



European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Nymusa

International Nonproprietary Name: **caffeine**

Procedure No. EMEA/H/C/001014

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Chiesi Farmaceutici SpA submitted on 06 May 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) through the centralised procedure for Nymusa, which was designated as an orphan medicinal product EU/3/03/132 on 17 February 2003. Nymusa was designated as an orphan medicinal product in the following indication: treatment of primary apnoea of premature newborns. The prevalence of the condition “Primary apnoea of premature newborns” is in the range of 0.5-1.2 per 10.000 individuals in the EU. The Orphan Drug Designation has been transferred to Chiesi Farmaceutici S.p.A. on 18 January 2007.

Despite existing authorised methods of treatment, the sponsor has satisfactorily justified the assumption that the medicinal product subject of the application might be of potential significant benefit for the treatment of primary apnoeas of premature newborns, particularly in terms of availability of caffeine citrate throughout the European Union.

The legal basis for this application refers to:

A - Centralised / Article 10(a) / Well-established use application.

Article 10(a) of Directive 2001/83/EC, as amended – relating to applications relying on well established medicinal use supported by bibliographic literature.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

The applicant applied for the following indication: Treatment of primary apnoea of premature newborns.

Protocol Assistance:

The applicant did not seek Protocol Assistance at the CHMP.

Licensing status:

Nymusa was not approved in any country at the time of application.

A formulation of caffeine citrate 25 mg/ml (12.5 mg caffeine base per ml), Cafèine Cooper, has been authorised in France for injectable and oral use in the treatment of apnoea of prematurity in newborn children since 31st December 1997. The formal indication stated in the Summary of Product Characteristics (SmPC) is “Traitement de l’apnée du nouveau-né prématuré.”

A caffeine citrate formulation was approved in UK in 2008 for “Treatment of apnoea of prematurity” (Caffeine 5mg/ml Solution for Injection, Viridian Pharma Ltd).

Cafcit injection (caffeine citrate injection 60 mg/3 ml) and Cafcit oral solution (caffeine citrate solution 60 mg/3 ml) were granted orphan status in the U.S. on 20 September 1998 and received marketing authorisation from the Food and Drug Administration (FDA) for the orphan indication “The short term treatment of apnoea of prematurity in infants between 28 and < 33 weeks gestational age” on 21 September 1999.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Andrea Laslop**

Co-Rapporteur: **Cristina Sampaio**

1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 06 May 2008.
- The procedure started on 28 May 2008.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2008. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 22-25 September 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 September 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 December 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 February 2009.
- During the CHMP meeting on 16-19 February 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 18 March 2009.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 17 April 2009.
- During the meeting on 20-23 April 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Nymusa on 23 April 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 April 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Apnoea of prematurity (AOP) is defined as "cessation of breathing for 20 seconds or longer, or as a brief episode if associated with bradycardia (HR<100 beats/min), cyanosis, or pallor". Primary (or idiopathic) apnoea of prematurity is a diagnosis of exclusion and implies that underlying causes of apnoea have been excluded.

Brief pauses in breathing (five to ten seconds) are a common event in preterm infants. Prolonged pauses can lead to hypoxaemia, decreased peripheral perfusion, cyanosis, reflex vagal bradycardia, and hypotonia.

AOP appears to be due to central immaturity of brainstem respiratory centres with an attenuated respiratory response to carbon dioxide (CO₂), a paradoxical response to hypoxia (resulting in apnoea rather than hyperventilation), and an exaggerated inhibitory response to airway (e.g. laryngeal) stimulation.

AOP is a common condition in preterm neonates affecting approximately 90% of extremely low birth weight infants (<1000g). The incidence varies inversely with gestational age (GA). The onset of primary AOP presents between the 2nd and 7th day of life. It usually resolves by 36 weeks post-menstrual age and does not predict future episodes of sudden infant death syndrome (SIDS).

Infants at risk for apnoea should be monitored with apnoea monitors. Gentle cutaneous stimulation may suffice for infants with mild and intermittent episodes. Prolonged and recurrent apnoeas may result in a need for supplemental oxygen, bag and mask ventilation, or intubation and positive pressure ventilation.

Methylxanthines such as theophylline and caffeine act as effective respiratory stimulants. Caffeine and its salts, in the form of magisterial preparations, have been extensively used in Europe for more than two decades for the short-term treatment of apnoea of prematurity in neonates.

Caffeine Citrate Chiesi, 60 mg/3 ml solution for intravenous infusion and oral solution was developed to meet the need often expressed in the scientific literature for a standardised preparation of caffeine citrate of suitable quality. Marketing authorization of the product will permit the European-wide availability of a preparation of caffeine citrate which is subject to the full assurances of an authorised product.

Caffeine is a trimethylxanthine structurally related to the methylxanthines theophylline and theobromine. Most of the pharmacodynamic effects of caffeine are attributed to adenosine receptor antagonism at both A1 and A2 receptor subtypes. Other mechanisms, such as phosphodiesterase inhibition, may play a role in some of caffeine's effects at higher plasma concentrations.

In the treatment of AOP, caffeine acts by increasing the sensitivity and probably also decreasing the threshold of the medullary respiratory centre to CO₂. In particular, caffeine can increase minute ventilation. Caffeine decreases the frequency of apnoeic episodes, increases respiratory rate and blood pH, decreases pCO₂, and improves the function of the respiratory muscles in premature infants with recurrent apnoea.

Nymusa (formerly Caffeine Citrate Chiesi) 60 mg/3 ml is a solution for intravenous infusion and for oral administration in the strength 20 mg caffeine citrate/ml. Caffeine citrate 20 mg/ml is equivalent to 10 mg caffeine base/ml.

The recommended posology is:

	Dose of caffeine citrate (Volume)	Dose of caffeine citrate (mg/kg body weight)	Route	Frequency
Loading dose	1.0 ml/kg body weight	20 mg/kg body weight	Intravenous infusion (over 30 minutes)	Once
Maintenance dose *	0.25 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 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 10mg/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 premature neonates and the progressively increasing capacity to metabolise caffeine in relation to post-menstrual age (see section 5.2 of the SPC). Where clinically indicated, caffeine plasma levels should be monitored. The diagnosis of AOP may need to be reconsidered if patients do not respond adequately to a second loading dose or a maintenance dose of 10 mg/kg/day (see section 4.4 of the SPC).

2.2 Quality aspects

Introduction

Nymusa is presented as a solution for infusion and oral solution. It contains caffeine as the active substance. Other ingredients include citric acid monohydrate, sodium citrate and water for injections.

The finished product is filled into clear 4 ml Pharm. Eur. type I glass ampoules containing a claimed volume of 3 ml of caffeine citrate solution (20mg/ml). To guarantee the claimed volume an overfilling is applied. The ampoules are packed in cardboard boxes.

Drug Substance

Caffeine is a well known active substance described in the European Pharmacopoeia (monograph number 0267). The chemical name of caffeine is 1,3,7-Trimethyl-3,7-dihydro-1*H*-purine-2,6-dione. It is a white or almost white, crystalline powder that is sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol (96 per cent). It also dissolves in concentrated solution of alkali benzoates or salicylates.

BASF Pharmachemikalien, the manufacturer of the active substance, has been granted a Certificate of Suitability of the European Pharmacopoeia for Caffeine (R1-CEP 1998-022-Rev 01) that has been provided within the current Marketing Authorisation Application. Therefore no further information about the manufacture, characterisation and stability of the active substance has been provided.

- Specification

The active substance is analysed according to the Pharm. Eur. monograph. In addition the finished product manufacturer is testing the microbiological characteristics the active substance of caffeine, since the finished product is sterile.

The active substance specification includes tests for appearance, identification, assay, acidity, related substances, sulphates, heavy metals, sulphated ash, loss on drying, total viable aerobic count and bacterial endotoxins.

Batch analysis data from 3 batches have been provided. The results demonstrated compliance to the Pharm. Eur. monograph and have shown suitable microbiological purity.

- Stability

The proposed re-test period, storage conditions and containers are according to the certificate of suitability.

Drug Product

- Pharmaceutical Development

Nymusa is presented as a sterile solution for infusion and oral solution. Caffeine is dissolved in water for injection. The pH of the aqueous solution is adjusted and controlled by citric acid monohydrate and sodium citrate. Addition of the buffering agents citric acid monohydrate and sodium citrate results in *in situ* formation of the highly water soluble caffeine citrate salt.

The chosen excipients are regarded to be suitable for their intended use. All excipients are monographed substances and are tested against monographed limits by Pharm. Eur. methods. In addition to the tests described in the monograph the excipients have been analysed for total viable aerobic count. Limits have been set in accordance to requirements of the Pharm. Eur. for microbiological quality of pharmaceutical preparations.

The medicinal product is provided in single dose containers covering a volume of 3 ml. The chosen ampoule size is based on the required loading dose, which may vary from 0.5 to 3ml. Since the formulation does not contain any preservatives any unused portions must be discarded after opening of the ampoules, which is clearly addressed in the SPC. The risk of withdrawal of more than one dose of the ampoules has been appropriately addressed by the risk management plan of the company. Since Nymusa is intended to be administered in a neonatal intensive care unit only, the overall risk is considered acceptable.

Caffeine citrate solution is filled into ampoules of colourless neutral glass with a high hydrolytic resistance. The glass complies with the requirements of Pharm. Eur. for Type I glass.

Since the product is intended to be administered by infusion after dilution, compatibility studies have been performed for the caffeine citrate solution and three possible solutions for infusion (5% Dextrose, 0.9% Sodium Chloride and 10% Calcium gluconate) for a total of 24 hours after dilution.

- Manufacture of the Product

The manufacturing process is a standard process for these kinds of formulations. Terminal sterilisation is performed in line with the requirements of the Ph.Eur.

All critical process parameters have been identified and controlled by appropriate in process controls, i.e. control of pH of the bulk solution, filter integrity before and after filtration, test of filling weight and filling height, control of the physical conditions within the autoclave and control of labelling and packaging of the ampoules.

The validation report from 3 production scale batches demonstrates that the process is reproducible and provides a product that complies with the in-process and finished product specifications.

- **Product Specification**

The finished product specification includes tests for appearance of solution, colour of solution, final packaging, extractable volume, pH, identification and content of drug substance, uniformity of dosage unit, degradation products, sterility and particulate contamination.

Batch analysis data from 3 production scale batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- **Stability of the Product**

Data from stability studies on three production scale batches have been provided. Samples were stored for twelve months at long term and intermediate conditions and for 6 months at accelerated conditions in accordance with ICH requirements. All batches have been investigated for physical and technological parameters.

In addition, supporting stability data of pilot scale batches have been performed covering the proposed shelf-life of 36 months.

In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects.

The quality of Nymusa is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well known and has is described in a Ph. Eur. monograph. The quality of the drug substance is regarded to be suitable for the intended use and appropriately controlled by the applicant. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that includes terminal sterilisation that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3 Non-clinical aspects

Introduction

Due to the bibliographic nature of this application and the date of origin of some of the submitted studies GLP aspects are not fully covered according to the present regulatory standards.

This is however acceptable due to the well established use of the product.

Pharmacology

- **Primary pharmacodynamics**

A thorough review of the mechanisms of action of caffeine in relation to the expected respiratory effects as well as proof of concept studies in newborn and adult animals has been provided in the application based on published studies. Proof of concept studies are available in different species and ages.

In newborn rabbits, the facilitatory effect of caffeine on the central mechanisms controlling the breathing pattern was indicated by: 1) the enhanced Hering-Breuer expiratory promoting effect; 2) lack of effect on the Hering-Breuer deflation reflex; 3) qualitatively similar effects of caffeine postvagotomy and prevagotomy. In rabbits, the respiratory system is in a more advanced stage than in humans at birth. Despite this fact that implies that the model here discussed is not ideal for preterm infants, the main effects intended for caffeine have been shown.

The Authors also discussed the potential clinical relevance of the increase in the strength of the Hering-Breuer expiratory promoting reflex following caffeine injection. This reflex may be elicited by a continuous airway distending pressure which is currently used to treat apnea in premature infants who have a strong inflation reflex as compared to adults. This could lead to decrease in minute ventilation as expiratory time is prolonged. In the presence of caffeine, this prolongation could be increased. Therefore, the Authors concluded that both types of treatment for apnoea should not be used together unless blood gases are checked to ensure that alveolar ventilation has not decreased. However, this preclinical issue has sufficiently been considered on a clinical level (Study 5.3.4.2.1., Laubsher B. et. al).

In piglets aged 1-5 days, the effects of caffeine 20 mg/kg iv infusion were also shown in situations of hypocapnic and hypercapnic hypoxia. The domestic pig reveals a similar developmental pattern of histological and ultrastructural lung maturation (term at approx. 115 days) during pregnancy to that of humans. Differentiation of fetal lungs follows similar steps and time-windows known from humans [Baskerville 1976]. However, pig fetuses are not viable when delivered preterm (e.g. 90 days of gestation). Therefore the newborn animals at term are expected to be at a more advanced stage of lung development than the intended target premature infants. In addition, lung tissue and function in the piglets would have been normal, which may not be the case in some target babies. Therefore, this model can be considered as partially relevant only for the patient condition in discussion. This study was designed on the basis of the adenosine receptor blocking properties of caffeine. It did not address the clarification of the mechanism of action of the methylxanthine. Anyway, it has shown that caffeine ameliorated the ventilatory depression in the biphasic response to hypoxia, at the dose which is proposed also in the current file. Therefore, despite the insufficiencies highlighted here, the study may be considered as supportive of the proposed use of caffeine citrate.

In premature baboons the respiratory benefits of 20 mg/kg given at 20 min and 24 h of age to very premature animals (D125 gestation) treated with surfactant, has also been shown. The animal model using extremely premature baboons delivered at 125 days (67% of term which is roughly equivalent to human gestation of 26-27 weeks) and treated with exogenous surfactant, mechanical ventilation and appropriate oxygen supply is described as a relevant model for BPD in premature newborn infants [Coalson et al, 1999, Am J resp Crit Care, 160:133].

These animals develop structural lesions characterized by severe alveolar hypoplasia with decreased and dysmorphic vascular growth. The baboon model shows similarities in pathology and ontogeny comparable to preterm infants. In this study, the dose of caffeine citrate used was the same as the proposed for the current indication. Since the animal model is relevant and the dose used is the same as that proposed in the target patient population, this study seems to be the most relevant as proof of concept. However, only 24 hours effects were covered while up to one month is possible with this treatment. Possibility for changes in the response pattern, including development of tolerance, was not addressed. However, since clinical data is available from the approximately 25 years of caffeine use in this situation, this type of uncertainty is superseded by the findings in the clinical setting.

- Secondary pharmacodynamics

The effects of Caffeine on renal function have been studied in comparison with theophylline in 4 groups of 5 to 10-day old New Zealand rabbits.

The neonatal rabbit is described as a good model for renal function in newborn infants. Renal effects observed with the 10mg/Kg of caffeine, decreased diuresis and increased tubular water absorption are relevant for treated premature infants. Nevertheless, only one high dose of caffeine is in principle to be given, followed by 5mg/Kg which might be expected to be safer. 6mg/Kg caffeine had no relevant effect in renal function in the rabbit model.

Caffeine influenced T4 and TSH release in the premature animals. This may be of clinical relevance, particularly because preterm infants depend on maternal thyroid hormones. The impact of caffeine treatment on the thyroid and pituitary functions of the preterm infants under long term treatment was discussed by the Applicant and is part of the Risk management plan (long-term effect on neurodevelopment and growth).

