received 20 mg/kg caffeine citrate loading dose intravenously. A maintenance daily dose of 5 mg/kg caffeine citrate was then administered either intravenously or orally (through a feeding tube) for up to 10-12 days. The protocol allowed infants to be "rescued" with open-label caffeine citrate treatment if their apnoea remained uncontrolled. In that case, infants received a second loading dose of 20 mg/kg caffeine citrate after treatment day 1 and before treatment day 8.
There were more days without any apnoea under caffeine citrate treatment (3.0 days, versus 1.2 days for placebo; p=0.005); also, there was a higher percentage of patients with no apnoeas for ≥ 8 days (caffeine 22% versus placebo 0%).
A recent large placebo-controlled multicentre study (n=2006) investigated short-term and long-term (18-21 months) outcomes of premature infants treated with caffeine citrate. Infants randomised to caffeine citrate received an intravenous loading dose of 20 mg/kg, followed by a daily maintenance dose of 5 mg/kg. If apnoeas persisted, the daily maintenance dose could be increased to a maximum of 10 mg/kg of caffeine citrate. The maintenance doses were adjusted weekly for changes in body weight and could be given orally once an infant tolerated full enteral feedings. Caffeine therapy reduced the rate of bronchopulmonary dysplasia [odds ratio (95% CI) 0.63 (0.52 to 0.76)] and improved the rate of survival without neurodevelopmental disability [odds ratio (95 %CI) 0.77 (0.64 to 0.93)].
The size and direction of caffeine effect on death and disability differed depending on the degree of respiratory support infants needed at randomisation, indicating more benefit for the supported infants [odds ratio (95%CI) for death and disability, see table below].

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

Subgroups	Odds ratio (95% CI)
No support	1.32 (0.81 to 2.14)
Non invasive support	0.73 (0.52 to 1.03)
Endotracheal tube	0.73 (0.57 to 0.94)

5.2 Pharmacokinetic properties

Caffeine citrate readily dissociates in aqueous solution. The citrate moiety is rapidly metabolized on infusion or ingestion.

Absorption

The onset of action of caffeine from caffeine citrate is within minutes of commencement of infusion. After oral administration of 10 mg caffeine base/kg body weight to preterm newborn infants, the peak plasma caffeine concentration (C_{max}) ranged from 6 to 10 mg/l and the mean time to reach peak concentration (t_{max}) ranged from 30 min to 2 h. The extent of absorption is not affected by formula feeding but t_{max} may be prolonged.

Distribution

Caffeine is rapidly distributed into the brain following caffeine citrate administration. Caffeine concentrations in the cerebrospinal fluid of preterm newborn infants approximate to their plasma levels. The mean volume of distribution (V_d) of caffeine in infants (0.8-0.9 l/kg) is slightly higher than that in adults (0.6 l/kg). Plasma protein binding data are not available for newborn infants or infants. In adults, the mean plasma protein binding *in vitro* is reported to be approximately 36%.

Caffeine readily crosses the placenta into the foetal circulation and is excreted into breast milk.

Biotransformation

Caffeine metabolism in preterm newborn infants is very limited due to their immature hepatic enzyme systems and most of the active substance is eliminated in urine. Hepatic cytochrome P450 1A2 (CYP1A2) is involved in caffeine biotransformation in older individuals.
Inter-conversion between caffeine and theophylline has been reported in preterm newborn infants; caffeine levels are approximately 25% of theophylline levels after theophylline administration and approximately 3-8% of caffeine administered would be expected to convert to theophylline.

Elimination

In young infants, the elimination of caffeine is much slower than that in adults due to immature hepatic and/or renal function. In newborn infants, caffeine clearance is almost entirely by renal excretion. Mean half-life ($t_{1/2}$) and fraction excreted unchanged in urine (A_e) of caffeine in infants are inversely related to gestational / postmenstrual age. In newborn infants, the $t_{1/2}$ is approximately 3-4 days and the Ae is approximately 86% (within 6 days). By 9 months of age, the metabolism of caffeine approximates to that seen in adults ($t_{1/2}$ = 5 hours and A_e = 1%).
Studies examining the pharmacokinetics of caffeine in newborn infants with hepatic or renal insufficiency have not been conducted.
In the presence of significant renal impairment, considering the increased potential for accumulation, a reduced daily maintenance dose of caffeine is required and the doses should be guided by blood caffeine measurements. In premature infants with cholestatic hepatitis a prolonged caffeine elimination half-life with an increase of plasma levels above the normal limit of variation has been found suggesting a particular caution in the dosage of these patients (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data revealed no major hazard for humans based on studies of repeated dose toxicity of caffeine. However, at high doses convulsions in rodents were induced. At therapeutic doses some behavioural changes in newborn rats were induced, most likely as a consequence of increased adenosine receptor expression that persisted into adulthood. Caffeine was shown to be devoid of mutagenic and oncogenic risk. Teratogenic potential and effects on reproductive performance observed in animals are not relevant to its indication in the preterm infant population.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate
Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed or concomitantly administered in the same intravenous line with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

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

Chemical and physical compatibility of the diluted solution has been demonstrated for 24 hours at 25ºC.

