Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

caffeine citrate, 20mg/mL, solution for infusion and oral solution (Peyona®)
SMC No. (814/12)

Chiesi Limited

09 August 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

caffeine citrate (Peyona®) is accepted for use within NHS Scotland.

Indication under review: treatment of primary apnoea of premature newborns.

In premature infants with apnoea of prematurity, caffeine citrate significantly reduced apnoeic episodes compared with placebo. A long-term placebo-controlled study demonstrated a reduced risk of disabilities relevant to these infants.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of caffeine citrate (Peyona®). This SMC advice is contingent upon the continuing availability of the PAS or an equivalent or lower list price in NHS Scotland.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

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Indication

Treatment of primary apnoea of premature newborns.

Dosing Information

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

The recommended dose regimen in previously untreated infants is a loading dose of caffeine citrate 20mg/kg body weight (equivalent to 10mg/kg caffeine base) administered by slow intravenous (iv) infusion over 30 minutes, using a syringe infusion pump or other metered infusion device.

After an interval of 24 hours, maintenance doses of 5mg/kg body weight (equivalent to 2.5mg/kg caffeine base) may be administered by slow intravenous infusion over 10 minutes every 24 hours. Alternatively, maintenance doses of 5mg/kg body weight (equivalent to 2.5mg/kg caffeine base) may be administered by oral administration, such as through a nasogastric tube every 24 hours.

Product availability date

May 2012. Designated orphan status by European Medicines Agency in 2003.

Summary of evidence on comparative efficacy

Apnoea of prematurity is defined as a pause in breathing in pre-term infants of at least 20 seconds, or as a brief episode if associated with cyanosis, pallor or bradycardia. Prolonged episodes of apnoea can lead to hypoxia and bradycardia which is thought to be harmful to the developing brain or cause dysfunction of the gut or other organs. Frequent apnoeic episodes can lead to respiratory failure that may require intubation and the use of intermittent positive pressure ventilation. Caffeine citrate is a methylxanthine that acts as a non-specific adenosine receptor antagonist to stimulate the central nervous system, increasing both tidal volume and frequency of ventilation.

A placebo-controlled, double-blind study assessed the efficacy of caffeine in reducing apnoeic episodes.[1] The study recruited preterm infants, post-conceptual age between 28 and 32 weeks, more than 24 hours after birth who had at least six episodes of apnoea (>20s duration) within a 24-hour period. The infants were randomised to caffeine citrate 20mg/mL (20mg/kg intravenous [iv] infusion loading dose over 30 minutes followed by daily maintenance dose of 5mg/kg given iv or orally), n=45, or placebo, n=39, for up to 12 days. Open-label rescue with caffeine citrate was available for infants not responding to treatment.

The primary outcome was “success”, defined as a ≥50% reduction in apnoeic episodes from baseline or as elimination of apnoea, and this was recorded on a daily basis up to 10 days. Eighty-two infants were included in the efficacy analysis (45 in the caffeine group and 37 in the placebo group). Significantly more caffeine- than placebo-treated infants had an aggregated 7 to 10 days of at least a 50% reduction in apnoeic episodes (69% versus 43%, respectively) and of elimination of apnoeic episodes (24% versus 0, respectively). In the caffeine group, 31% (14/45) of patients were transferred to open-label caffeine citrate, compared with 43% (16/37) of patients in the placebo group.

The Caffeine for Apnoea of Prematurity (CAP) study was a multi-centre randomised, placebo-controlled study that assessed the short- and long-term efficacy and safety of caffeine citrate therapy.[2,3] Eligible infants had a very low birth weight of 500 to 1,250g and were considered candidates for methylxanthine therapy during the first 10 days of life for the following reasons: to prevent apnoea, to treat apnoea or to facilitate extubation. A total of 2,006 patients were randomised in a 1:1 ratio to caffeine citrate (loading dose of 20mg/kg iv, followed by a maintenance dose of 5 to 10mg/kg/day orally or iv) or placebo, with stratification for study centre.

The primary endpoint was a composite of death or survival with severe disability (cerebral palsy, cognitive delay, deafness or blindness) at a corrected age of 18 to 21 months. This composite endpoint was recorded in 40% (377/937) of caffeine-treated patients and 46% (431/932) of placebo-treated patients: odds ratio adjusted for study centre of 0.77 (95% confidence interval [CI]: 0.64 to 0.93). In terms of the components of the composite, caffeine compared with placebo significantly reduced the incidence of cerebral palsy (4.4% versus 7.3%, respectively) and cognitive delay (34% versus 38%, respectively). There were no significant differences between treatment groups in the incidence of death, hearing loss or blindness.

Pre-specified short-term secondary outcomes assessed up to first discharge home included: death, bronchopulmonary dysplasia, ultrasonographic signs of brain injury, necrotising enterocolitis, and retinopathy of prematurity. There were no significant differences between the groups for any of these outcomes except the incidence of bronchopulmonary dysplasia; 36% (350/963) in the caffeine group and 47% (447/954) in the placebo group.