- Safety pharmacology programme

No conventional safety pharmacology studies on Caffeine were found in the literature. However, studies on behaviour, gastric tolerance and effects on necrotizing enterocolitis in rats as well as effects on cardiovascular system in rats and dogs are cited and discussed in the toxicology section of this report.

- Pharmacodynamic drug interactions

No conventional pharmacodynamic drug interaction studies on Caffeine were found in the literature. Interactions data are discussed in the clinical setting.

Pharmacokinetics

Analysis of the extensive literature allowed a full characterization of the pharmacokinetic profile of Caffeine in the most relevant species used in pharmaco-toxicological studies and in particular in neonatal animals. Dose-dependent kinetics have been reported in humans, as in animals, suggesting a saturation of metabolic transformations. In the neonatal period, elimination of Caffeine is impaired in animals and humans, due to the immaturity of the hepatic enzyme systems. In mature animals, Caffeine is metabolised in the liver, mostly in microsomes. There are some interspecies differences between Caffeine metabolism in experimental animals and humans. Some metabolites of Caffeine also have marked pharmacological activity. Thus, 1,3-dimethylxanthine (theophylline) and 1,7-dimethylxanthine (paraxanthine) are to be taken into account when considering the biological actions of Caffeine.

Due to the high solubility of caffeine in water, different routes of administration (oral or parenteral) had no relevant impact on the PK characteristics. Metabolic differences between different animal species (rodents) and humans were identified. However, a progressive increase in the activity of the hepatic enzyme system is evident during neonatal development. I.e. this effect is the same in premature neonatal animals and humans, as caffeine undergoes very little biotransformation and - in the neonatal period of humans and animals - the caffeine half-life is increased.

A potential of caffeine to induce its own metabolism has been shown only for doses above 100mg/kg – and therefore seems to be out of clinical relevance for the intended indication.

In summary preclinical aspects on pharmacokinetics were appropriately reviewed and considerations on PK drug interactions were addressed accordingly in the SPC.

Toxicology

No toxicological studies have been conducted by Chiesi on Caffeine or Caffeine Citrate. There are, however, numerous published data on acute, repeated, mutagenicity and oncogenicity studies as well as reproductive toxicities defining the safety profile of Caffeine. The more significant published studies are summarized and discussed below. For the evaluation of the safety profile of Caffeine particular attention was paid to the “Cafcit (Caffeine Citrate) - Summary Basis for Approval. NDA-FDA 20-793, 1997” (Study 4.2.3.1.2) and to “Caffeine monograph issued by OECD SIDS (Organization for Economic Co-operation and Development - Screening Information Data Set) UNEP Publications 2003” (Study 4.2.3.1.3), where the toxicity profile of Caffeine is well defined and discussed.

- Single dose toxicity

Due to the lack of reliable toxicokinetic investigations in the published toxicity studies, the safety margins with respect to the clinical dose have been calculated on mg/kg basis considering the daily intravenous or oral clinical doses: 10 mg/kg of Caffeine base by infusion on day 1 as a loading dose followed by 2.5 mg/kg, orally or by infusion, as the maintenance dose.

The acute toxicity of caffeine expressed as LD50 seemed similar in different species, rodents and nonrodents. The information in newborns has only been collected in one study in rats, where the neonatal animals (2 days of age) were more sensitive than the adult ones. In terms of CNS, 2 days old rats are less mature than term infants, and therefore the young animals used may be relevant as a model of premature infants, in terms of CNS immaturity. The fact that after oral and intravenous bolus administration the blood levels at LD50 were similar despite the different values obtained for each

route supports the need for discussion on whether blood concentrations need to be monitored in neonates, particularly the younger ones. This is reinforced for the suggestion that in neonatal rats the metabolism is slower.

- Repeat dose toxicity (with toxicokinetics)

The revised repeated dose toxicity studies of caffeine were not in compliance with current international guidelines and the experimental designs of several differed from those currently required for regulatory purposes. Nevertheless the studies may be considered as contributive to the description of the toxicity of Caffeine following repeated treatment. They allowed the identification of the main clinical signs at high doses, including convulsions and psychotic like reactions (animal biting and self mutilation more often in younger animals), anorexia and loss of body weight gain. The main morphological changes seen at lethal doses were: lung (congestion, oedema, thrombosis and haemorrhage) and gastrointestinal effects (mild hyperaemia, mild to moderate inflammation with some ulcers). An effect on spermatogenic cells with testicular atrophy was also seen.

The NOAEL appeared to be 5 and 20 times the clinical loading (10 mg/kg on day 1) and maintenance (2.5 mg/kg up to 12 days) doses. These safety margins were calculated on a mg/kg basis dividing the NOAEL for the clinical doses and adjusting the value obtained by 3. This correction was made because the animals were treated via drinking water or diet, routes of administration which result in a lower absorption of the drug substance and are influenced by several factors (stability of the substance, spilling and pollution of food or water, etc). Consequently the safety margins are only indicative. With the exception of one study, the information discussed derives from adult animals.

The main targets of concern raised from these studies are the gastro-intestinal tract, the kidney and the lung where haemorrhages were observed in animals treated with high doses of caffeine.

Since the target population will be premature infants, some studies in juvenile animals addressing the potential safety of caffeine when administered to immature systems, have been included in the file. Three studies where the effects of postnatal Caffeine exposure on growth, and/or activity and/or learning are included in the Application.

Oral by gavage: the effects of low dose Caffeine exposure during the first week of life was investigated in rats from day 1 to day 6 of age. This time period is proposed to provide an animal model equivalent to the human third trimester or premature infant exposure.

- Treated animals grew more slowly, were hypoactive at two weeks of age, and were impaired on an operant spatial learning task as adults.
- The timing of the appearance of developmental landmarks, adult body weight and adult brain weight, however, were not affected by postnatal Caffeine exposure.
- Neither of the two developmental measures of behaviour (eye-opening and righting reflex) were altered by Caffeine treatment.

Oral through maternal milk: Sprague Dawley rat pups were exposed to caffeine in maternal milk through exposure of 23-30 mg/kg, or 94-135 mg/kg to the dams throughout lactation for 21 days.

- No significant difference between weights of treated and untreated animals were seen.
- Offspring of Caffeine-treated dams showed significantly earlier onset of auditory startle and air righting reflexes.
- There were no dose-related effects and no difference in eye-opening between treated and control groups.
- No direct effects of treatment were observed on eight measures of open field activity.
- locomotor activity in animals exposed to Caffeine via dam milk was not different to control group.

Subcutaneous route: The behavioural responses of 1- and 10-day-old Long Evans rats to Caffeine (0, 5, 20, 40 and 80 mg/kg subcutaneously) were determined using several behaviours readily exhibited by the neonatal rat.

- After single doses, in pups of both ages activity as well as attachment latencies in the on nipple suckling test increased, while weight gain and attachment frequencies in on mother and on nipple suckling tests decreased.
- In addition, the home orientation of 10-day-old rats was disrupted.
- Similar effects were found in 1-day-old pups exposed to theophylline.
- Long term exposure (9 days) to Caffeine during gestation (1-day-old pups) or on Days 1-9 of lactation (10-day-old pups) increased the pup activity levels and altered the activity increase observed following an acute Caffeine challenge.

Additionally, other studies suggest an effect of caffeine in thyroid and pituitary function which may be of relevance in premature infants who are highly dependent on maternal hormones and therefore will be deficient on these.

In conclusion, the potential for caffeine to affect the cardiovascular system in a dose-dependent way is well known, and the studies described above in rats and dogs have reiterated this knowledge.

- Genotoxicity

In their literature search, the Applicant has identified more than 150 in vitro and in vivo mutagenicity tests on caffeine reported in the literature. Multiple tests have been included and discussed in the submitted file. The main battery including Ames test and chromosomal aberration was negative. The in vivo micronucleus test was positive only at substantially high dose of 300mg/Kg. No specific concern is raised from the studies discussed in the file. Furthermore, caffeine is a component of dietary coffee and is present in multiple pharmaceutical formulations. The available information is considered sufficient to support the nongenotoxic potential of caffeine.

- Carcinogenicity

In view of the maximal intended duration of the caffeine treatment of premature newborns (37 days at maximum), carcinogenicity studies would not be needed unless a cause of concern exists, taking into consideration the fact that the target population is low age pediatric. From the studies here discussed, no concern on pro-carcinogenic potential for caffeine is raised. When applied concomitantly with different carcinogens, caffeine administration has reduced the number of tumors for some carcinogens, increased for other or had no effect. This information is of difficult interpretation and its relevance for the current application may be limited. Indeed, it may be more important in relation to widespread use of caffeine in the multiple dietary components available.

The CHMP was of the opinion that there is no concern of tumorigenesis by caffeine in the context of indication and use proposed in this application.

- Reproduction Toxicity

Reproductive toxicity studies from literature allow the understanding of effects of caffeine in male fertility, on embryofetal development and on pre-post natal development. As a conclusion, adverse testicular and sperm effects that may affect fertility of males exposed even in premature stage to caffeine cannot be excluded. Also growth retardation especially on ossification may be expected after administration of caffeine to premature infants.

- Local tolerance

Local tolerance studies at the gastrointestinal tract in rodents have shown a potential for caffeine to increase the development of gastric ulcers in adult animals when these have been exposed postnatally to caffeine. Aminophylline aggravated the signals and consequences including mortality associated to a rat model of necrotising enterocolitis. This may represent a risk for preterm babies treated with caffeine, but has been addressed on a clinical level and was noted in the SPC.

- Other toxicity studies

The effect of caffeine on the cardiovascular system was investigated in a rat (Sprague Dawley) study which results demonstrated that long term administration (117 weeks) of caffeine (50mg/Kg/day) markedly reduced lifespan due to cardiovascular disease.

In dogs, dose-dependent arrhythmogenic potential was also seen. At low doses (1.25 mg/Kg) benign arrhythmias (sinus arrhythmia, atrial ectopics, tachycardia) due to vagal stimulation, and at a higher dose of 5mg/Kg more severe pattern was observed (ventricular tachycardia, multifocal ventricular premature contractions, atrial flutter and fibrillation).

No skin or eye irritancy potential was identified for caffeine in rabbits.

Ecotoxicity/environmental risk assessment

An environmental risk assessment has been provided. A revised PEC surface water (0.008 µg/L) below the action limit was obtained for a F_{pen} of 0.0008%. The revised F_{pen} was based on a disease prevalence of 1.18/10000 inhabitants per year and assuming 20 mg of caffeine citrate as the maximum daily dose and a 25 days mean treatment duration. No published data was provided by the applicant to justify either the disease prevalence or the assumption of 1kg as the maximum body weight of premature newborns or even the treatment duration. However, natural substances are exempted from an environmental risk assessment because they are unlikely to result in significant risk to the environment. Consequently no further steps in ERA were required.

Discussion on the non-clinical aspects

The toxicological profile of caffeine has been appropriately described in the file in the multiple studies presented in the extensive bibliographic revision performed.

The information included suggests a higher toxicity in caffeine in low ages and as compared to adults. Death due to acute toxicity is related to respiratory arrest and convulsions. The need for monitoring of plasma levels, particularly in the younger premature is discussed in the clinical section.

Under repeated treatment, target organs of toxicity were the stomach, the kidney, the lung and the reproductive tract. Behavioural changes could be seen in some studies in young animals at therapeutic levels. Consequently section 5.3 of the SPC was amended accordingly.

Growth and ossification retardation is suggested from reproductive toxicity studies, where embryotoxicity was observed, as well as increased toxicity on lactating animals. In addition, decreased male fertility with sperms decrease and testicular changes of treated males was observed, irrespective of age. Also, embryotoxicity was observed in association to treated males. No genotoxic or carcinogenic concerns are raised from studies revised. The limited duration of treatment and the life threatening condition here discussed would not require carcinogenicity studies to be conducted in the absence of a specific concern. Increased propensity for ulcer development in the adult stage, and higher susceptibility to necrotising enterocolitis is also raised from the published information revised.

The main safety aspects of caffeine administration to premature newborns have been highlighted in the extensive literature publications submitted. Some of these aspects would have benefited from further discussion. However, since there is an extensive clinical experience with caffeine, including in premature newborns, additional nonclinical studies were not required.

2.4 Clinical aspects

Introduction

GCP

Due to the bibliographic nature of this application and the date of origin of some of the submitted studies GCP aspects are not fully covered according to the present regulatory standards. The GCP status of the different studies is unknown.

According to Article 8.3 (ib) of Directive 2001/83/EC, as amended, a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive

2001/20/EC was provided. This statement indicates that “clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC” together with a listing of all trials (protocol number) and third countries involved (see LoQ). For the main trial (study 5.3.5.1.1) and for the CAP-study (study 5.3.5.1.6) this statement was provided by the Applicant; for the supportive trials the information is confined to declaration of protocol approval by an ethical board or compliance with the declaration of Helsinki.

Pharmacokinetics

- Absorption

Literature data on caffeine pharmacokinetics in young infants indicate that orally administered caffeine citrate is rapidly and completely bioavailable for preterm neonates; supporting data are, however, scarce and inconsistent (t_{max} 0.5 -2 hours in one study and 4.6 hours in another).

Absolute bioavailability was not fully examined in preterm neonates. Comparison of the PK parameters obtained in studies where IV and oral doses of caffeine citrate were administered suggests that oral and IV pharmacokinetics of caffeine citrate are similar and absolute bioavailability of orally administered caffeine citrate is nearly 100%.

No effect of formula feeding on the extent of absorption of caffeine citrate in premature infants has been detected. Mean t_{max} was, however, prolonged from 3.4 hours in the fasted state to 5.9 hours after feeding.

- Distribution

Plasma protein binding is ca. 35% and almost exclusively to albumin.

Cerebrospinal fluid caffeine levels in treated preterm neonates are close to and appear to be in rapid equilibrium with their plasma levels.

Caffeine ingested by the mother crossed the placenta and caffeine concentrations that are close to therapeutic levels are often found in cord blood of preterm infants at birth.

Caffeine ingested by nursing mothers appears in breast milk within about 15 minutes of maternal ingestion in concentrations comparable to those in plasma. Monitoring of serum caffeine levels is advisable when caffeine therapy is planned in infants born to mothers who consumed caffeine prior to delivery or in infants whose mothers consume caffeine while breast-feeding. This is reflected in the SPC.

The mean volume of distribution of caffeine in infants is about 0.8-0.9 L/kg, which is slightly higher than that in adults (0.6 L/kg).

- Elimination

In adults, biotransformation of caffeine occurs in the liver via microsomal cytochrome P450 mono-oxygenases (CYP1A2) and via the soluble enzyme xanthine oxidase. In premature neonates CYP1A2 is not yet expressed.

The predominant process of caffeine metabolism in preterm infants is conversion to theophylline via N7-demethylation. As a result, caffeine metabolism and excretion is very slow in premature neonates.

Interconversion between caffeine and theophylline has been reported with 25% of theophylline converted to caffeine via methylation and between 3-8% of caffeine converted to theophylline via CYP1A2. Because theophylline is metabolised to caffeine in neonates, it is essential that baseline plasma concentrations of caffeine are measured in infants previously treated with theophylline when caffeine therapy is planned.

A delay in caffeine elimination has been observed in breast-fed as compared to formula fed infants.

No proper dose escalation studies were performed. There is only limited information on dose proportionality from three of the submitted studies. However, results give supporting evidence to assume dose linearity for the investigated dose-range (2.5 - 3mg/kg to 30mg/kg).

