EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Blectifor

International non-proprietary name: caffeine citrate

Procedure No. EMEA/H/C/004100

Note

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

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List of abbreviations

AP or AOP	Apnoea of prematurity
API	Active Pharmaceutical Ingredient
ARR	adjusted risk ratio
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
BBB	blood-brain barrier
BPD	bronchopulmonary dysplasia
CEP	Certificate of Suitability of the EP
CI	confidence interval
CNS	central nervous system
CoA	Certificate of Analysis
CPAP	continuous positive airway pressure
CVS	cardiovascular system
ET	endotracheal
FPM	Finished Product Manufacturer
GA	gestational age
IPC	In-process control
IVH	intraventricular haemorrhage
LT	Less than
MA	Marketing Authorization
MAH	Marketing Authorisation Holder
NEC	necrotising enterocolitis
NMT	Not more than
NNT	number needed to treat
OR	odds ratio
PCA	post-conceptional age
PD	pharmacodynamic
PDA	patent ductus arteriosus
Ph.Eur.	European Pharmacopoeia
PK	pharmacokinetic

PMA	post-menstrual age
PNA	post-natal age
PPV	positive pressure ventilation
RCT	randomised controlled trial
RDS	respiratory distress syndrome (= hyaline membrane disease of newborn)
ROP	retinopathy of prematurity
RS	respiratory system
SD	standard deviation
VLBW	very low birthweight
WFI	Water for Injections

1. Recommendations

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Blectifor 10 mg/ml solution for injection and oral solution, an orphan medicinal product in prevention of bronchopulmonary dysplasia in preterm neonates is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (Section VI)

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Legal basis

The applicant has not addressed all of the requirements for demonstration of the well-established use of caffeine (citrate) in BPD. Specifically, the systematic and documented use in the EU for the intended indication has not been sufficiently addressed so far. The applicant´s strategy for study search and inclusion in their qualitative synthesis should be explained and coherence of results between relevant submitted clinical trials should be discussed.

Module 1 (Quality)

Information on GMP compliance is missing for Southmeads Hospital, Bristol, UK BS10 5NB (site not presented in Module 1). According to the information provided in dossier section 3.2.P.5.3 this site is responsible for stability testing of the finished product. A GMP certificate covering this function should be provided.

Clinical

Based on remaining uncertainties pertaining to the definition of bronchopulmonary dysplasia, the underlying pathomechanisms and risk factors for its development, the role of caffeine citrate in prevention of BPD is not clear at the moment. The present broad wording of the indication is not supported by the compiled literature and the target population needs to be further characterised. Based on the proposed endpoint definition no definite conclusion on the significance of the caffeine effect in BPD prevention can be drawn.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

No GMP inspection is requested.

GCP inspection(s)

GCP compliance of the published clinical data discussed in this assessment report cannot be claimed.

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 submitted

clinical studies were approved by local ethics committees; GCP compliance is not declared, however. This limitation is not considered a major issue for a full bibliographic application.

New active Substance status

This is a full bibliographical application in accordance with Article 10a of Directive 2001/83/EC, a “well established use” application. Based on the review of the data the CHMP considers that the active substance caffeine citrate contained in the medicinal product Blectifor 10 mg/ml solution for injection and oral solution is not to be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication for Blectifor 10mg/ml Solution for Injection and Oral Solution is prevention of bronchopulmonary dysplasia (BPD) in preterm neonates. The applicant defines BPD as “the clinical need for continuing oxygen therapy at a postmenstrual age of 36 weeks” and states that no clinical paper or review article included in this application used any other definition of BPD, except as an addition for comparison.

Several BPD definitions have been proposed and investigated since the 1980s. The progression is nicely outlined in a key publication by Maitre et al., 2015 (not provided by the Applicant) including attempts to differentiate severity levels/grades of BPD.