A post-hoc sub-group analysis based on indication was conducted on the primary outcome at 18 to 21 months corrected age. In infants treated for apnoea, death or disability was recorded in 141/400 caffeine patients compared with 153/367 placebo patients, an estimated odds ratio of 0.76 (95% CI: 0.57 to 1.02). Tests for heterogeneity between the sub-groups revealed no evidence of a statistically important sub-group effect.[4]

A follow-up study assessed children who had participated in the CAP study at a corrected age of five years.[5] The primary outcome was a composite of death before a corrected age of five years, or survival with at least one of the following: motor impairment, cognitive impairment, behaviour problems, poor general health, severe hearing loss, and bilateral blindness. This was recorded in 21% (176/833) of patients in the caffeine group and in 25% (200/807) of patients in the placebo group, a non-significant adjusted odds ratio of 0.82 (95% CI: 0.65 to 1.03).

Summary of evidence on comparative safety

Very limited data are available on the comparative safety of caffeine in apnoea of prematurity. Refer to the summary of product characteristics for details of adverse effects.

In the short-term placebo-controlled study the most frequently reported adverse events were: constipation (caffeine citrate [17%] versus placebo [21%]) and rash (8.7% versus 7.7%, respectively). Six patients experienced necrotising enterocolitis following discontinuation of study drug (caffeine citrate n=4, placebo n=2), in one caffeine patient this was thought to be possibly related to caffeine citrate.[1]

In the CAP study, a small proportion of patients (37/2,006) had doses withheld or reduced due to symptoms and signs suggestive of caffeine-induced toxicity (caffeine n=23, placebo n=14). The effect of caffeine on growth was modest and transient. During the first three weeks after randomisation,

infants in the caffeine group gained less weight than infants in the placebo group, with no significant difference at four and six weeks. At 18 to 21 months corrected age, there were no differences between the groups for the mean and median percentiles for the three growth measurements: height, weight and head circumference.[2,3]

A Cochrane review has evaluated caffeine versus theophylline for apnoea in preterm infants and included results of three studies involving a total of 66 infants.[6] Adverse effects, as indicated by tachycardia or feed intolerance leading to change in dosing, were lower in the caffeine group (relative risk 0.17, 95% CI: 0.04 to 0.72). This was consistent across the three studies.

Summary of clinical effectiveness issues

The European Medicines Agency (EMA) awarded orphan status to caffeine citrate 20mg/mL in 2003. However, a non-proprietary caffeine citrate product (10mg/mL) has been marketed in the UK since 2008 and accepted by SMC for use in NHS Scotland. Clinical experts consulted by SMC advised that an unlicensed oral caffeine citrate preparation is also currently used in neonatal units throughout Scotland. Peyona® was granted a marketing authorisation from the EMA based on a bibliographic application, using the same pivotal studies that supported the non-proprietary caffeine citrate product.

The primary outcomes of the two studies were direct health outcomes. A greater proportion of infants treated with caffeine citrate compared with placebo had ≥50% reduction in the number of apnoea episodes in seven days out of the first ten of treatment.[1] In the CAP study, neonatal caffeine citrate therapy was associated with an improved rate of survival without disability at a corrected age of 18 to 21 months, compared with placebo.[3] Results of the 5-year follow-up study provide reassurance about the long-term safety of using caffeine citrate in the neonatal period.[5]

The CAP study was well designed and conducted. However, a limitation was that it recruited infants considered eligible for caffeine therapy for several indications: treatment of apnoea, prevention of apnoea, and facilitation of extubation. In the sub-group of infants receiving therapy for the licensed indication (treatment of apnoea, approximately 40% of the study population), post-hoc analysis estimated the odds ratio of survival without disability at a corrected age of 18 to 21 months was of a similar magnitude to the full study population.

The EMA highlighted limitations to the short-term outcome study: the primary outcome reported in the published paper was not selected *a priori,* and the result of the outcome used to estimate sample size not reported at all; there was a high drop-out rate in both groups and the imputation method, last observation carried forward, introduced substantial bias; and the choice of statistical test for the primary outcome was considered non-optimal.[7]

There may be service implications related to the safe introduction of Peyona®. A safety concern relates to the prescribing, supply and administration of caffeine products, specifically the risk of confusing dosage of caffeine (as the base) versus the citrate salt. Caffeine citrate 2mg is equivalent to caffeine (as base) 1mg. The British National Formulary for Children (2013) notes that all preparations will be required to be labelled as caffeine citrate, and strongly recommends that they should be prescribed in terms of caffeine citrate.[8] The Medicines and Healthcare products Regulatory Authority highlighted the risk of confusion and error with the availability of different strengths of caffeine citrate in the UK and has advised that all products should be prescribed as caffeine citrate.[9,10]

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing caffeine citrate 20mg/mL (Peyona®) with caffeine citrate 10mg/mL (non-proprietary) for treatment of primary apnoea of premature newborns. The analysis was carried out over a one-year time horizon.