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

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear glass 1 ml ampoule coded by 2 blue rings.
Pack size of 50 ampoules.

6.6 Special precautions for disposal and other handling

Aseptic technique must be strictly observed throughout handling of the medicinal product since no preservative is present.

Gencebok should be inspected visually for particulate matter and discoloration prior to administration. Ampoules containing discoloured solution or visible particulate matter should be discarded.

Gencebok 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%) or calcium gluconate 100 mg/ml (10%) immediately after withdrawal from the ampoule.
The diluted solution must be clear and colourless. Undiluted and diluted parenteral solutions must be inspected visually for particulate matter and discoloration prior to administration. The solution must not be used if it is discoloured or foreign particulate matter is present.

For single use only. Any unused portion left in the ampoule should be discarded. Unused portions should not be saved for later administration.

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Gennisium Pharma
Faculté Cochin – Paris Biotech Santé
24 rue du Faubourg St Jacques
75014 Paris - France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1465/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 August 2020

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Cenexi
52 rue Marcel et Jacques Gaucher
94120 Fontenay Sous-Bois
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall agree with the National Competent Authorities the final text of a card suitable for display in neonatal intensive care units. The card shall contain the following key elements and be provided to all neonatal intensive care units where the medicinal product is likely to be used at launch of the medicinal product:

- That Gencebok is for the treatment of primary apnoea
- That treatment with Gencebok must be provided in a neonatal intensive care unit and initiated and supervised by a physician experienced in neonatal intensive care
- Details of the loading and maintenance dosages and that caffeine may accumulate in premature newborn infants because of its long half-life.
- That the dose of caffeine expressed as caffeine base is one half the dose of caffeine expressed as caffeine citrate (10 mg caffeine citrate is equivalent to 5 mg caffeine base) and

that prescriptions should clearly indicate that caffeine citrate is to be administered.

- That Gencebok is containing 10 mg caffeine citrate, equivalent to 5 mg caffeine base and should be administered according to the following dosing scheme:

	Dose of caffeine citrate (Volume)	Dose of caffeine citrate (mg/kg body weight)	Route	Frequency
Loading dose	2.0 ml/kg body weight	20 mg/kg body weight	Intravenous infusion (over 30 minutes)	Once
Maintenance dose*	0.5 ml/kg body weight	5 mg/kg body weight	Intravenous infusion (over 10 minutes) or by oral administration	Every 24 hours*

* Beginning 24 hours after the loading dose

- That the medicinal product should be used immediately after opening the ampoule and unused portions left in the ampoule should be discarded
- That baseline plasma levels may need measuring because of an increased risk of toxicity if
    - The neonate has been previously treated with theophylline
    - The mother has been consuming large amounts of caffeine prior to delivery or breast feeding
- That caffeine and theophylline should not be used concurrently
- That if caffeine and doxapram are used concurrently, the patient should be closely monitored
- That additional plasma caffeine monitoring and dosage adjustment may be necessary in at risk situations such as preterm infants:
    - With cholestatic hepatitis
    - With significant renal impairment
    - With seizure disorders
    - With cardiac disease
    - less than 28 weeks gestational age and/or body weight <1000g particularly when receiving parenteral nutrition
    - with co-administration of medicinal products known to interfere with caffeine metabolism
- That cardiac disorders (including arrhythmias) may arise in newborn infants with pre-existing cardiac disease
- That all suspected adverse reactions should be reported in accordance with national reporting requirements
- In particular, if convulsions, seizures, necrotising enterocolitis, symptoms and signs of caffeine withdrawal, medically abnormal decrease in infant weight gain or interactions with other medicines are suspected as being associated with the use of caffeine citrate, these should be reported to <insert local name and address of Gennisium Pharma>.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Gencebok 10 mg/ml solution for infusion
caffeine citrate
(equivalent to 5 mg/ml of caffeine base)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml ampoule contains 10 mg of caffeine citrate (equivalent to 5 mg of caffeine base).