The apparently mostly applied definition of BPD, i.e. ‘use of supplemental oxygen at 36 weeks postmenstrual age’ bases on a seminal publication by Shennan et al., 1988. It has been fundamentally criticized for being subjective, not formally addressing the actual need for oxygen support, not further specifying ‘oxygen supply’ and for its moderate performance in terms of predictive properties for long-term outcomes. It is also worth noting that this definition stems from a time where intensive care differed markedly from nowadays’ standards. Inclusion of physiologic criteria (i.e. weaning attempts, saturation targets) to determine the need for oxygen and to improve the BPD definition has been stipulated, but such have not been used frequently, at least in caffeine trials.

In 1979 the US National Institute for Health proposed a diagnosis defined by continued oxygen for first 28 days plus compatible clinical and X-ray changes. In 2001 the National Institute for Child Health and Human Development produced a consensus statement which suggested modifying this to oxygen dependency for ≥28 days, specifying oxygen concentration requirements at 36 weeks PMA to give an indication of severity of lung damage. BPD can be classified as mild, moderate or severe according to the degree of respiratory support. "Mild" implies that oxygen saturation may be maintained in room air. "Moderate" cases require oxygen supplements at <30%. “Severe" cases (representing no more than 7% of children with BPD (Papoff, Cerasaro et al. 2012)) require oxygen supplements at >30%, or actual ventilation. For infants born after 32 weeks gestation (for whom a 28 day period takes them past 36weeks), the same “mild”, “moderate”, and “severe definitions” are used, but applied at day 56 or discharge from NNU, whichever comes sooner. This situation however is rarely applicable clinically, because BPD is now very uncommon in this age group.

Another, more physiological, definition proposed in 2004 by Walsh was a "failure to maintain a saturation value greater than 90% when challenged with 21% oxygen at 36 weeks PMA." (Walsh, Yao et al. 2004). Use of this definition reduces variation in BPD rates as a result of interunit differences in oxygen supplementation policies.

2.1.2. Epidemiology

According to the conclusion of the COMP (Opinion dated 05/06/2014) the prevalence of "patients at risk of bronchopulmonary dysplasia" is between 1 and 3 people per 10000 individuals in the EU (EMA/COMP/89532/2014).

Depending on the definition used, the incidence of BPD at week 36 varies substantially (e.g. 25% vs. 35% for physiologic vs. clinical definition, respectively, in Walsh et al., 2014; 40.2%, 58.6% and 32% for clinical/NIH/physiological definition, respectively, in Pondexter et al. 2015) and the magnitude of difference between incidence rates has been likened to the reported effect sizes for putative BPD-preventive agents over placebo (e.g., ~10% reduction in BPD incidence for caffeine (citrate) compared to placebo in the CAP trial). This issue bears importance when it comes to the synthesis of results across trials/publications, for judging the external validity of individual trial results and the actual meaningfulness of the observed effect size.

Also, reliable background rates seem hard to determine as incidence rates of BPD can depend on many variables, such as study centre and respective NICU (ventilation) protocols or concomitant medication with e.g. corticosteroids or Vitamin A products.

The vast majority of cases seem to occur in infants who weigh less than 1500g at birth and who are born at a gestational age of less than 32 weeks, i.e. the more severely premature infant. This represents less than 2% of all live births (www.europeristat.com (Valls-i-Soler, Pijoan et al. 2008)), approximately 53,000 births per year in Europe. The majority of these children will require respiratory support within the first few weeks of life. Very few cases occur outside this "at risk" population; within this population, the incidence of BPD is usually described as being between 20 and 40%.

2.1.3. Aetiology and pathogenesis

The key aetiological factor in BPD is exposure of the immature lung to the extrauterine environment, with oxygen toxicity and pneumatic ventilator trauma adversely affecting alveolar development. The degree of prematurity, the dose and duration of oxygen supplementation, and the duration and type of ventilation have been linked to the risk of developing the disease. Inflammation seems to be an important process in the pathogenesis of BPD. Oxygen toxicity as well as volume/pressure-related ventilation damage are considered key factors in causing inflammation and lung damage. As inflammation continues, fibrosis in interstitial tissues takes place, resulting in scarring of the lungs.