The comparator within the analysis contains the same active ingredient, and has the same route of administration. The difference between the preparations of the medicines is the concentration. The comparator is appropriate.

The health outcomes of the two medicines are assumed to be the same, owing to the fact that the two medicines have the same active ingredient.

The results of the analysis are based on the findings of The Scottish Neonatal and Paediatric Pharmacist Group's three-week survey of all neonatal centres in Scotland. The survey recorded the total number of caffeine citrate doses administered in the neonatal centres over a three week period, with the three week data then extrapolated to estimate the number of doses per year. The number of ampoules needed to meet the dose requirements was then calculated for both caffeine citrate 20mg/mL and caffeine citrate 10mg/mL. Owing to the different concentrations of the medicines, the number of ampoules required of caffeine citrate 20mg/mL was less than for caffeine citrate 10mg/mL. The number of ampoules required was then combined with the relative prices of the medicines to estimate an average cost per patient. The costs were based on whole ampoules as the analysis assumed no ampoule sharing. No other medicine and resource use costs were included in the analysis.

A Patient Access Scheme (PAS) has been submitted by the company and assessed by the Patient Access Scheme Assessment Group as acceptable for implementation in NHS Scotland. The submitted PAS offers a discount on the list price of the medicine.

The average cost of the comparator caffeine citrate 10mg/mL is £180.56 per patient. Without the PAS, the average cost of caffeine citrate 20mg/mL is £448.50 per patient.

There were no weaknesses with the economic analysis that may have altered the overall results of the evaluation.

Given the results with the PAS, the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants, endorsed by the European Association of Perinatal Medicine, were updated and published in 2013.[11] The guideline recommends that caffeine should be used in babies with apnoea. For off-label

indications, the guideline also recommends caffeine is used to facilitate weaning from mechanical ventilation and to consider it for all babies at high risk of needing mechanical ventilation who are managed on non-invasive respiratory support.

Additional information: comparators

Caffeine citrate 10mg/mL solution for injection and oral solution.

Cost of relevant comparators

Drug	Dose Regimen	Cost per week (£)		
		Weight = 1kg	Weight = 2kg	Weight = 3kg
caffeine citrate 20mg/mL (Peyona®)	**Loading dose: 20mg/kg Daily maintenance: 5 to 10mg/kg**	**121**	**138 for first week, then 121 thereafter.**	**155 for first week, then 121 to 242 thereafter.**
caffeine citrate 10mg/mL (non-proprietary)	Loading dose: 20mg/kg Daily maintenance: 5 to 10mg/kg	39 for first week, then 34 thereafter	49 for first week, then 34 to 68 thereafter	59 for first week, then 69 to 103 thereafter.

Costs from BNF for Children (www.bnf.org) on 27 May 2013. Cost calculations do not account for dose alterations in line with weight change.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 608 in year 1 and 627 in year 5, with an estimated uptake rate of 100% in all 5 years.

Without PAS: The gross impact on the medicines budget was estimated to be £273k in year 1 and £281k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £163k in year 1 and £168k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1) Erenberg A, Leff RD, Haack DG et al. Caffeine citrate for the treatment of apnea of prematurity: a double-blind placebo-controlled study. Pharmacotherapy 2000; 20: 644-52.

2) Schmidt B, Roberts RS, Davis P et al. Caffeine for apnea of prematurity. New England Journal of Medicine 2006; 354: 2112-21.

3) Schmidt B, Roberts RS, Davis P et al. Long-term effects of caffeine therapy for apnea of prematurity. New England Journal of Medicine 2007; 357: 1893-902.

4) Davis PG, Schmidt B, Roberts RS et al. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. Journal of Pediatrics 2010; 156: 382-7

5) Schmidt B, Anderson PJ, Doyle LW et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012; 307: 275-82.

6) Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD000273. DOI: 10.1002/14651858.CD000273.pub2.

7) European Medicines Agency. CHMP Assessment Report – Nymusa. Available from www.ema.europa.eu [April 2009]

8) British National Formulary for Children. Chapter 3.5.1 Respiratory stimulants. Available from www.bnf.org [Accessed 20 May 2013]

9) Medicines and Healthcare products Regulatory Agency. Drug Safety Update (2012); 5(11): A2. Available from www.mhra.gov.uk

10) Medicines and Healthcare products Regulatory Agency. Direct Healthcare Professional Communication. Important name change: caffeine for treatment of apnoea on prematurity – all available products to be known and expressed as caffeine citrate. 1 August 2013.

11) Sweet DG, Carnielli V, Greisen G et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants – 2013 update. Neonatology 2013; 103: 353-368.

This assessment is based on data submitted by the applicant company up to and including 12 July 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration.. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed

Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.