3. LIST OF EXCIPIENTS

Citric acid monohydrate, sodium citrate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
50 ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intravenous use
Oral use
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Use immediately after opening or diluting.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gennisium Pharma
Faculté Cochin – Paris Biotech Santé
24 rue du Faubourg St Jacques
75014 Paris - France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1465/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Gencebok 10 mg/ml infusion
caffeine citrate
(equivalent to 5 mg/ml of caffeine base)
IV/oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg/1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Gencebok 10 mg/ml solution for infusion
caffeine citrate

Read all of this leaflet carefully before treatment with this medicine because it contains important information for your newborn
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your baby's doctor.
- If your newborn gets any side effects, talk to your baby's doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Gencebok is and what it is used for

Gencebok contains the active substance caffeine citrate, which is a stimulant of the central nervous system, belonging to a group of medicines called methylxanthines.

Gencebok is used in the treatment of interrupted breathing in premature babies (primary apnoea of premature newborns).
These short periods when premature babies stop breathing are due to the baby's breathing centres not being fully developed.
This medicine has been shown to reduce the number of episodes of interrupted breathing in premature newborns.

2. What you need to know before your baby is given Gencebok

Do not use Gencebok
- If your newborn is allergic to caffeine citrate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your baby's doctor before your newborn is given Gencebok.
Prior to starting treatment for apnoea of prematurity with Gencebok other causes of apnoea should have been excluded or properly treated by your baby's doctor.

Gencebok should be used with caution. Please inform your baby's doctor:

- If your newborn suffers from seizures
- If your newborn suffers from any heart disease
- If your newborn has kidney or liver problems
- If your newborn has frequent regurgitation
- If your newborn produces more urine than usual
- If your newborn has a reduced weight gain or food intake
- If you (the mother) consumed caffeine prior to delivery

Other medicines and Gencebok

Tell your baby's doctor if your newborn is taking, have recently taken or might take any other medicines.
Please inform your baby's doctor if your newborn has been previously treated with theophylline. Do not use the following medicines during the treatment with Gencebok without talking to your baby's doctor. The doctor may need to adjust the dose or change one of the medicines to something else:
- theophylline (used to treat breathing difficulties)
- doxapram (used to treat breathing difficulties)
- cimetidine (used to treat gastric disease)
- ketoconazole (used to treat fungine infections)
- phenobarbital (used to treat epilepsy)
- phenytoin (used to treat epilepsy)

This medicine may increase the risk for serious intestinal disease with bloody stools (necrotising enterocolitis) when administered with medicines used to treat gastric disease (such as antihistamine H2 receptor blockers or proton-pump inhibitors that reduces gastric acid secretion).

Pregnancy and breast-feeding
If you (the mother) are breast-feeding while your infant is treated with Gencebok, you should not drink coffee or take any other high caffeine product as caffeine passes into breast milk.

Gencebok contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free'.

3. How to use Gencebok

Gencebok should only be used in a neonatal intensive care unit in which adequate facilities are available for patient surveillance and monitoring. Treatment should be initiated under supervision of a physician experienced in neonatal intensive care.

Dose
Your baby's doctor will prescribe the right amount of Gencebok based on your baby's weight. The starting dose is 20 mg per kg body weight (equivalent to 2 ml per kg body weight).
The maintenance dose is 5 mg per kg body weight (equivalent to 0.5 ml per kg body weight) every 24 hours.

Route and method of administration
Gencebok will be infused by controlled intravenous infusion, using a syringe infusion pump or other metered infusion device. This method is also known as "a drip".
Some of the doses (maintenance doses) may be given by mouth.
It may be needed that your baby's doctor decides to check the levels of caffeine in a blood test periodically throughout treatment to avoid toxicity.

Duration of treatment
Your baby's doctor will decide exactly how long your newborn must continue therapy with Gencebok. If your baby has 5 to 7 days without apnoea attacks, the doctor will stop the treatment.

If your newborn receives more Gencebok than he/she should
Your newborn may experience fever, rapid breathing (tachypnoea), jitteriness, muscular tremor vomiting, high blood levels of sugar (hyperglycemia), low blood levels of potassium (hypokalaemia), high blood levels of certain chemicals (urea), elevated number of certain cells (leukocyte) in blood and seizures if he/she receives more caffeine citrate than he/she should.
In the event of this happening treatment with Gencebok should be stopped immediately and your baby's doctor should treat the overdose.