The genesis of BPD has been described as multifactorial by several authors. The iatrogenic noxes ventilation support and/or oxygen supply have nonetheless been described as main drivers for BPD development so far. Any effect of caffeine (citrate) in terms of BPD prevention is therefore likely indirect, i.e. mediated via reducing the need for, duration or invasiveness of mechanical ventilation, positive pressure ventilation or oxygen support during the first weeks of life.

2.1.4. Clinical presentation, diagnosis prognosis

BPD is a disease of the modern era of neonatal intensive care medicine, being first described in 1967 (Northway, Rosan et al. 1967), soon after positive pressure ventilation of premature infants had entered clinical practice. Because there are no diagnostic tests which are specific for BPD, and because lung biopsy is too invasive to be feasible in this age group, BPD in clinical practice is poorly characterised pathologically. BPD is only rarely fatal in the modern era of neonatal medicine and so autopsy findings have only been reported in a few cases. Hence, the clinical features remain the basis for diagnosis.

The prognosis of BPD is variable, and has been reported to depend on disease severity at diagnosis. For the individual patient, the pathological changes in vessel and alveolar formation are permanent and irreversible once they have occurred. However, the respiratory function of the child improves as they get older, due to the natural genesis of more alveoli throughout the first few years of life. Most patients recover to become independent of oxygen supplements within weeks; few, very severe cases may continue to need oxygen supplements in the months after birth.

It has been shown that after discharge home from the neonatal unit children, who have had BPD, have an increased risk of readmission to hospital with respiratory problems. Beyond infancy, symptoms improve but studies show that there is still more coughing and wheezing than controls, with increased asthma medication use at school. Pulmonary function tests, even in asymptomatic individuals, show a higher rate of abnormality: reduced airflow on spirometry, impaired gas diffusion capacity (Schmalisch, Wilitzki et al. 2012, Chang, Assaf et al. 2015) due to lack of respiratory membrane area and reduced pulmonary capillary density, increased airway responsiveness. CT scans are abnormal in 80%, showing linear opacities, air trapping and a tendency to emphysema. Overall though, reduction in aerobic capacity is slight.

It is not known whether these abnormalities will cause problems in old age, when respiratory reserve naturally declines. This is because BPD is a disease of the modern intensive care era, having been described less than 50 years ago; nobody who had BPD in infancy is currently old enough to demonstrate old age-related changes.

2.1.5. Management

As outlined above, BPD has been related to long-term pulmonary sequelae such as lower-respiratory tract infections, reduced lung-function, hyper responsiveness, etc. (Eber & Zach 2001) and prevention of such late morbidities is considered an important therapeutic goal. There is no authorised product available in the community to prevent (or treat) BPD and an unmet medical need can thus be assumed.

As already described above, the pathological changes of BPD are largely irreversible once they have occurred. Treatment of BPD is confined to mitigation of damage, and trying to minimise further damage or infection while waiting for new alveoli to develop during the first months of postnatal life (Gien and Kinsella 2011, Kair, Leonard et al. 2012, Papoff, Cerasaro et al. 2012). The indication considered in this application is prevention, not treatment, of BPD. Treatment of established BPD is currently limited to ventilation and/or oxygen supplementation until the child has grown sufficiently to develop more alveoli that can take over the function of the damaged lung, thus treatments which might themselves aggravate the severity of the disease.

Respiratory support strategies minimising the duration of positive pressure ventilation *(*PPV), such as use of continuous positive airway pressure (CPAP) ventilation, or high-frequency ventilation, where

possible, or which lessen the concentration of inspired oxygen required, are considered helpful (Clark, Gerstmann et al. 2001, Ambalavanan and Carlo 2004, Gien and Kinsella 2011, Kugelman and Durand 2011, Greenough and Ahmed 2012).