Inter-patient variability, as determined based on population pharmacokinetics, was approx. 25% for clearance and approx. 11% for volume of distribution. Intra-patient error (standard deviation, SD) was 3.9 mg/L. Interpretability of reported intra-subject variability is very limited.

In neonates, caffeine is eliminated predominantly via renal excretion according to first-order kinetics; approximately 86% of the drug is excreted unchanged in the urine within 6 days, compared with 4% in adults.

In infants, mean elimination half-life ($t_{1/2}$) of caffeine and fraction excreted unchanged in urine (A_e) are inversely related to gestational age.

Maturation of different caffeine metabolising systems from birth to ca. 9 months of age follows a pattern based on the following findings:

- The caffeine elimination half-life and CL varied linearly with GA and exponentially with PNA, the plateau being reached during the second trimester of life.
 - Half-life is prolonged during the neonatal period and for as many as 38 weeks gestation in premature babies: Half-lives approximately 20-fold longer (102.9 h, range 40 - 230 h) than in adults (5-6 hours) and an 11-fold decrease in body clearance relative to adult are observed.
 - It is suggested that N3-demethylation is more important in young infants than in adults and that maturation of N1-demethylation occurs later than 19 months of age.
 - 8-hydroxylation is mature as early as 1 month of age and may be higher in infants than in adults.
 - By 9 months of age, the metabolism of caffeine approximates that seen in adults ($t_{1/2} = 5\text{h}$; $A_e = 1\%$) and correlates closely with the rise in metabolite production.
- Dose proportionality and time dependencies

No proper dose escalation studies were performed. There is only limited information on dose proportionality from three of the submitted publications. However, results give supporting evidence to assume dose linearity for the investigated dose-range (2.5 - 3mg/kg to 30mg/kg).

In theory, repeated daily dosing as proposed for the maintenance of caffeine citrate treatment in AOP could result in accumulation of caffeine, due to its long elimination half-life in premature newborns. In the submitted clinical studies that applied once daily maintenance regimens and reported PK data, no accumulation of caffeine in plasma of premature infants was however observed.

In the main efficacy study by Erenberg, measurement of PK parameters in the course of the 10 – 12 day study period was a secondary objective. It is described that for 17 infants who completed double-blind caffeine treatment, plasma samples obtained on day 10 (n=14) and on day 8 (n=3) were within the reported therapeutic range of 8-20 $\mu\text{g/ml}$.

In the PK study by JV Aranda (J Pediatr 1979; repeated dosing with a maintenance dose of 2.5mg/kg/day was carried out in 10 infants for a mean of 19 days, yielding steady state plasma concentrations between 7.4 and 19.4mg/L.

The SPC section 4.2 therefore states that:

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 (20 mg caffeine citrate are equivalent to 10 mg caffeine base).

	Dose of caffeine citrate (Volume)	Dose of caffeine citrate (mg/kg body weight)	Route	Frequency
Loading dose	1.0 ml/kg body weight	20 mg/kg body weight	Intravenous infusion (over 30 minutes)	Once
Maintenance dose *	0.25 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

The CHMP discussed whether a second loading dose of 20mg/kg body weight might be appropriate if an infant shows insufficient response to the first loading dose, i.e. at the beginning of treatment with caffeine citrate. This approach was supported by data from the Erenberg study. After further discussion at CHMP, it was agreed to propose a second loading dose of 10-20mg/kg maximum.

It was however doubtful whether this approach would be successful if insufficient response became evident in the course of the treatment (in an infant that previously responded well to caffeine citrate).

In the large Schmidt study in 2006 premature infants, the adjustment strategy was to increase the daily maintenance dose up to 10mg/kg. Although no specific efficacy/safety data for this subgroup is available, there were no safety concerns in this study overall, and only 23 of 1006 infants in the caffeine group had doses of caffeine citrate withheld or reduced due to suspected toxicity. Therefore, the CHMP concluded that for infants with caffeine plasma levels below or at the lower end of the therapeutic range this option might be considered, given the ICU conditions of monitoring of heart rate, blood pressure, renal function, body weight, etc., and under continuous monitoring of caffeine plasma levels to recognise and minimise the risk of accumulation.

The following wording was agreed upon for Section 4.2 in the SPC (to follow after the above-mentioned paragraph):

In preterm 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 10mg/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 premature neonates 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 AOP may need to be reconsidered if patients do not respond adequately to a second loading dose or a maintenance dose of 10 mg/kg/day (see section 4.4).

- Special populations

No specific studies concerning renal, hepatic impairment are provided. This is adequately reflected in the SPC:

The safety of caffeine citrate in patients with renal insufficiency has not been established. 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).

A publication referring that the female neonate demonstrates a higher rate of caffeine metabolism than the male is cited. The clinical significance of this finding was considered doubtful by the CHMP.

A population pharmacokinetic study in Asian populations shows that PK parameters values are comparable to other studies involving Caucasian populations.

Based on the therapeutic indication the section on elderly patients is not applicable.

- Pharmacokinetic interaction studies

Caffeine has the potential to interact with active substances that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2. Even though in premature newborns metabolism is limited, it nevertheless seems prudent to advise caution, including the use of plasma caffeine monitoring, in the case of concomitant use of potential interacting drugs such as cimetidine and ketoconazole.

Phenobarbitone therapy concomitantly with caffeine citrate was reported to possibly induce the hepatic metabolism of caffeine at 44-45 weeks post-conceptual age.

Dexamethasone may increase caffeine clearance by enzyme induction. Mexiletine is known to alter the disposition of caffeine and theophylline in adults. Caffeine is reputed to inhibit iron absorption in adults.

The stimulatory effects of caffeine and doxapram on the cardio-respiratory and central nervous system might mutually potentiate.

Pharmacodynamics

- Mechanism of action

The pharmacodynamics of caffeine has been extensively studied. The pharmacological effects of caffeine are mediated primarily via the antagonism of the actions of adenosine at A1 and A2A receptors in the CNS. At high (potentially toxic) concentrations, caffeine increases cyclic 3,5 AMP by inhibition of phosphodiesterase, and translocates intracellular calcium via inhibition of ryanodine receptors.

- Primary and Secondary pharmacology

In ventilated neonates, caffeine increased respiratory system compliance and reduced supplementary oxygen requirements. A respiratory effect of caffeine (increased ventilation, tidal volume and respiratory flow) in premature neonates was obtained at very low doses: 2.5mg/kg caffeine, with corresponding caffeine plasma concentrations of about 3 mg/L.

The demonstrated cardiovascular effects were increased left ventricular output and stroke volume and, transiently, mean arterial blood pressure.

Information on the relation between plasma concentration and effect is fragmentary. The PK/PD relationship between caffeine plasma levels and frequency of apnoea per day was not addressed.

Clinical efficacy

Only one of the submitted publications was a study specifically performed for regulatory purposes (study 5.3.5.1.1) to support an application to the FDA for marketing authorization for Cafcit, a preparation of caffeine citrate solution 20 mg/ml. This study is regarded by the Applicant as the main study for the current submission.

The remainder of the dossier comprises publications of investigator-led clinical scientific trials, and this is reflected in the heterogeneity of their approach. They are summarized in the table below.

Study ID	No. of study centres	Design	Study Posology	Subjects by arm entered/ completed	Study duration	Gender M/F GA (weeks), Mean \pm SD (range)	Diagnosis Incl. criteria	Primary Endpoint
Erenberg Study 5.3.5.1.1	9 neonatal ICU	Prospective, randomised, double-blind, parallel, placebo – controlled, open label rescue arm	Caffeine: caffeine citrate loading dose of 20 mg/kg IV, followed by 5 mg/kg/day IV or orally	Caffeine 45/21 Placebo 37/12	Up to 10 (12) days	51/31 Caffeine 29.8 \pm 1.7 Placebo 29.9 \pm 1.4 (25 – 32)	28-32wks post-conception and \geq 24h after birth, 6 or more apnoea episodes within 24h	Success =50% reduction in apnoea episodes from baseline on each study day (1 to 10)

Study ID	No. of study centres	Design	Study Posology	Subjects by arm entered/ completed	Study duration	Gender M/F GA (weeks), Mean \pm SD (range)	Diagnosis Incl. criteria	Primary Endpoint
Murat Study 5.3.5.1.2	1	Prospective, randomised, parallel, no treatment-controlled comparison	Caffeine citrate loading dose of 20 mg/kg IM, followed by 5 mg/kg/day orally	Caffeine 9/9 No treatment 9/3	Up to 15 days	---- Caffeine 30.1 \pm 0.6 Control 29.8 \pm 0.5 (29 - 35)	Premature infants with ≥ 3 apnoea attacks (≥ 20 sec), with bradycardia, within 24 hours	Apnoea attacks, Apnoea index: number of apnoea attacks per 100 minutes
Bairam Study 5.3.5.1.3	1	Prospective, randomised, double-blind, parallel, active-controlled	Caffeine: loading dose 10 mg/kg IV, maintenance dose 1.25 mg/kg twice daily Theophylline: loading dose 6 mg/kg IV, maintenance dose 2 mg/kg twice daily	Caffeine 10 Theophylline 10	Up to 7 days	---- Caffeine 30.3 \pm 0.8 Theophylline 30.5 \pm 1.5 (range not indicated)	Premature infants with ≥ 3 apnoea episodes (≥ 15 sec) within 24 hours or ≥ 6 within 2 hours or ≥ 8 within 6 hours recording	Number of cardiorespiratory abnormalities (apnoea ≥ 15 sec, bradycardia < 80 beats/min, apnoea plus bradycardia < 100 beats/min) at baseline and days 3 and 7
Brouard Study 5.3.5.1.4	1	Prospective, randomised, parallel, active-controlled	Caffeine citrate loading dose 20 mg/kg IM, maintenance dose 5 mg/kg/day orally Theophylline ethylenediamine: loading dose of 5.5 mg/kg IV, maintenance dose range 0.8 to 2.5 mg/kg tid	Caffeine 8 Theophylline ethylenediamine 10	Up to 5 days	---- Caffeine 30.5 \pm 0.7 Theophylline ethylenediamine 30.5 \pm 0.4 (range not indicated)	3 or more severe apnoeic attacks (apnoea for > 10 sec with bradycardia < 80 bpm for ≥ 30 sec or < 60 bpm for ≥ 15 seconds)	Apnoea frequency; average number of severe apnoea attacks per 100 minutes on days 0, 1 and 5
Scanlon Study 5.3.5.1.5	1	Prospective, randomised, parallel, active-controlled comparison	Caffeine: Group A: loading dose of caffeine citrate 25 mg/kg orally, maintenance dose 6 mg/kg/day Group B: loading dose 50 mg/kg orally, maintenance dose 12 mg/kg/day Theophylline: loading dose of 7.5 mg/kg orally, maintenance dose 3 mg/kg three times daily	Caffeine: Group A 16 Group B 14 Theophylline: 14	Up to 5 days	24/20 Caffeine Group A 28.7 \pm 1.2 Group B 28.2 \pm 1.1 Theophylline 27.9 \pm 1.4 (range not indicated)	Infants of less than 31 weeks gestation who had either 10 or more apnoeic attacks in 8 hours or 4 apnoeas in one hour	Number of apnoeas in 24 hours at baseline (day 0) to days 1 and 2 Number of severe apnoea attacks per 100 minutes on days 0, 1 and 5

Study ID	No. of study centres	Design	Study Posology	Subjects by arm entered/completed	Study duration	Gender M/F GA (weeks), Mean \pm SD (range)	Diagnosis Incl. criteria	Primary Endpoint
Aranda Study 5.3.5.2.1	1	Prospective, non-controlled study	Caffeine citrate loading dose of 20 mg/kg IV followed within two to three days by 5 to 10 mg/kg once or twice daily	18	6 days (mean)	---- 27.5 \pm 0.6 (range not indicated)	preterm neonates with at least 3 recurrent apnoeic spells per day (apnoea >30 seconds and bradycardia <100 bpm)	Number of apnoeic spells before and after caffeine treatment

- Dose response studies

No dose-response studies are reported. The dose is proposed on the basis on the most common dose used in available studies which is also the dose used in the Cafcit study.

- Main studies

Study 5.3.5.1.1 *Erenberg A et al. Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study. Pharmacotherapy 2000; 20 (6): 644-52*

This prospective, randomised, double-blind, placebo-controlled multicentre trial studied the effects of caffeine citrate treatment in 85 preterm infants with AOP (82 patients -45 assigned to caffeine and 37 to placebo -were included in the efficacy analysis and 85 in the safety analysis).

METHODS

Study Participants

Infants between 28 and 32 weeks post-conception and more than 24 hours after birth who had six or more apnoea episodes (defined as cessation of breathing for more than 20 seconds) in 24 hours were eligible. Eligible infants were randomly assigned to treatment with caffeine citrate or placebo for up to 12 days.

Exclusion criteria:

- Infants with identifiable causes of apnoea (CNS disorders, primary lung disease, generalized, metabolic and cardiovascular disturbances, abnormal temperature, obstructive apnoea);
- BUN >20mg/dl, serum creatinine >1.5mg/dl, urine output <1ml/kg/hour after the first 48 hours of life;
- Serum AST/ALT >3-times the upper limit of normal;
- Infants required mechanically assisted ventilation;
- Received methylxanthines or H₂ antagonists for regurgitation within last 7 days before enrolment;
- Current use of (or effects of) CNS active drugs at the time of enrolment.

Treatments

Double-blind treatment: Caffeine citrate 20 mg/kg or equal volume of placebo was administered IV over 30 minutes, followed after approximately 24 hours by once daily administration of caffeine citrate solution 5 mg/kg/day orally or IV, or an equal volume of placebo. Initially, up to 10 days of double-blind therapy were planned, but the protocol was amended to allow for up to 12 days.

Open-label rescue: Infants failing double-blind therapy were eligible to receive open-label rescue with caffeine citrate after treatment day 1 and before treatment day 8. In the open-label phase of the study, a loading dose of 20mg/kg caffeine citrate was administered IV, followed by a maintenance dose of

6mg/kg/day, orally or IV. Duration of treatment of open-label caffeine was up to 12 days, including the double-blind treatment days.

Study treatments:

Caffeine citrate: 10mg/ml caffeine base, 5mg/ml citric acid (monohydrate) and 8.3mg/ml sodium citrate (dehydrate).

Placebo: 5mg/ml citric acid (monohydrate) and 8.3mg/ml sodium citrate (dehydrate).

Objectives

The primary objective of this study was to evaluate the efficacy and safety of caffeine citrate for the treatment of apnoea of prematurity.

The secondary objective was to obtain plasma concentrations of caffeine citrate in premature infants receiving the product for up to 12 days.

Outcomes/endpoints

The primary endpoint was 'success' which was defined as 50% or greater reduction in apnoea episodes from baseline and elimination of apnoea. It was summarised as number (%) of infants who were successes on each study day, and number of days (0-10) that an infant was classified as success.

The primary endpoint was changed in a final amendment of the study protocol, and was defined as the difference in the number of apnoea episodes (rates) between caffeine citrate and placebo treatment groups during 24-48 hours after the double-blind loading dose; results of this endpoint have not, however, been reported in the publication.

Sample size

The sample size was based on the assumption that 70% or more of caffeine-treated infants and 20% or less of placebo-treated infants would experience at least a 50% reduction of apnoea events within 24-48 hours after the double-blind loading dose, compared with baseline rates.