If you have any further questions on the use of this medicinal product, ask your baby's doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. However, it is difficult to distinguish them from frequent complications occurring in premature babies and complications due to the disease.

While under treatment with Gencebok, your newborn may experience some of the following reactions:

Serious side effects
Side effects where the frequency cannot be estimated from the available data
- serious intestinal disease with bloody stools (necrotising enterocolitis)

The following other side effects may also be considered serious by your baby's doctor in the context of the global clinical evaluation.

Other side effects

Common reported side effects (may affect up to 1 in 10 people)
- local inflammatory reactions at the infusion site
- cardiac disorders such as fast heart beat (tachycardia)
- changes of sugar in blood or serum (hyperglycaemia)

Uncommon reported side effects (may affect up to 1 in 100 people)
- stimulation of central nervous system such as convulsion
- cardiac disorders such as irregular heart beat (arrhythmia)

Rare reported side effects (may affect up to 1 in 1,000 people)
- allergic reactions

Side effects where the frequency cannot be estimated from the available data
- bloodstream infection (sepsis)
- changes of sugar in blood or serum (hypoglycaemia), failure to grow, feeding intolerance
- stimulation of central nervous system such as irritability, nervousness and restlessness; brain injury
- deafness
- regurgitation, increase in stomach aspirate
- increase of urine flow, increase of certain urine components (sodium and calcium)
- changes in blood tests (reduced levels of haemoglobin after prolonged treatment and reduced thyroid hormone at the start of treatment)

Reporting of side effects
If your newborn gets any side effects, talk to your baby's doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Gencebok

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
The medicinal product does not require any special storage conditions.
Ampoules of all parenteral solutions must be inspected visually for particulate matter prior to administration. After opening the ampoules, the medicinal product should be used immediately.

6. Contents of the pack and other information

What Gencebok contains
The active substance is caffeine citrate.
Each ml contains 10 mg caffeine citrate (equivalent to 5 mg/ml of caffeine base).
Each 1 ml ampoule contains 10 mg caffeine citrate (equivalent to 5 mg of caffeine base).
The other ingredients are citric acid, sodium citrate and water for injections.

What Gencebok looks like and content of the pack
Gencebok is a solution for infusion.
Gencebok is a clear, colourless solution, supplied in glass ampoules coded by 2 blue rings. Each carton contains 50 ampoules.

Marketing Authorisation Holder
Gennisium Pharma
Faculté Cochin – Paris Biotech Santé
24 rue du Faubourg St Jacques
75014 Paris - France

Manufacturer (batch release)
Cenexi
52 rue Marcel et Jacques Gaucher
94120 Fontenay Sous-Bois
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Gennisium Pharma
Tél/Tel: +33 9 70 19 79 90
info@gennisium.com

Lietuva
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

България
Gennisium Pharma
Тел.: +33 9 70 19 79 90
info@gennisium.com

Luxembourg/Luxemburg
Gennisium Pharma
Tél/Tel: +33 9 70 19 79 90
info@gennisium.com

Česká republika
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Magyarország
Gennisium Pharma
Tel.: +33 9 70 19 79 90
info@gennisium.com

Danmark
Nordic Prime ApS
Tlf: +45 75 15 13 40
info@nordicprime.dk

Malta
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Deutschland
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Nederland
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Eesti
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Ελλάδα
Gennisium Pharma
Τηλ: +33 9 70 19 79 90
info@gennisium.com

España
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

France
Gennisium Pharma
Tél: +33 9 70 19 79 90
info@gennisium.com

Hrvatska
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Ireland
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Ísland
Nordic Prime ApS
Sími: +45 75 15 13 40
info@nordicprime.dk

Italia
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Κύπρος
Gennisium Pharma
Τηλ: +33 9 70 19 79 90
info@gennisium.com

Latvija
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Norge
Nordic Prime ApS
Tlf: +45 75 15 13 40
info@nordicprime.dk

Österreich
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Polska
Mercapharm Sp. z o. o.
Tel.: +48 57 33 55 888
info@mercapharm.com.pl

Portugal
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

România
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Slovenija
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Slovenská republika
Gennisium Pharma
Tel: +33 9 70 19 79 90
info@gennisium.com

Suomi/Finland
Nordic Prime ApS
Puh/Tel: +45 75 15 13 40
info@nordicprime.dk

Sverige
Nordic Prime ApS
Tel: +45 75 15 13 40
info@nordicprime.dk

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

The following information is intended for healthcare professionals only:
For detailed information refer to the enclosed Summary of Product Characteristics of Gencebok.