Non-caffeine (citrate) drug therapies for the prevention of BPD are limited and none are approved in the EU. Vitamin A treatment, used to prevent deficiency in preterm infants, was found to reduce the incidence of BPD by approximately 10% (Schmidt, Roberts et al. 2008, Kugelman and Durand 2011). Other drugs tested in the context of BPD prevention include steroids and surfactant, among others with varying results reported (e.g. reviewed in Beam et al., 2014).

2.2. About the product

Blectifor is a solution for IV injection or oral administration containing caffeine citrate. Caffeine is a methylxanthine, and in therapeutic concentrations acts as a nonspecific inhibitor of adenosine receptors. The role of caffeine citrate pharmacology and its mode of action in the proposed preventive setting are not entirely clear.

It belongs to the pharmacotherapeutic group of psychoanaleptics and is a xanthine derivative; the ATC code is N06BC01.

Blectifor is intended for the prevention of bronchopulmonary dysplasia in preterm neonates. The recommended dose regimen is a loading dose of 20 mg caffeine citrate per kilogram body weight and, after an interval of 24 hours, maintenance doses of 5 mg per kilogram body weight may be administered every 24 hours until no further respiratory support is required.

2.3. The development programme/compliance with CHMP guidance/scientific advice

This application for marketing authorisation is submitted as full bibliographical application in accordance with Article 10a of Directive 2001/83/EC as amended relying on a “well established use” of caffeine citrate in the EU for more than 10 years. Evidence needs to be provided that caffeine citrate has been extensively used for more than a decade and has recognised efficacy and an acceptable safety in the proposed indication (see section 2.5).

As this is a full bibliographic application the risk/benefit profile is determined on the basis of historical studies with caffeine citrate and available literature; no clinical data have been generated for this MAA by the Applicant.

No formal scientific advice was sought by the applicant from the CHMP.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Drug Substance:

GMP compliance is sufficiently confirmed for the active substance manufacturer. Respective QP declarations are provided from the proposed batch release sites. Moreover, EudraGMP reference (certificate issued by the German authority) is provided.

Drug Product:

GMP compliance is sufficiently confirmed for one of the proposed batch release sites. EudraGMP reference is provided in the application form for following certificates, covering all activities proposed to be performed by this company:
(certificate issued by the Belgian authority) and
(certificate issued by the Belgian authority)

However, the provided information on GMP compliance is not sufficient for following sites:

- One of the proposed batch release sites:
  EudraGMP reference is provided (certificate issued by the British authority). However, this GMP certificate does not cover all proposed functions of the site (manufacture of sterile drug product including terminal sterilisation by moist heat, primary- and secondary packaging, quality control: chemical-physical, microbiological non-sterility and batch release). A respectively updated GMP certificate should be provided.
- One of the proposed sites for quality control testing:
  EudraGMP reference (certificated issued by the British authority) is provided. However, this GMP certificate is only valid for veterinary medicinal products. It can be seen from EudraGMP that there is a respective GMP certificate valid for human medicinal products, issued by the British authority). This certificate covers the proposed function of this site (quality control: sterility) However, the EudraGMP reference in the application form should be updated respectively.

Moreover, according to the information provided in dossier another site is responsible for stability testing of the finished product. Accordingly a GMP certificate covering this function should be provided. Moreover, this site should be included in application form section 2.5.1.2.

GLP

Due to the bibliographic nature of this application and especially because of the date of the examinations cited GLP aspects are not covered according to the current standards. However, due to the broad data basis and detailed knowledge provided this is not considered to be of concern for the purposes of this application.

GCP

GCP compliance of the published clinical data discussed in this assessment report cannot be claimed.