A significance level of 5% and a power of 95% required 23 infants per group, for a total of 46 infants. As there was no information on placebo success rates, it was decided to recruit 39 infants per group.

85 preterm infants were included in the study.

Randomisation

Infants were randomised to treatments using computer-generated random numbers in blocks of six.

Blinding (masking)

There is no information on precautions to maintain blinding in the publication of the study. Determination of caffeine plasma concentrations could have led to unblinding. It is stated that a contract laboratory assessed the caffeine blood levels but the results were not made available to the investigator.

Statistical methods

The applicant states that Chi-square (χ^2) and analysis of variance tests were used to compare demographic data between groups. Data were adjusted for length of baseline period and length of study day by scaling to 24 hours. The number (%) of successes and failures was analysed by χ^2 test for each study day. A subject withdrawn from the study or moved to open-label caffeine was classified as success or failure, and this classification was carried forward on subsequent days until the end of the double-blind period (LOCF). The number of days that infants were classified as success or failure was analysed by t-test. In relation to baseline characteristics, the analysis was based on 3 success categories among infants randomised to caffeine citrate: no days with zero apnoea, 1-6 days of zero apnoea events, and at least 7 days of zero apnoea events.

PK data was described using a one-compartment open model with first-order absorption and elimination.

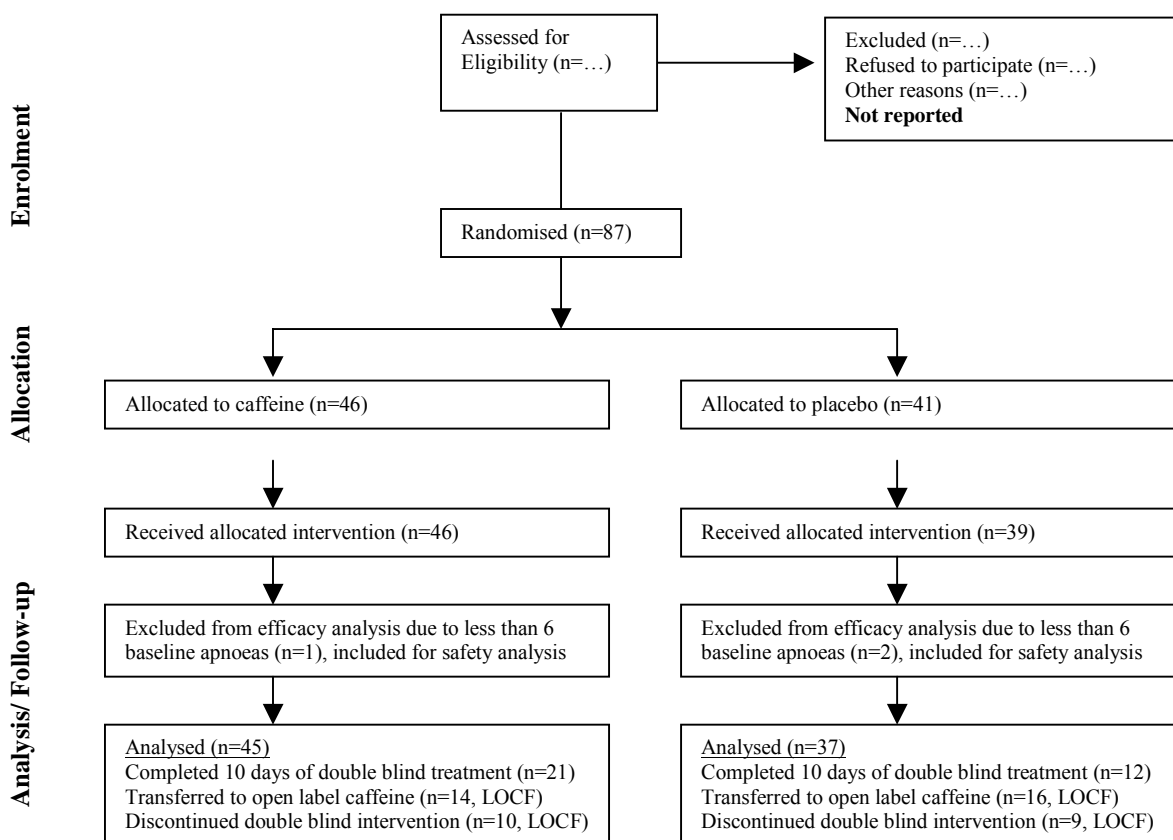
The CHMP noted that the description of statistical methods does not reflect the finally defined primary efficacy endpoint (difference in apnoea rate during second day of treatment). The description of methods above refers to group comparisons of the proportion of patients fulfilling a certain success criterion. The performed “success”-comparisons on a day-by-day basis using the Chi-square test can not be considered the optimal analysis method for a dataset with repeated measurement structure. The chosen approach of consecutive tests ignores the correlation structure of the data. Moreover, no adjustments for multiplicity were considered. For the analyses of aggregated success endpoints (such as “at least 7 days of 50% or greater reduction in apnoea episodes comp. to baseline) the Chi-square test can be considered adequate.

The use of LOCF to impute missing success-information for withdrawals and for patients transferred to open label treatment is seen very problematic, because of two reasons:

- Several patients who were transferred to open label caffeine or were permanently discontinued ... had a reduction of $\geq 50\%$ in their apnoea rate the day they were transferred or discontinued from the trial. No information was provided regarding the reasons for transferring patients to open label treatment. Under such circumstances, “success” was carried forward until day 10. However, additional data analysis from patients staying under blinded conditions could not justify carrying forward success information. Less than 50% of patients who once achieved a reduction of apnoea rate $\geq 50\%$ could maintain this “success” until the end of treatment. Hence, it can not be excluded that the LOCF leads to an anti-conservative analysis approach, introducing substantial bias when estimating the treatment effect.
- The choice of the imputation method in this specific case was considered to have a major impact on the efficacy results and their interpretation, as missing data from 49 patients (~60% from the defined efficacy analysis set) had to be imputed (carried forward). In such a situation, usually sensitivity analyses (using alternative imputation strategies, e.g. classification of all transferred and withdrawn patients as non-success patients as worst case scenario) should be carried out.

RESULTS

Participant flow



There were many switches to open label and withdrawals (see table below). By the use of the LOCF method the authors were able to include all but 5 of the randomised patients in the final efficacy analysis. The concerns associated with this approach are expressed in the comments on Statistical methods, above.

Table 2. Number of Infants Completing Therapy, Transferring to Open-Label Caffeine Citrate, or Withdrawing from Study

	Treatment Group	
	Caffeine Citrate (n=45)	Placebo (n=37)
Completed at least 10 days of double-blind* therapy	21 (46.7)	12 (32.4)
Transferred to open-label caffeine citrate	14 (31.1)	16 (43.3)
Withdrawn from double-blind treatment	10 (22.2)	9 (24.3)
Adverse event	2 (4.4)	1 (2.7)
Apnea recurrence	5 (11.1)	6 (16.2)
Investigator discretion	2 (4.4)	2 (5.4)
Transferred to referring hospital	1 (2.2)	0 (0)

*Values are number (%)

*Difference between groups was not statistically significant (p=0.19).

Conduct of the study

The study was conducted in nine neonatal intensive care units (ICU) in the U.S.

Baseline data

The groups were comparable for baseline characteristics except for some imbalance with respect to gender and race (see table below).

Table 1. Baseline Characteristics of Infants Included in the Efficacy Analysis

	Treatment Group		p Value
	Caffeine (n=45)	Placebo (n=37)	
Gestational age at birth (wks)			0.78 ^a
Number	45	37	
Mean ± SD	29.8 ± 1.7	29.9 ± 1.4	
Range	25.0–32.0	26.0–32.0	
Postconceptual age at time of entry (wks)			1.00 ^a
Number	45	37	
Mean ± SD	30.6 ± 1.3	30.6 ± 1.3	
Range	28.0–32.7	28.0–33.0	
Baseline number of apnea attacks			0.84 ^a
Number	45	37	
± SD	9.6 ± 4.1	9.8 ± 3.8	
Range	6.0–23.0	6.0–18.0	
Weight at entry (g)			0.48 ^a
Number	45	35	
Mean ± SD	1247.6 ± 282.45	1203.4 ± 262.84	
Range	695.0–1955.0	767.0–1955.0	
Sex, no (%)			0.17 ^b
Male	25 (55.6)	26 (70.3)	
Female	20 (44.4)	11 (29.7)	
Race, no (%)			0.09 ^b
Caucasian	16 (35.6)	20 (54.1)	
Non-Caucasian	29 (64.4)	17 (45.9)	

^aAnalysis of variance testing for differences between groups.

^bχ² test comparing groups.

Numbers analysed

A total of 82 patients (45 assigned to caffeine and 37 to placebo) were included in the efficacy analysis and 85 in the safety analysis.

Outcomes and estimation

The safety outcomes were assessed by means of vital signs, laboratory values and adverse events (AEs).

Caffeine citrate was significantly more effective than placebo in reducing apnoea episodes by at least 50% in six days ($p < 0.05$), and approached statistical significance ($p < 0.10$) in three days. Caffeine citrate was also significantly better at eliminating apnoea in 5 days ($p < 0.05$) and approached significance in two days ($p < 0.10$).

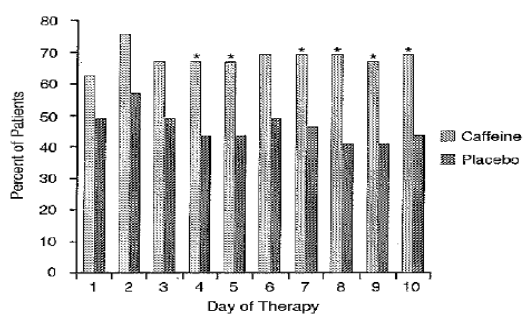


Figure 1. The percentage of infants with at least a 50% reduction in apnea events on each of the respective double-blinded phase study days. * = statistical significance ($p < 0.05$) between groups on days 4, 5, 7, 8, 9, and 10.

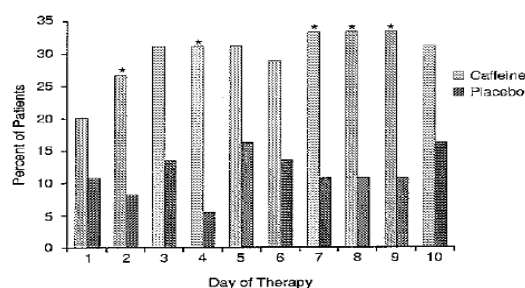


Figure 2. The percentage of infants with elimination of apnea events on each of the respective double-blinded phase study days. * = statistical significance ($p < 0.05$) between groups on days 2, 4, 7, 8, and 9.

The number of infants with an aggregate of 7-10 days of at least a 50% reduction in apnoea events or elimination of apnoea was significantly higher in the caffeine citrate group than in the placebo group (68.9% versus 43.2%, $p = 0.02$, and 24.4% versus 0%, $p = 0.005$, respectively). This additional endpoint has apparently not been specified as primary outcome measure a priori, however.

In an additional analysis of the subset of data obtained exclusively under double blind conditions without imputation (FDA review, ref.5.4.32), almost none of the reported statistical significances could be maintained. According to FDA reviewer's report and analysis, there was no statistically

significant difference in the primary endpoint as specified in the protocol between caffeine citrate and placebo, and no difference in the efficacy of caffeine and placebo on the secondary endpoints.

However, it has to be noted that the group comparison of estimates of treatment effects consistently indicates an advantage of caffeine treatment. Further important signals indicating efficacy of caffeine citrate treatment could be revealed by the FDA review: 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%).

Noticeably, there was a high percentage of patients with $>50\%$ reduction of apnoea in the placebo group.

Several flaws and methodological problems were identified during assessment of this trial: change/choice/analysis of primary efficacy endpoint finally reported, applied imputation methods for withdrawn and transferred patients, no correction for multiplicity.

There is some uncertainty about the representativeness of the studied population in terms of comorbidities and comedications. Additionally, another flaw is the absence of double-blind data beyond 10 days.

The study gives some evidence for the efficacy of caffeine citrate treatment in premature infants with AOP. Study results support to a certain extent the claim that caffeine citrate is able to reduce the number of apnoea episodes in preterm infants.

- Analysis performed across trials (pooled analyses and meta-analysis)

Ref. 5.4.42 *Henderson-Smart DJ, Steer P. Methylxanthine treatment for apnea in preterm infants. Cochrane Database Syst Rev 2004; (4).*

The review included 5 randomised studies: 3 studies with theophylline and 2 studies (Erenberg, study 5.3.5.1.1; Murat, study 5.3.5.1.2) using caffeine for apnoea treatment, enrolling a total of 192 infants. Outcome measures were treatment failure ($<50\%$ reduction in apnoea, or use of intermittent positive pressure ventilation (IPPV), or death during study), use of IPPV, death before hospital discharge, and side effects; efficacy was assessed after 2-10 days.

The authors found that compared with control (placebo or no drug therapy), methylxanthine administration to premature infants with AOP was followed by less treatment failure: summary relative risk (RR) 0.43 (95% CI 0.31- 0.60), risk difference (RD) -0.40 (95% CI -0.16, -0.01), and number needed to treat (NNT) 13 (95% CI 6 - 100). The observed effects were similar for the two trials evaluating caffeine.

The systematic Cochrane Review concludes short-term efficacy of methylxanthines in reduction of apnoea frequency and use of mechanical ventilation in premature infants with AOP. As the review is based on data from the published trials it must be assumed that the limitations of the Erenberg study were not accounted for. The authors also conclude that it is not clear whether merely reducing the number of apnoeic episodes alters longer-term outcome.

Another Cochrane Collaboration Systematic Review by Steer PA (ref. 5.4.79) compared caffeine with theophylline for apnoea in preterm infants (see Supportive Studies below).

- Clinical studies in special populations

None

- Supportive studies

Five publications of non regulatory studies of efficacy and safety of caffeine citrate/methylxanthines in the proposed indication are regarded as supportive studies.

Study 5.3.5.1.2 *Murat I et al. Efficacy of caffeine in the treatment of recurrent idiopathic apnea in premature infants. J. Pediatr. 1981; 99 (6): 984-9.*

The prospective, randomised controlled study investigated the efficacy of caffeine citrate in treating recurrent apnoea in 18 premature infants (29-35 weeks gestation). Infants received a loading dose of

20 mg/kg of caffeine citrate by intramuscular injection followed by oral maintenance doses of 5 mg/kg daily. There was no placebo blinding, treated patients were compared with an untreated control group. Treatment was discontinued on day 15 if <3 apnoeic episodes were recorded, and a follow up was performed one week after the end of treatment.

The apnoea index (defined as the average number of apnoeic attacks per 100 minutes, obtained from the total number recorded in 24 hours) was compared between the groups on day 0, day 1 and day 5.

Caffeine treatment resulted in a significant decrease of severe apnoea and of mild apnoea in the treated group compared with the control group (see table below).

Table 4: Apnoea Index Before and After Randomised Trial in Treated and Control Group (Murat Study 5.3.5.1.2)

Mean ± SEM	Severe apnoea			Mild apnoea		
	Treated	Control	P	Treated	Control	P
Day 0	1.17 ± 0.39 n=9	0.65 ± 0.12 n=9	NS	2.48 ± 0.37 n=9	2.12 ± 0.51 n=9	NS
Day 1	0.24 ± 0.08 n=9	0.74 ± 0.17 n=9	<0.01	1.24 ± 0.25 n=9	1.78 ± 0.34 n=9	<0.01
Day 5	0.11 ± 0.05 n=9	0.57 ± 0.26 n=6	<0.01	0.92 ± 0.16 n=9	1.89 ± 0.49 n=6	<0.01
Day 15	0.034 ± 0.006 n=9	0.12 ± 0.08 n=3	-	0.63 ± 0.04 n=9	0.89 ± 0.44 n=3	-

(Apnoea index: Average number of apnoea attacks per 100 mins)

The study was not blinded, but as the apnoea index was calculated from 24-hours recordings the potential for bias appears small. In spite of some uncertainties (small patient numbers, composition of study drug not indicated, intramuscular application of loading dose), the study provides supportive evidence for efficacy of caffeine citrate in the sought indication.

Study 5.3.5.1.3 *Bairam A et al. Theophylline versus caffeine: comparative effects in treatment of idiopathic apnea in the preterm infant. J Pediatr. 1987; 110 (4): 636-9.*

Study 5.3.5.1.4 *Brouard C et al. Comparative efficacy of theophylline and caffeine in the treatment of idiopathic apnea in premature infants. Am J Dis Child. 1985; 139 (7): 698-700.*

Study 5.3.5.1.5 *Scanlon JE et al. Caffeine or theophylline for neonatal apnoea? Arch Dis Child 1992; 67: 425-8.*

The three trials applied random or quasi-random patient allocation of premature neonates to caffeine treatment compared with theophylline and aminophylline. They excluded patients in whom apnoea was attributable to a specific underlying cause. Measures of the severity of apnoea and of the response to treatment were similar to the definitions in the main study.

Bairam A. et al. 1987 (Study 5.3.5.1.3)	Brouard C et al. 1985 (Study 5.3.5.1.4)	Scanlon JE et al. 1992 (Study 5.3.5.1.5)
Prospective, randomised, DB, parallel, active-controlled comparison	Prospective, randomised, parallel, active-controlled comparison	Prospective, randomised, parallel, active-controlled comparison
To compare the efficacy and safety of caffeine with theophylline in apnoea of prematurity	To compare the efficacy theophylline ethylenediamine and caffeine sodium citrate in idiopathic apnoea in premature infants	To compare the efficacy theophylline with that of caffeine administered in two different dose regimens in preterm infants with frequent and clinically significant apnoeic attacks.
20 infants Caffeine 10 Theophylline 10	16 infants Caffeine 8 Theophylline ethylenediamine 8	44 infants Caffeine: - group A: 16 - group B: 14 Theophylline: 14
Mean 30 (range not given)	Mean 30.5 (range not given)	Mean 28-29 weeks (range not given)
Theophylline	Theophylline ethylenediamine (Aminophylline)	Theophylline
Caffeine: loading dose of caffeine 10mg/kg IV, maintenance dose 1.25mg/kg q 12 hours Theophylline: loading dose of 6 mg/kg IV, maintenance dose 2 mg/kg 12 hourly	Caffeine: loading dose of 20 mg/kg caffeine citrate IM, maintenance dose 5 mg/kg/day orally adjusted to maintain plasma caffeine between 8 and 16 mg/L Theophylline ethylenediamine: loading dose of 5.5 mg/kg IV, maintenance dose adjusted to maintain plasma theophylline between 5 and 10 mg/L (dose range 0.8 to 2.5 mg/kg 8 hourly)	Caffeine - group A: loading dose of caffeine citrate 25mg/kg ; maintenance 6mg/kg/day Caffeine – group B: loading dose of caffeine citrate 50mg/kg ; maintenance 12mg/kg/day Theophylline: loading dose of 7.5 mg/kg orally, maintenance dose 3 mg/kg three times daily
Up to 7 days	Up to 5 days	Up to 5 days
Number of cardiorespiratory abnormalities (apnoea ≥ 15 sec, bradycardia < 80 bpm, and apnoea + bradycardia) per 100 min, at baseline and days 3 and 7.	Apnoea frequency; average number of severe apnoea attacks per 100 min on days 0 (baseline), 1 and 5	Number of apnoeas in 24 hours at baseline (day 0) to days 1 and 2 Number of severe apnoea attacks per 100 min on days 0,1 and 5
AEs, vital signs, weight, GI intolerance, general behaviour and laboratory values	AEs	AEs, vital signs laboratory values

The efficacy results of the three active-controlled studies were evaluated in a Cochrane Collaboration Systematic Review. *Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev. 2004;(2) (ref. 5.4.79).*

The review did not include the high dose caffeine group (n=14) in the Scanlon study, and therefore reviewed the data of 66 infants. The overall quality of the studies is described as fair/good.

There was no difference in the failure rate (<50% reduction in apnoea/bradycardia) of treatment with caffeine or theophylline at 1 to 3 days (two studies) or 5 to 7 days (one study). The authors concluded that caffeine appears to have similar short-term effects on apnoea/bradycardia as theophylline, but caffeine has a better safety profile.

Study 5.3.5.2.1 *Aranda JV et al. Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. J Pediatr. 1977; 90: 467-72.*

The prospective non-controlled study was the first trial to explore the efficacy of caffeine in the treatment of APO in premature infants and to establish a dose schedule appropriate for the limited elimination of caffeine in this population. 18 preterm neonates with at least three recurrent apnoeic spells per day (apnoea >30 seconds and bradycardia <100 bpm with or without cyanosis) were included in the study. Mean birth weight and gestational age were 1065g and 27.5 weeks, respectively, mean post-natal age at start of caffeine citrate treatment was 18.2 days. Caffeine citrate was administered with a loading dose of 20 mg/kg IV followed within two to three days by 5 to 10 mg/kg once or twice daily, for a mean of 6 days.

All infants except one showed a significant decrease in the frequency of apnoeic episodes associated with caffeine therapy. Mean (\pm SEM) frequencies of apnoea spells were 13.6 ± 2.5 and 2.1 ± 0.6 apnoea episodes per day before and after initiation of caffeine treatment, respectively ($p < 0.001$).

- Discussion on clinical efficacy

According to the publication of the main efficacy study (5.3.5.1.1), Nymusa was significantly more effective than placebo in reducing apnoea episodes by at least 50% in six days ($p < 0.05$), and approached statistical significance ($p < 0.10$) in three days. Caffeine citrate was also significantly better at eliminating apnoea in 5 days ($p < 0.05$) and approached significance in two days ($p < 0.10$).

The number of infants with an aggregate of 7-10 days of at least a 50% reduction in apnoea events or elimination of apnoea was significantly higher in the caffeine citrate group than in the placebo group (68.9% versus 43.2%, $p = 0.02$, and 24.4% versus 0%, $p = 0.005$, respectively).

The key efficacy findings come from a randomised, double-blind, placebo-controlled trial. The main study (report and data analysis) has a number of limitations, however:

- The primary endpoint was changed in a final amendment of the study protocol; results of this endpoint have not been reported, however. The additional endpoint “percentage of infants with success for an aggregate of 7-10 days” (see above) has apparently not been specified as primary outcome measure *a priori*.
- The imputation method (LOCF) used in the final efficacy analysis introduces substantial bias when estimating the treatment effect. Missing data from 49 patients (~60% from the defined efficacy analysis set) had to be imputed. An additional data analysis (FDA review) from patients staying under blinded conditions reveals that carrying forward success information was not justified, however: Less than 50% of patients who once achieved a reduction of apnoea rate $\geq 50\%$ could maintain this “success” until the end of treatment. No sensitivity analyses using alternative imputation strategies, e.g. classification of all transferred and withdrawn patients as non-success patients as worst case scenario, were carried out.
- Only 46.7% of infants in the caffeine group and 32.4% in the placebo group completed 10 days of double-blind therapy; a large number of infants in both groups were switched to open label caffeine citrate and withdrawn. No information is provided regarding the reasons for transferring patients to open label treatment.

Efficacy of caffeine citrate treatment in reducing the frequency of apnoea episodes in premature infants is supported by the results of several small studies, either RCT controlled with no-treatment, or RCT comparing 2 active treatments. The small patient numbers however preclude a confirmatory approach.

The data supporting efficacy of caffeine citrate in treating primary apnoea of prematurity are scant. In fact there is a single, small RCT demonstrating this efficacy, study 5.3.5.1.1. Therefore, small trials might give false, large positive effects and publication bias might affect the positive picture constructed by the data discussed in this report.

The CAP study (Caffeine for Apnoea of Prematurity trial group, NEJM 2006) submitted in support of the safety of caffeine citrate is a large RCT regarded as extremely important in support of the benefit/risk conclusions. It finds a beneficial effect of caffeine citrate in terms of clinically relevant, disability related outcomes. The data from this trial are clearly robust. Of 937 infants assigned to caffeine for whom adequate data at a corrected age of 18-21 months were available, 377 (40.2%) died or survived with a neurodevelopmental disability, compared with 431 of the 932 infants (46.2%) assigned to placebo (OR adjusted for centre 0.77; 95% CI 0.64 to 0.93; $p = 0.008$). The effect was mainly driven by lower rates of cerebral palsy (4.4% and 7.3% for caffeine and placebo, respectively; adjusted OR 0.58, 95% CI 0.39 – 0.87; $p = 0.009$). The rates of death before 18 months, deafness, and blindness did not differ significantly between the groups.

From a regulatory point of view, the major draw-back of the CAP study is that approximately 60% of infants received caffeine for prevention of apnoea and for facilitation of extubation, and, apparently, infants with apnoea secondary to underlying diseases were not excluded.

Following CHMP's request, a post hoc subgroup analysis published by the CAP investigators was submitted by the Applicant. It is reassuring that there was little evidence of a differential treatment effect of caffeine over subgroups defined by the clinical indication for starting the study.

Another important finding of the subgroup analysis was that the size and the direction of the caffeine effect on death or disability differed depending on the degree of respiratory support infants needed at randomisation ($p=0.032$). The OR (95% CI) was 1.32 (0.81 – 2.14) for no support, 0.73 (0.52 – 1.03) for non-invasive support and 0.73 (0.57 – 0.94) for endotracheal tube, respectively. The most severely affected infants, i.e. infants receiving respiratory support, appeared to have more neurodevelopmental benefit from caffeine treatment than unsupported infants. Also, infants who started treatment early had a greater reduction in time on ventilation.

Clinical safety

- Patient exposure

The actual numbers of infants enrolled and exposed in clinical studies with caffeine citrate, according to the indication, are given in the tables below.

Table 6.1: Study Drug Exposure in the Pivotal Study (Erenberg Study 5.3.5.1.1)

Study	Group	Infants treated	Dose	Duration
Erenberg 5.3.5.1.1	Caffeine citrate Placebo (DB) → caffeine citrate open-label	46 39 → 17	20 mg/kg IV loading dose followed by maintenance of 5 mg/kg/day IV or orally. Treatment was originally for up to 10 days but this was revised up to 12 days treatment. Infants failing double-blind treatment could receive open-label caffeine citrate after day 1 and before day 8. An additional loading dose of 20 mg/kg was administered at the switch to open-label followed by a daily maintenance of 6 mg/kg to day 12.	In the caffeine group, 21 infants completed 10 days of double-blind phase, compared with 12 in the placebo group. 14 of the caffeine group and 17 of the placebo group switched to open-label caffeine.

Table 6.2: Study Drug Exposure in the Supportive Studies in the Claimed Indication

Study	Group	Infants treated	Dose	Duration
Murat 5.3.5.1.2	Caffeine No treatment	9 9	20 mg/kg caffeine citrate intramuscular (IM) followed by a maintenance dose of 5 mg/kg/day orally.	Mean duration of treatment 24 days, range 15-40.
Bairam 5.3.5.1.3	Caffeine Theophylline	10 10	10 mg/kg loading dose, maintenance dose: 1.25 mg/kg 12 hourly IV. 6 mg/kg loading dose, maintenance dose: 2 mg/kg 12 hourly IV.	up to 7 days. up to 7 days.
Brouard 5.3.5.1.4	Caffeine Theophylline	8 8	20 mg/kg loading dose caffeine citrate IM, maintenance dose: 5 mg/kg/day orally adjusted to maintain plasma caffeine between 8 and 16 mg/L. 5.5 mg/kg loading dose aminophylline IV, maintenance dose adjusted to maintain plasma theophylline between 5 and 10 mg/L; dose range 0.8 to 2.5 mg/kg 8 hourly).	5-day treatment period.
Scanlon 5.3.5.1.5	Caffeine Group A Caffeine Group B Theophylline	16 (12 analysed) 14 (12 analysed) 14 (12 analysed)	25 mg/kg loading dose caffeine citrate orally, maintenance dose: 6 mg/kg/day orally. 50 mg/kg loading dose caffeine citrate orally, maintenance dose: 12 mg/kg/day orally. 7.5 mg/kg loading dose aminophylline, maintenance dose: 3 mg/kg three times daily.	Not clearly specified (up to five days).
Aranda 5.3.5.2.1	Caffeine citrate	18	20 mg/kg loading dose caffeine citrate IV followed within two to three days by 5 to 10 mg/kg once or twice daily. Mean total dose: 113.0 ± 27.4 mg/kg.	Mean 6.0 days treatment ± standard error (SE) 1.9.

Table 6.3: Study Drug Exposure in Supportive Studies in The Claimed Indication and in Other Indications Combined (Schmidt Study 5.3.5.1.6)

Study	Group	Infants treated	Indication	Dose	Duration
Schmidt 5.3.5.1.6	Caffeine citrate	429 234 341 2 <hr/> Total: 1006	Treatment of apnoea Prevention of apnoea Removal of endotracheal tube Other	20 mg/kg loading dose caffeine citrate IV followed by a maintenance dose of 5 mg/kg/day IV or orally. It was recommended that therapy continue until the infant had tolerated at least 5 consecutive days without positive airway pressure.	Median 37 days caffeine treatment (interquartile (IQ) range, 24 to 46) vs 36 (IQ range, 23 to 46) placebo (P = 0.68).
	Placebo	401 220 378 1 <hr/> Total: 1000	Treatment of apnoea Prevention of apnoea Removal of endotracheal tube Other		

Table 6.4: Study Drug Exposure in the Supportive Studies in Other Indications

Study	Group	Infants treated	Indication	Dose	Duration
Bucher 5.3.5.4.1	Caffeine	25	prophylaxis for apnoea	20 mg/kg caffeine citrate IV precisely 48 hours after delivery followed by a maintenance dose of 10 mg/kg at 72 and 96 hours of age.	4 days.
	No treatment	25			
Romagnoli 5.3.5.4.2	Caffeine 5 mg/kg maintenance	13	prophylaxis for apnoea	10 mg/kg caffeine citrate IV loading dose followed by a maintenance dose of 5 mg/kg daily.	Maintenance was mean \pm SD 18.4 \pm 3 days.
	Caffeine 2.5 mg/kg maintenance	10		10 mg/kg caffeine citrate IV loading dose followed by a maintenance dose of 2.5 mg/kg daily.	Maintenance was mean \pm SD 15 \pm 1 days.
	Control	14		Previous series of infants not treated pharmacologically.	
Larsen 5.3.5.4.3	Aminophylline	109 (98 analysed)	prophylaxis for apnoea	6.2 mg/kg loading dose followed by a maintenance dose of 3.1 mg/kg IV or by gastric tube twice daily.	up to 10 days.
	Caffeine	105 (82 analysed)		20.2 mg/kg loading dose caffeine citrate followed by a maintenance dose of 2.5 mg/kg iv or by gastric tube twice daily.	up to 10 days.
Welborn 5.3.5.4.4	Caffeine	9	apnoea prophylaxis after general anaesthesia	5 mg/kg caffeine citrate IV following induction of anaesthesia.	Single dose
	Placebo	11		Saline IV following induction of anaesthesia.	
Welborn 5.3.5.4.5	Caffeine	16	apnoea prophylaxis after general anaesthesia	10 mg/kg caffeine citrate IV following induction of anaesthesia.	Single dose
	Placebo	16		Saline IV following induction of anaesthesia.	
Steer 5.3.5.4.6	Caffeine 20 mg/kg	113	prevention of extubation failure	80 mg/kg caffeine citrate IV loading dose followed by a maintenance dose of 20 mg/kg/day.	Not specified.
	Caffeine 5 mg/kg	121		20 mg/kg caffeine citrate IV loading dose followed by a maintenance dose of 5 mg/kg/day.	
Steer 5.3.5.4.7	Caffeine 3 mg/kg	42	prevention of extubation failure	6 mg/kg caffeine citrate IV loading dose followed by 3 mg/kg/day IV or orally.	up to 6 days.
	Caffeine 15 mg/kg	40		30 mg/kg caffeine citrate IV loading dose followed by 15 mg/kg/day IV or orally.	up to 6 days.
	Caffeine 30 mg/kg	45		60 mg/kg caffeine citrate IV loading dose followed by 30 mg/kg/day IV or orally.	up to 6 days.

In the clinical pharmacology studies a total of 474 premature neonates or infants received at least one dose of caffeine; 81 received only single doses and 393 had repeated administrations of caffeine. In total, 130 premature neonates or infants received a loading dose of 20 mg/kg caffeine citrate followed by maintenance at 5 mg/kg at least initially.

To support the safety of caffeine citrate treatment in premature infants, the Applicant submitted two publications of a large study (Study 5.3.5.1.6):

Schmidt B A et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006; 354: 2112-21. and Schmidt B et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007; 357(19): 1893-902

The objective of this study (the CAP study: Caffeine for Apnoea of Prematurity trial group) was to evaluate the short- and long-term efficacy and safety of caffeine therapy in infants of very low birth weight. The study was a multicentre, randomised, blinded, placebo-controlled trial.

Infants with a birth weight of 500 to 1250g were eligible for enrolment if their clinicians considered them candidates for caffeine therapy in the first 10 days of life. Caffeine was given for treatment of apnoea, for prophylaxis of apnoea, and for prophylaxis of apnoea following extubation.

2006 infants were randomly assigned to receive caffeine (20mg/kg caffeine citrate bolus followed by 5-10 mg/kg/d maintenance) or placebo; 1006 were assigned to caffeine citrate and 1000 to placebo. The median number of treatment days was 37 in the caffeine and 36 in the placebo group. The groups were comparable for baseline characteristics (see table below).

Study	Group	n	Gestational age, weeks	Birth weight, g	Sex, n (%)	
			Mean ± SD	Mean ± SD	Male	Female
Schmidt 5.3.5.1.6	Caffeine	1006	27 ± 2	961 ± 180	498 (50%)	508 (50%)
	Placebo	1000	27 ± 2	952 ± 181	530 (53%)	470 (47%)

Short-term outcome

Caffeine citrate significantly reduced the frequency of bronchopulmonary dysplasia (defined as the need for supplemental oxygen at a post-menstrual age of 36 weeks). The rates of death before the first discharge home, ultrasonographic signs of brain injury, and necrotising enterocolitis (NEC) did not differ significantly between the two groups (see table below).

Table 12: Death, Bronchopulmonary Dysplasia, Retinopathy of Prematurity, Brain Injury and NEC before First Discharge Home in the Supportive Study (Schmidt Study 5.3.5.1.6)

Outcome	Caffeine (N=1006) n (%)	Placebo (N=1000) n (%)	Odds ratio Adjusted for centre (95% CI)	p-value
Death	52 (5.2%)	55 (5.5%)	0.93 (0.63-1.38)	0.73
Bronchopulmonary dysplasia ^a	350 (36.3%)	447 (46.9%)	0.63 (0.52-0.76)	<0.001
Retinopathy of prematurity ^b	322 (39.2%)	362 (43.2%)	0.84 (0.68-1.03)	0.09
Brain injury ^c	126 (13.0%)	138 (14.3%)	0.90 (0.69-1.18)	0.44
NEC	63 (6.3%)	67 (6.7%)	0.93 (0.65-1.33)	0.63

^a assessed in 963 infants in the caffeine group and 954 in the placebo group who were alive at 36 weeks postmenstrual age

^b assessed in 822 infants in the caffeine group and 838 in the placebo group

^c assessed by cranial ultrasonography in 967 infants in the caffeine group and 966 in the placebo group

Only 37 (1.8%) of infants, 23 in the caffeine group and 14 in the placebo group, had doses of the study drug withheld or reduced because of clinical symptoms suggesting caffeine-induced toxicity; caffeine plasma levels were not monitored in the study.

Long-term outcome

The final publication of the study (Schmidt, NEJM 2007) reported that of the 937 infants assigned to caffeine citrate for whom adequate data on the primary outcome at a corrected age of 18 to 21 months were available, 377 (40.2%) died or survived with a neurodevelopmental disability, compared with 431 of the 932 infants (46.2%) assigned to placebo. Treatment with caffeine citrate as compared with placebo reduced the incidence of cerebral palsy (4.4% versus 7.3%) and of cognitive delay (33.8% versus 38.3%). The rates of death before 18 months, deafness, and blindness did not differ significantly between the two groups (see table below).

Outcome	Caffeine n/total n (%)	Placebo n/total n (%)	Odds ratio Adjusted for centre (95% CI)	p-value
Composite of death or disability	377/937 (40.2%)	431/932 (46.2%)	0.77 (0.64-0.93)	0.008
Death before 18 months	62/974 (6.4%)	63/970 (6.5%)	0.97 (0.67-1.40)	0.87
Cerebral palsy	40/909 (4.4%)	66/901 (7.3%)	0.58 (0.39-0.87)	0.009
Cognitive delay (MDI<85)	293/867 (33.8%)	329/858 (38.3%)	0.81 (0.66-0.99)	0.04
Severe hearing loss	17/909 (1.9%)	22/905 (2.4%)	0.77 (0.40-1.45)*	0.41
Bilateral blindness	6/911 (0.7%)	8/905 (0.9%)	0.74 (0.26-2.15)*	0.58

MDI=Mental Development Index

* odds ratio not adjusted for centre because there were too few events

The study addressed several longstanding concerns about possible risks due to the pharmacological effects of caffeine: the long-term risk concerning neurodevelopment due to possible effects of caffeine on cerebral blood flow and to inhibition of adenosine receptors, and the potential failure to thrive due to increased metabolic rate and oxygen consumption with caffeine (see also Serious Adverse Events and Deaths below).

Evidence of a small but significant improvement in the rate of survival without neurodevelopmental disability in premature infants treated with caffeine citrate was provided. The effect was mainly driven by significantly lower rates of cerebral palsy at 18 to 21 months in the caffeine group as compared with the placebo group. Also, a significant contribution of the component cognitive delay was observed.

Except for a temporary reduction in weight gain, caffeine treatment had no apparent short-term or long-term risks.

Apparently, infants with secondary apnoea due to underlying conditions were not excluded from the study. Infants treated for documented apnoea were only about 40% of the study population; approximately 20% received caffeine for the prevention of apnoea and 35-40% for the facilitation of extubation. A post-hoc subgroup analysis revealed little evidence of a differential treatment effect of caffeine over these subgroups.

Further safety information is available from studies in premature neonates using caffeine citrate for prevention of apnoea (Studies 5.3.5.4.1, *Bucher, Eur J Pediatr 1988*; 5.3.5.4.2, *Romagnoli, Ther Drug Monit 1992*; and 5.3.5.4.3 *Larsen, Acta Paediatr 1995*), or in the prophylaxis of apnoea following general anaesthesia (Studies 5.3.5.4.4 and 5.3.5.4.5, *Welborn, Anesthesiology 1988 and 1989*), or in the prevention of extubation failure (Studies 5.3.5.4.6, *Steer, Arch Dis Child Fetal Neonatal Ed 2004*; and 5.3.5.4.7, *Steer, J Paediatr. Child Health 2003*).

516 infants were exposed to caffeine. Caffeine citrate was used for prevention of apnoea in premature infants in different clinical settings for short time periods, up to ten days (5.3.5.4.3), and in dose regimens deviating from that presently proposed (see IV.2 Patient Exposure, Studies with caffeine citrate in other indications, D80AR-Clinical). In study 5.3.5.4.6, a follow up after 12 months was performed. Studies 5.3.5.4.1, 5.3.5.4.4 and 5.3.5.4.5 compared caffeine with placebo, but only study 5.3.5.4.1 reported safety data (no side effects, such as tachycardia, jitteriness or vomiting in either group). Studies 5.3.5.4.2, 5.3.5.4.6 and 5.3.5.4.7 compared different dosing groups of caffeine citrate; their results indicate dose dependence of some side effects of caffeine, such as tachycardia and feed

intolerance (see Adverse Events below). Caffeine had a better safety profile than aminophylline (less tachycardia, smaller amount of gastric aspirate) in study 5.3.5.4.3.

Studies where caffeine was compared with other xanthines were too small and not powered for a formal statistical analysis, either as non-inferiority or superiority. The results on efficacy measured from baseline are of limited value given that there is no placebo group and the placebo effect can be sizable.

The data on prevention of apnoea are of low quality. Even though the studies were not submitted to support efficacy of caffeine citrate, it is relevant that the Cochrane review does not point to an effect; this might be due to the low power of the studies or the inadequacy of the population studied or because in fact there is no effect. This cannot be overruled by a study with historical controls that suggests a beneficial effect. In fact, the data on prevention of apnoea is rather limited and unconvincing. However, in the large RCT (5.3.5.1.6) 40% of the population received caffeine for prevention of AOP. Data from these collateral indications has little value for the discussion of efficacy in primary apnea; positive results, however, might suggest the sharing of a common mechanism of action for the different apnoeas/indications and might imply efficacy of caffeine treatment across categories/indications. It is also important because study 5.3.5.1.6 includes all these types of apnoeas and does not separate the subgroups.

- Adverse events

Adverse Events (AEs) in the Main study 5.3.5.1.1 (Erenberg, 2000)

The number of infants discontinued from double-blind phase because of an AE did not differ between the groups. Two (4.4%) infants in the caffeine citrate group were discontinued, one for dyspnoea and the other one for septicaemia, while one (2.7%) infant in the placebo group was discontinued for necrotising enterocolitis (NEC).

4 infants receiving caffeine citrate and 2 receiving placebo experienced NEC after discontinuation of the study drug. NEC was assessed to be possibly related to caffeine citrate in one of the 4 infants.

Three deaths due to NEC occurred within 30 days after discontinuation of the study drug; all three infants had underlying disorders in addition to AOP. Two of these infants had been assigned to caffeine; one was originally in the placebo group but was transferred to the open-label caffeine group on the same day that he required small bowel resection.

The most common AE in the caffeine group was constipation (17% of infants); the incidence was similar for the placebo group (21%). Rash was also a common event in both groups.

A table of AEs by study phase, System Organ Class (SOC) and Preferred Term (MedDRA) is given below.

Table 10: Adverse Events by Study Phase, System Organ Class and Preferred Term in the Pivotal Study (Erenberg *Study 5.3.5.1.1*) Reviewed According to MedDRA

SYSTEM ORGAN CLASS • Preferred Term	Caffeine citrate		Placebo		P-value double-blind phase
	Double-blind (N=46)	Open-label (N=14)	Double-blind (N=39)	Open-label caffeine (N=17)	
At least 1 Adverse Event	25 (54.3%)	11 (78.6%)	24 (61.5%)	11 (64.7%)	0.5187
INFECTIONS AND INFESTATIONS					
• Sepsis	2 (4.3%)	4 (28.6%)	0	2 (11.8%)	
• Oral candidiasis	0	0	0	1 (5.9%)	
• Urinary tract infection	0	0	1 (2.6%)	0	
BLOOD AND LYMPHATIC SYSTEM DISORDERS					
• Anaemia	3 (6.5%)	3 (21.4%)	7 (17.9%)	4 (23.5%)	
• Disseminated intravascular coagulation	1 (2.2%)	0	0	0	
• Lymphadenopathy	0	1 (7.1%)	0	0	
METABOLISM AND NUTRITION DISORDERS					
• Hypovolaemia	0	1 (7.1%)	0	0	
• Acidosis	1 (2.2%)	0	0	1 (5.9%)	
• Hyperkalaemia	0	0	0	1 (5.9%)	
• Hypocalcaemia	0	1 (7.1%)	0	0	
• Hyponatraemia	0	2 (14.3%)	2 (5.1%)	0	
• Hypoproteinaemia	0	1 (7.1%)	0	0	
NERVOUS SYSTEM DISORDERS					
• Hydrocephalus	0	0	1 (2.6%)	0	
• Cerebral haemorrhage	1 (2.2%)	1 (7.1%)	0	0	
EYE DISORDERS					
• Conjunctivitis	1 (2.2%)	0	1 (2.6%)	0	
• Retinal disorder	1 (2.2%)	0	0	0	
CARDIAC DISORDERS					
• Bradycardia	0	1 (7.1%)	0	0	
• Cardiovascular disorder	0	1 (7.1%)	0	0	
• Tachycardia	0	1 (7.1%)	0	0	
VASCULAR DISORDERS					
• Haemorrhage	1 (2.2%)	0	0	0	

Table 10, continued

<i>System Organ Class</i> • Preferred Term	Caffeine citrate		Placebo		P-value double- blind phase
	Double-blind (N=46)	Open-label (N=14)	Double-blind (N=39)	Open-label caffeine (N=17)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
• Apnoea	0	1 (7.1%)	1 (2.6%)	0	
• Dyspnoea	1 (2.2%)	0	0	1 (5.9%)	
• Pulmonary oedema	1 (2.2%)	0	0	0	
• Respiratory disorder	0	1 (7.1%)	0	0	
GASTROINTESTINAL DISORDERS					
• Abdominal distension	1 (2.2%)	0	1 (2.6%)	0	
• Constipation	8 (17.4%)	2 (14.3%)	8 (20.5%)	3 (17.6%)	
• Enterocolitis	2 (4.3%)	2 (14.3%)	1 (2.6%)	1 (5.9%)	
• Gastritis	1 (2.2%)	0	0	0	
• Gastrointestinal disorder	2 (4.3%)	2 (14.3%)	3 (7.7%)	1 (5.9%)	
• Gastrointestinal haemorrhage	1 (2.2%)	0	0	0	
• Small intestinal perforation	0	0	0	1 (5.9%)	
• Mouth ulceration	0	0	1 (2.6%)	0	
• Vomiting	0	0	0	2 (11.8%)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
• Dry skin	1 (2.2%)	0	0	1 (5.9%)	
• Rash	4 (8.7%)	0	3 (7.7%)	1 (5.9%)	
• Skin disorder	1 (2.2%)	0	0	0	
• Dermatitis bullous	0	0	1 (2.6%)	0	
RENAL AND URINARY DISORDERS					
• Renal failure	1 (2.2%)	0	0	0	
• Renal impairment	0	0	1 (2.6%)	0	
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS					
• Neonatal disorder	4 (8.7%)	2 (14.3%)	2 (5.1%)	2 (11.8%)	
CONGENITAL, FAMILIAL AND GENETIC DISORDERS					
• Patent ductus arteriosus	1 (2.2%)	1 (7.1%)	2 (5.1%)	2 (11.8%)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
• Generalized oedema	0	0	0	1 (5.9%)	
• Injection site inflammation	1 (2.2%)	0	0	0	
• Injection site reaction	4 (8.7%)	1 (7.1%)	5 (12.8%)	1 (5.9%)	
• Impaired healing	1 (2.2%)	0	0	0	
INVESTIGATIONS					
• Drug level increased	0	1 (7.1%)	0	0	
• Gamma-glutamyltransferase increased	0	0	1 (2.6%)	0	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
• Injury	1 (2.2%)	0	0	0	

Assessment of adverse events in the study is complex due to different study phases and differences in length of treatment. The FDA performed a post hoc safety data analysis of AEs for all patients who ever received caffeine versus those who never received caffeine, by treatment for the double-blind phase only and by original randomisation. These analyses revealed no significant differences in the incidence of AEs between study groups except for sepsis. The reason for the higher incidence of sepsis in the caffeine group was not clear.

The higher incidence of NEC in the caffeine group, though statistically not significant, raises awareness, as NEC is a serious emergency event in premature infants. NEC is further discussed in Serious AEs and Deaths below.

Adverse Events in Supportive Study 5.3.5.1.6 (Schmidt, 2006 and 2007)

Adverse event data were obtained from the primary caregiver at follow-up, or from the children's medical charts, where possible. The data obtained are summarised in the following table. The profile for caffeine was similar to that of placebo.

Table 14: Adverse Events after First Discharge Home in the Supportive Study (Schmidt Study 5.3.5.1.6)

Adverse event	Caffeine n (%)	Placebo n (%)
Hospital admission – number of children with data	907	899
Number of children with at least one admission	432 (47.6%)	448 (49.8%)
Medical reason: Respiratory infection	231 (25.5%)	232 (25.8%)
Asthma	37 (4.1%)	49 (5.5%)
Failure to thrive	22 (2.4%)	15 (1.7%)
Seizure disorder	6 (0.7%)	8 (0.9%)
Shunt infection	1 (0.1%)	0
Shunt blockage	1 (0.1%)	1 (0.1%)
Meningitis (in absence of shunt)	1 (0.1%)	2 (0.2%)
Head injury	3 (0.3%)	0
Other neurological problem	4 (0.4%)	2 (0.2%)
Other non-neurological medical problem	125 (13.8%)	133 (14.8%)
Surgical reason: Gastrostomy	9 (1.0%)	12 (1.3%)
Other gastrointestinal surgery	13 (1.4%)	14 (1.6%)
Ventriculoperitoneal shunt placement or revision	5 (0.6%)	2 (0.2%)
Ear, nose, throat surgery	34 (3.7%)	47 (5.2%)
Ligation of patent ductus arteriosus	1 (0.1%)	4 (0.4%)
Ophthalmologic surgery	12 (1.3%)	21 (2.3%)
Urogenital surgery	13 (1.4%)	17 (1.9%)
Inguinal hernia repair	78 (8.6%)	63 (7.0%)
Other surgery	7 (0.8%)	16 (1.8%)

Table 14: Adverse Events After First Discharge Home in the Supportive Study (Schmidt Study 5.3.5.1.6), Continued

Adverse event	Caffeine n (%)	Placebo n (%)
Chronic drug use – number of children with data ^a	905	898
Inhaled corticosteroids	168 (18.6%)	174 (19.4%)
Systemic corticosteroids	21 (2.3%)	26 (2.9%)
Bronchodilators	169 (18.7%)	189 (21.0%)
Anticonvulsants	5 (0.6%)	7 (0.8%)
Diuretics	24 (2.7%)	25 (2.8%)
Respiratory support – number of children with data	907	901
Supplemental oxygen	145 (16.0%)	172 (19.1%)
Positive airway pressure ^b	15 (1.7%)	20 (2.2%)
Additional vision problems – number of children with data	903	893
Unilateral blindness	7 (0.8%)	6 (0.7%)
Prescription glasses – myopia	21 (2.3%)	16 (1.8%)
Prescription glasses - hypermetropia	11 (1.2%)	11 (1.2%)
Prescription glasses - strabismus	5 (0.6%)	10 (1.1%)
Additional hearing problems – number of children with data	909	905
Hearing loss of any severity	145 (16.0%)	157 (17.8%)

^a drugs were prescribed for at least 2 months after first discharge home

^b data on use of positive airways pressure after first discharge home was missing for one child

Adverse Events in other submitted studies

The Cochrane review by Steer (ref. 5.4.79) of studies comparing caffeine citrate versus theophylline in the treatment of AOP (studies 5.3.5.1.3, 5.3.5.1.4, and 5.3.5.1.5) found that side effects, as indicated by tachycardia or feed intolerance leading to change in dosing, were lower in the caffeine group (RR 0.17, 95% CI 0.04 – 0.72; RD -0.29, 95% CI -0.47 – -0.10). This was consistent across the three studies. Similar results are reported in study 5.3.5.4.3 comparing aminophylline and caffeine in the prevention of AOP.

In study 5.3.5.4.1 investigating caffeine prophylaxis of apnoea in preterm neonates, no side effects such as tachycardia, jitteriness or vomiting were observed in either group (caffeine or placebo). Study 5.3.5.4.2 reported a higher frequency of side effects, such as hyperglycaemia (5 of 13 infants), hypertension (1/13), tachycardia >180bpm (11/13) and vomiting/feeding problems (11/13), in the group receiving the higher maintenance dose of caffeine compared with the lower maintenance dose group and a previous non-treated control group.

No AEs were reported in the trials of caffeine treatment to prevent apnoea following general anaesthesia in premature neonates (studies 5.3.5.4.4 and 5.3.5.4.5).

Two studies report the effects of caffeine citrate in the prevention of extubation failure. Study 5.3.5.4.7 was a trial of three dose regimens of caffeine citrate (3, 15 and 30 mg/kg orally or IV following loading doses of caffeine citrate of 6, 30 or 60 mg/kg IV, respectively, for up to six days). Tachycardia and feeding intolerance were higher, and weight gain was lower in the 15 mg/kg and 30 mg/kg groups, but these differences were not statistically significant. The second study (5.3.5.4.6) compared the efficacy and safety of two caffeine citrate dose regimens (5 mg/kg or 20 mg/kg IV following a loading dose of 20mg/kg or 80 mg/kg IV, respectively).

There were no statistically significant differences between the two dosing regimens with regard to tachycardia, jitteriness, feeding intolerance, duration of intravenous nutrition, major morbidity or pre-discharge mortality. No difference in the overall weight gain between the groups was observed over the duration of therapy, while the time to regain birth weight was significantly longer for infants in the higher dose group (14.8 ± 5.3 vs. 12.9 ± 5.0 days, mean ± SD; p<0.01). At 12 months, there was no statistically significant difference in death, disability or mean general quotient between the groups.

AEs reported in publications of academic clinical trials can be unreliable due to underreporting and non-systematic approach to the listing. This is more so in older and small trials. Thus, the data available is to be taken with some caution. The CHMP noticed that the rates are usually higher for placebo, when this is present. There are many supportive studies without any mention to AEs, which is a sign of underreporting. Still we consider the database generated by study 5.3.5.1.6 an important database due to its size and duration of follow-up. Furthermore it contains a placebo arm for control, which is also relevant. Taking into consideration the data of this study the CHMP considered there was no important, unexpected safety sign.

- Serious adverse event/deaths/other significant events

Data from the submitted studies were not collected in a uniform way and serious adverse events (SAEs) are not detailed as such.

The most common AEs considered likely to be serious by the Applicant were: deafness (9.1%), brain injury (7.9%), necrotising colitis (4.4%), tachycardia (2.0%) and sepsis (1.8%). The following AEs were also reported in the placebo group and at a higher incidence than in the caffeine citrate group: deafness (14.4%), brain injury (12.7%) and necrotising colitis (6.2%); tachycardia and sepsis were not reported in the placebo group. With the exception of failure to thrive, all other SAEs in the caffeine citrate group were reported at an incidence below 1.0%.

Necrotising enterocolitis (NEC)

NEC is a serious emergency event occurring in about 10% of infants weighing less than 1500 g, and prematurity is the most important risk factor for NEC. Reports of decreased splanchnic blood flow in newborns after supra-therapeutic doses of caffeine (Lane, 1999; ref. 5.4.54) led to speculations that this effect might contribute to gut ischaemia and to NEC. A causal relationship between caffeine/methylxanthine treatment and NEC has not been established, however.

There was a higher incidence of NEC in the caffeine group than in the placebo group in the main efficacy study (5.3.5.1.1). Overall, 6 cases of NEC were observed: 4 cases of NEC occurred in 46 infants assigned to caffeine (8.6%); 2 infants received caffeine in the double-blind treatment phase and 2 were switched to open-label caffeine. 2 cases of NEC occurred in 39 infants assigned to placebo; one infant received only placebo treatment, while the other infant developed NEC after being switched to open label caffeine.

In the CAP study in 2006 premature infants (5.3.5.1.6), there was no difference in the rate of NEC between the caffeine and the placebo group at the first discharge home: 6.3% and 6.7% for caffeine and placebo, respectively.

Neurological development and growth

The long-term results of the CAP study (NEJM 2006) showed an improved rate of survival without neurodevelopmental disability (the primary endpoint of the trial) in infants randomly assigned to caffeine therapy, assessed at a corrected age of 18 to 21 months. In particular, the incidences of cerebral palsy and cognitive delay were reduced in the caffeine treatment group.

Growth, as indexed by height, weight, and head circumference, was not affected by caffeine treatment.

Cerebral haemorrhage, brain injury

One case of cerebral haemorrhage is reported in the caffeine group in the Erenberg study; no cerebral haemorrhage occurred in the placebo group.

The publication of the Schmidt study does not report cerebral haemorrhage specifically, but analysed the rates of brain injury assessed by cranial ultrasonography at hospital discharge. The rates were comparable for both groups (13.0% and 14.3% for infants in the caffeine and placebo group, respectively).

Only two of the supportive studies report intraventricular haemorrhage (5.3.5.4.6 and 5.3.5.4.7).

Deaths

Three deaths were reported in the main study (Erenberg, 2000): 2 patients randomised to caffeine treatment and 1 patient randomised to placebo. This last patient received open-label caffeine for 8 days. All deaths were secondary to complications from NEC.

In the supportive study by Aranda (5.3.5.2.1), one infant in the caffeine group died of disseminated cytomegalovirus infection at a PNA of 59 days, 30 days after the last dose of caffeine.

In the large study by Schmidt (5.3.5.1.6), there was no difference in the rate of death between the caffeine and the placebo group at the first discharge home (5.2% versus 5.5%, for caffeine and placebo, respectively) and death at 18 months (6.4% versus 6.5%, for caffeine and placebo, respectively).

- Laboratory findings

In the main study by Erenberg (5.3.5.1.1), values for sodium, potassium, calcium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, AST, ALT, gamma-GTP, and haematocrit were compared between the caffeine and the placebo groups. No clinically significant differences were identified between infants in the double-blind caffeine and the placebo groups or those who received open-label caffeine.

There was no information from other submitted studies.

- Safety in special populations

N/A

- Safety related to drug-drug interactions and other interactions

N/A

- Discontinuation due to adverse events

In the clinical programme, 11 of the 14 studies reported either that no adverse events (AEs) had occurred that led to discontinuation, or quoted the incidence. Overall, the rate of discontinuation due to AEs on caffeine for these studies combined was 2.8% (45/1611), compared with 1.4% (15/1087) on placebo and 16.7% (5/30) on theophylline.

In the main study (5.3.5.1.1), two infants (4.4%) in the caffeine group and one infant (2.7%) in the placebo group were withdrawn from the double-blind treatment due to adverse events. Discontinuation due to AEs is not reported in the Schmidt study; it is only stated that 1.8% of infants, 23 in the caffeine group and 14 in the placebo group, had doses of the study drug withheld or reduced because of clinical symptoms suggesting caffeine-induced toxicity.

In the PK study by Lee TC (Ref. 5.3.3.5.1) 119 preterm infants received maintenance doses of caffeine of 3mg/kg, 15mg/kg and 30mg/kg after a loading dose of 6mg/kg, 30mg/kg or 60mg/kg for up to 6 days. It is reported that there were no untoward effects necessitating discontinuation of caffeine treatment before the scheduled end of treatment.

- Discussion on clinical safety

The safety data on the acute use of Nymusa are scant. This is mostly due to the lack of complete databases and the need to rely on published reports of clinical trials, which are known to be affected by under- and selective reporting.

The large, CAP study is reassuring from a safety point of view, showing that there is no relevant safety issue for the use of caffeine citrate. Additionally, PMS data from authorised caffeine citrate products reveal no new or unsuspected safety issues.

Duration of treatment in the main placebo-controlled trial was 10 to 12 days. Median duration of caffeine treatment was 37 days in the CAP study. In clinical practice, treatment is usually continued until the child 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, persistence of apnoeas and other clinical considerations; this is now reflected in the SPC. There still remains some uncertainty concerning the optimal duration of treatment; this is addressed in the RMP.

Necrotising enterocolitis was identified as a potential risk of caffeine treatment in the main efficacy study. NEC is a relatively common serious emergency event occurring in approximately 10% of very low birth weight infants (<1500g). It is life-threatening and can result in long-term consequences, such as strictures and short bowel syndrome due to intestinal resection. Studies indicating reduced splanchnic blood flow in newborns who received 50mg/kg of caffeine citrate (Lane, 1999; ref. 5.4.54) had raised the possibility of a causal relationship. In the CAP study in 2006 premature infants, however, there was no difference in the rate of NEC between the caffeine and the placebo group at the first discharge home: 6.3% versus 6.7%, for caffeine and placebo, respectively. NEC is addressed as a potential risk in the RMP.

In the non-clinical setting, behavioural deficits were observed in newborn rats in the therapeutic dose range, most likely caused by persistence of upregulated adenosine receptors into adulthood. The clinical relevance of this finding for humans is unclear. There is no data on intellectual, behavioural and somatic development of treated infants in childhood or adulthood.

Risk Management plan

The Applicant presented the Safety Specification summarizing following important identified risks of a medicinal product, important potential risks, and important missing information, structured as follows:

Identified risks for caffeine citrate include those which are known adverse effects characteristic of the methylxanthine class. Some have been further identified in clinical trials:

- Toxicity due to maternal caffeine ingestion;
- Increase in caffeine plasma levels in premature infants with cholestatic hepatitis;
- Irritability, restlessness and jitteriness at higher caffeine levels;
- Cardiac compromise in infants with pre-existing cardiac disease, including arrhythmias;
- Increased sodium and calcium excretion which may be associated with increased urine flow rate and increased creatinine clearance;
- Hypoglycaemia and hyperglycaemia;
- Phlebitis and local inflammatory changes following inadvertent infiltration of skin and subcutaneous tissues at the site of infusion;
- Treatment-related convulsions/seizures;
- Reactions suggesting hypersensitivity.

Important identified risks are defined in Volume 9A as “An identified risk that could impact on the risk-benefit balance of the product or have implications for public health”. According to this definition, the following might reasonably be considered as important identified risks:

- Toxicity due to maternal caffeine ingestion;
- Increase in caffeine plasma levels in premature infants with cholestatic hepatitis;
- Cardiac compromise in infants with pre-existing cardiac disease, including arrhythmias.
- Treatment-related convulsions/seizures.

Potential risks are defined in Volume 9A as “An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed”.

According to this definition, the following might reasonably be considered as potential risks:

- Decrease in weight gain / failure to thrive;

- Caffeine withdrawal;
- Necrotising enterocolitis;
- Medication errors.

Important potential risks are defined in Volume 9A as “An identified risk, potential risk or missing information that could impact on the risk-benefit balance of the product or have implications for public health”.

According to this definition, all of the above risks might reasonably be considered as important potential risks.

Evaluation of the need for a Risk Minimisation plan:

In considering the need for risk minimisation activities, the Applicant pointed out that extemporaneous preparations of caffeine have been used for many years by neonatologists and that the proposed SPC requires initiation to be under the supervision of a physician experienced in neonatal intensive care and that treatment should be administered only in a NICU.

A laminated card highlighting the appropriate dosing regimen, the approved therapeutic indications and the key warning and precautionary statements from the SPC will be made available for neonatal units that may use the product. Further, sales representatives will be specifically briefed on these points and encouraged to emphasise the relevant messages to the relevant HCPs that they meet.

The laminated card is annexed to the RMP.

As a part of the communication of the identified and potential risks, and to inform of the availability of an approved product within the EU, a single presentation that can be used for either infusion or oral/nasogastric administration, the material planned for HCP communication including the laminated card highlighting the appropriate dosing regimen, approved therapeutic indications and key warnings has been in general endorsed by CHMP.

The restricted prescription status should be regarded as an additional risk minimisation activity

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Toxicity due to maternal caffeine ingestion	<ul style="list-style-type: none"> - Routine pharmacovigilance, targeted follow-up; - Study/Registry to monitor normal use and collect ADRs. 	<ul style="list-style-type: none"> - Warnings in Sections 4.4 and 4.6 of SPC that in neonates 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. Breast feeding mothers of neonates treated with caffeine should not ingest caffeine containing foods and beverages

		<p>or medicinal products containing caffeine).</p> <ul style="list-style-type: none"> - Dear Healthcare Professional Communication; - Card for neonatal intensive care units stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and administration only in a neonatal intensive care unit.
Increase in caffeine plasma levels in premature infants with cholestatic hepatitis	<ul style="list-style-type: none"> - Routine pharmacovigilance, targeted follow-up; - Study/Registry to monitor normal use and collect ADRs. 	<ul style="list-style-type: none"> - Warning in Section 4.4 and additional information in Section 5.2 of the SPC concerning use in preterm neonates with impaired hepatic function); - Dear Healthcare Professional Communication; - Card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and administration only in a neonatal intensive care unit.
Increase in caffeine plasma levels in premature infants with clinically relevant renal insufficiency	<ul style="list-style-type: none"> - Routine pharmacovigilance, targeted follow-up; - Study/Registry to monitor normal use and collect ADRs. 	<ul style="list-style-type: none"> - Warning in Section 4.4 and additional information in Section 5.2 of SPC concerning use in preterm neonates with impaired renal function); - Dear Healthcare Professional Communication; - Card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and administration only in a neonatal intensive care unit.
Cardiac disorder in infants with pre-existing cardiac disease, including arrhythmias	<ul style="list-style-type: none"> - Routine pharmacovigilance, targeted follow-up; - Study/Registry to monitor normal use and collect ADRs. 	<ul style="list-style-type: none"> - Warning in Section 4.4 of SPC concerning use in newborns with known cardiovascular disease and the risk of tachyarrhythmias in susceptible individuals); - Labelled in section 4.8 of the SPC - Dear Healthcare Professional Communication; - Card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician

		experienced in neonatal intensive care and administration only in a neonatal intensive care unit.
Treatment-related convulsions / seizures	<ul style="list-style-type: none"> - Routine pharmacovigilance, targeted follow-up; - Study/Registry to monitor normal use and collect ADRs. 	<ul style="list-style-type: none"> - Warning in Section 4.4 of SPC that extreme caution must be exercised if caffeine citrate is used in newborns with seizure disorders); - Labelled in section 4.8 of the SPC - Dear Healthcare Professional Communication; - Card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and administration only in a neonatal intensive care unit.
Decrease in weight gain / failure to thrive	Routine pharmacovigilance, targeted follow-up if ADRs of special interest reported	<ul style="list-style-type: none"> - Labelled in section 4.8 of the SPC - Dear Healthcare Professional Communication; - Card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and administration only in a neonatal intensive care unit.
Caffeine withdrawal	Routine pharmacovigilance, targeted follow-up if ADRs of special interest reported	<ul style="list-style-type: none"> - Dear Healthcare Professional Communication; - Card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and administration only in a neonatal intensive care unit.
Necrotising enterocolitis	Routine pharmacovigilance, targeted follow-up if ADRs of special interest reported	<ul style="list-style-type: none"> - Warning in section 4.4 and 4.8 of SPC that those treated with caffeine citrate should be carefully monitored for the development of necrotising enterocolitis); - Dear Healthcare Professional Communication; - Card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and

		administration only in a neonatal intensive care unit.
Medication errors	Routine pharmacovigilance, targeted follow-up if errors reported.	<ul style="list-style-type: none"> - Content as caffeine citrate/base clearly stated in SPC, package leaflet and label. - Warning in section 4.2 of SPC and labelling about caffeine citrate/base. - Dear Healthcare Professional Communication; - Card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and administration only in a neonatal intensive care unit.
Rare adverse drug reactions	Routine pharmacovigilance.	None
Drug interactions	Routine pharmacovigilance.	<ul style="list-style-type: none"> - Warnings in Sections 4.4 and 4.5 of SPC (Caffeine citrate should not be used with theophylline or doxapram; potential for interactions through cytochrome P450 1A2) - Dear Healthcare Professional Communication; - Additional: card for neonatal ICUs stating precautions; - Restricted prescription status limiting use to physician experienced in neonatal intensive care and administration only in a neonatal intensive care unit.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.4 of this CHMP Assessment Report.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Nymusa (formerly Caffeine Citrate Chiesi) is intended for the “Treatment of primary apnoea of premature newborns”.

Severe apnoea may lead to hypoxaemia and hypotension, and ultimately to brain hypoxia and/or ischemia, and thus negatively affect the newborn’s neurodevelopment and survival. Premature infants with severe and frequent apnoeic episodes require intensive care treatment, supplemental oxygen or intubation and positive pressure ventilation.

AOP treatment aims at avoidance of hypoxaemic/ischaemic brain damage in the newborn. On the other hand, early discontinuation of positive pressure ventilation and oxygen supplementation should be targeted, because of the risks associated with these interventions (e.g. bronchopulmonary dysplasia and retinopathy of prematurity). This is all the more important as apnoea of prematurity is a self-limiting condition; it usually resolves by 36 weeks post-menstrual age and does not predict future episodes of sudden infant death syndrome (SIDS).

Caffeine citrate, in form of magisterial formulations, is widely used as a respiratory stimulant in the treatment of AOP in Europe.

Quality

The quality of Nymusa is considered to be acceptable, when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The toxicological profile of caffeine has been appropriately described in the file in the multiple studies presented in the extensive bibliographic revision performed.

The information included suggests a higher toxicity in caffeine in low ages and as compared to adults. Death due to acute toxicity is related to respiratory arrest and convulsions. The need for monitoring of plasma levels, particularly in the younger prematures is discussed in the clinical section.

Under repeated treatment, target organs of toxicity were the stomach, the kidney, the lung and the reproductive tract. Behavioural changes could be seen in some studies in young animals at therapeutic levels. Consequently section 5.3 of the SPC was amended accordingly.

Growth and ossification retardation is suggested from reproductive toxicity studies, where embryotoxicity was observed, as well as increased toxicity on lactating animals. In addition, decreased male fertility with sperms decrease and testicular changes of treated males was observed, irrespective of age. Also, embryotoxicity was observed in association to treated males. No genotoxic or carcinogenic concerns are raised from studies revised. The limited duration of treatment and the life threatening condition here discussed would not require carcinogenicity studies to be conducted in the absence of a specific concern. Increased propensity for ulcer development in the adult stage, and higher susceptibility to necrotising enterocolitis is also raised from the published information revised.

Efficacy

According to the publication of the main efficacy study (5.3.5.1.1), Nymusa was significantly more effective than placebo in reducing apnoea episodes by at least 50% in six days ($p < 0.05$), and approached statistical significance ($p < 0.10$) in three days. These efficacy findings come from a randomised, double-blind, placebo-controlled trial. The main study has however a number of limitations:

- The primary endpoint was changed in a final amendment of the study protocol
- The imputation method (LOCF) used in the final efficacy analysis introduces substantial bias when estimating the treatment effect. No sensitivity analyses were carried out.
- Only 46.7% of infants in the caffeine group and 32.4% in the placebo group completed 10 days of double-blind therapy; a large number of infants in both groups were switched to open label caffeine citrate and withdrawn..

Efficacy of caffeine citrate treatment in reducing the frequency of apnoea episodes in premature infants was also supported by the results of several small published studies.

The CAP study (5.3.5.1.6) submitted in support of the safety of caffeine citrate is a large RCT regarded by the CHMP as extremely important. It finds a beneficial effect of caffeine citrate in terms of clinically relevant, disability related outcomes. The data from this trial are clearly robust. Of 937 infants assigned to caffeine for whom adequate data at a corrected age of 18-21 months were available, 377 (40.2%) died or survived with a neurodevelopmental disability, compared with 431 of the 932 infants (46.2%) assigned to placebo.

From a regulatory point of view, the major draw-back of the CAP study is that approximately 60% of infants received caffeine for prevention of apnoea and for facilitation of extubation, and, apparently, infants with apnoea secondary to underlying diseases were not excluded.

Following CHMP's request, a post hoc subgroup analysis published by the CAP investigators was submitted by the Applicant. It is reassuring that there was little evidence of a differential treatment effect of caffeine over subgroups defined by the clinical indication for starting the study.

Another important finding of the subgroup analysis was that the size and the direction of the caffeine effect on death or disability differed depending on the degree of respiratory support infants needed at randomisation ($p=0.032$). The OR (95% CI) was 1.32 (0.81 – 2.14) for no support, 0.73 (0.52 – 1.03) for non-invasive support and 0.73 (0.57 – 0.94) for endotracheal tube, respectively. The most severely affected infants, i.e. infants receiving respiratory support, appeared to have more neurodevelopmental benefit from caffeine treatment than unsupported infants. Also, infants who started treatment early had a greater reduction in time on ventilation.

Overall therefore the CHMP considered that the efficacy of Nymusa in reducing apnoea episodes is established.

Safety

The safety data on the acute use of Nymusa are scant. This is mostly due to the lack of complete databases and the need to rely on published reports of clinical trials, which are known to be affected by under- and selective reporting.

The large, CAP study is reassuring from a safety point of view, showing that there is no relevant safety issue for the use of caffeine citrate. Additionally, PMS data from authorised caffeine citrate products reveal no new or unsuspected safety issues.

Duration of treatment in the main placebo-controlled trial was 10 to 12 days. Median duration of caffeine treatment was 37 days in the CAP study. In clinical practice, treatment is usually continued until the child 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, persistence of apnoeas and other clinical considerations; this is now reflected in the SPC. There still remains some uncertainty concerning the optimal duration of treatment; this is addressed in the RMP.

Necrotising enterocolitis was identified as a potential risk of caffeine treatment in the main efficacy study and is addressed as a potential risk in the RMP.

In the non-clinical setting, behavioural deficits were observed in newborn rats in the therapeutic dose range, most likely caused by persistence of upregulated adenosine receptors into adulthood. The clinical relevance of this finding for humans is unclear. There are no data on intellectual, behavioural and somatic development of treated infants in childhood or adulthood.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these

- User consultation

The section intended for healthcare professionals (HCP) of neonatal intensive care units in the proposed Package Leaflet is only an excerpt of the proposed SPC. For safety reasons, HCP should be offered access to the full information on the product; therefore, it was recommended to enclose the complete SPC in the packages. This is in line with the updated *Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, January 2009)*.

Although Nymusa is intended to be administered exclusively at neonatal intensive care units, an additional Package leaflet for lay persons (primarily parents), as proposed, was considered useful to inform them about their baby's medication.

The validated questionnaire consisted of 15 questions concerning the information in the Package Leaflet, 1 question concerning the healthcare professional section and 4 questions concerning the layout and design.

After a pilot phase with 3 subjects, 10 males and 10 females in the age of 21 to 78 years were recruited by an advertisement.

The age range of the selected test population was not considered representative for care-givers (parents) of newborn babies (40% of the subjects were older than 50 years), but, since this population

will receive the Package Leaflet only on special request and just for information, the provided user testing was considered sufficient.

According to the *Guideline on the readability* the result of the user testing is sufficient, since each question was correctly answered (information correctly found and understood) by at least 85% of participants. Due to the outcome of the pilot phase and the test round, it was considered necessary to better emphasize that Caffeine Citrate Chiesi “should only be used in a neonatal intensive care unit”, in the first paragraph of section 3 in the PL: this was the aspect with the lowest readability index in the test.

Risk-benefit assessment

Caffeine is a well-known pharmacological product. Caffeine citrate is currently used in the form of magisterial formulations in the treatment of AOP in Europe (except for France and UK, where formulations of caffeine citrate have been authorised in 1997 and 2008, respectively). The use of a well standardised caffeine citrate formulation could lessen the risk of preparation errors as compared to magisterial preparations.

According to the publication of the main efficacy study (5.3.5.1.1), caffeine citrate was significantly more effective than placebo in reducing apnoea episodes by at least 50% in six days ($p < 0.05$), and approached statistical significance ($p < 0.10$) in three days. These efficacy findings come from a randomised, double-blind, placebo-controlled trial. The main study has however a number of limitations, which were discussed above

The submission of the CAP study (5.3.5.1.6), a large RCT, in support of the safety of caffeine citrate was regarded by the CHMP as extremely important for the assessment of the benefit risk balance. The CAP study showed a beneficial effect of caffeine citrate in terms of clinically relevant, disability related outcomes. The data from this trial are clearly robust. Of 937 infants assigned to caffeine for whom adequate data at a corrected age of 18-21 months were available, 377 (40.2%) died or survived with a neurodevelopmental disability, compared with 431 of the 932 infants (46.2%) assigned to placebo.

From a regulatory point of view, the major draw-back of the CAP study is that infants with apnoea secondary to underlying diseases were not excluded. The post hoc subgroup analysis reassured the CHMP that there was little evidence of a differential treatment effect of caffeine over subgroups defined by the clinical indication for starting the study.

Another important finding of the subgroup analysis was that the most severely affected infants, i.e. infants receiving respiratory support, appeared to have more neurodevelopmental benefit from caffeine treatment than unsupported infants. Also, infants who started treatment early had a greater reduction in time on ventilation.

The target population of premature newborns is particularly fragile. The frequency and severity of known AEs of caffeine citrate is not well characterized. However, as the product will be applied by specialists under intra-hospital conditions of monitoring, the risks associated with these uncertainties seem manageable. Also, the Applicant agreed to install a study/registry which will help to better define the frequency and severity of adverse drug reactions and address areas of remaining uncertainties related to duration of treatment and conditions of use.

Overall therefore the CHMP considered that the efficacy of Nymusa in reducing apnoea episodes is established.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: see as detailed in section 2.3.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Nymusa in the treatment of apnoea of prematurity was favourable and therefore recommended the granting of the marketing authorisation.