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 submitted clinical studies were approved by local ethics committees, GCP compliance is not declared, however. This limitation is not considered a major issue for a full bibliographic application.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

The application for Marketing Authorisation for Blectifor 10mg/ml Solution for Injection and Oral Solution is submitted using the Centralised Procedure under article 3 (1) indent 4 of Regulation (EC) No.726/2004, pursuant to the “mandatory scope” foreseen for Orphan Designated Medicinal Products.

The application is submitted as full bibliographical application in accordance with Article 10a of Directive 2001/83/EC as amended relying on a “well established use” of caffeine citrate in the EU for more than 10 years.

In accordance with the provisions of Annex I of Directive 2001/83/EC as amended, evidence is needed that caffeine citrate has been extensively used for more than a decade and has recognised efficacy and an acceptable safety in the proposed indication.

There is no formal CHMP guidance for bibliographical applications, however, requirements and instructions are outlined in the respective legal text of Article 10a of Directive 2001/83/EC, the Notice to applicants Vol 2A and also in the "European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure" (EMA/339324/2007, 1 December 2016) in section 1.6.3 (excerpt):

According to Article 10a of Directive 2001/83/EC, as amended it is possible to replace results of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product have been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply.

The following criteria for the demonstration of such well-established use should be taken into account:

• the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods;

• the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments;

For such applications, the provisions of the Annex I to Directive 2001/83/EC apply in like manner. They are considered as full and independent applications. Applicants should submit Modules 1, 2 and 3 as described in Part I of Annex I to Directive 2001/83/EC. For Modules 4 and 5, a detailed scientific bibliography shall address all required pre-clinical and clinical characteristics, and should be summarised in Module 2. As with any other full application, if parts of the dossier are incomplete, particular attention must be paid to justify such absences in the non-clinical/clinical overviews.

As outlined in Notice to Applicants Vol 2A, for an application based on Article 10a, well-established use needs to be demonstrated based on: data documenting at least 10 years of systematic and documented use in the EU for the intended indication, scientific interest as indicated by published scientific literature on the concerned topic as well as coherence of results. It is uncertain whether these criteria can be regarded fulfilled for the data supporting the claimed indication.

This application includes approx. 140 literature references dated 1967-2016 addressing the pharmacological and clinical properties of caffeine, mostly in preterm neonates and many in the context of BPD prevention. Several systematic reviews on the topic have been published recently which confirms the scientific interest in the concerned topic. The quantitative and systematic use of caffeine citrate in the claimed indication of 'BPD prevention' in the EU has not been addressed, however, and this needs to be done (e.g. by using data from NICU registries). The coherence of results between identified clinical trials was not addressed sufficiently by the applicant, as discussed in further detail below.

Further information is requested before well-established use (as defined by the above criteria) of caffeine citrate in the prevention of BPD can be concluded.

- Accelerated procedure

N/A

- Conditional approval

N/A

- Exceptional circumstances

N/A

- Biosimilar application

N/A

- 1 year data exclusivity

N/A

- Significance of paediatric studies

N/A

3. Scientific overview and discussion

This is a full bibliographical application relying on the demonstration of well-established use of caffeine citrate in the targeted indication “prevention of BPD in preterm neonates”; no new non- clinical or clinical data have been generated by the applicant.

Blectifor is a solution for injection or oral administration containing caffeine citrate. The proposed indication is prevention of bronchopulmonary dysplasia (BPD). BPD can develop in preterm neonates as a consequence of exposure of the immature lung to the extra-uterine environment, with oxygen toxicity and pneumatic ventilator trauma adversely affecting alveolar development.

Caffeine is a methylxanthine, in therapeutic concentrations it acts as a nonspecific inhibitor of adenosine receptors. Several caffeine effects are assumed to be beneficial in the targeted indication, such as central stimulation of respiration in the brainstem on the one hand and multiple effects on the cellular level in the lung on the other hand. Anti-oxidant, anti-inflammatory and anti-fibrotic effects have also been suggested in some (non-) clinical studies.

3.1. Quality aspects

3.1.1. Introduction

A valid CEP for Caffeine has been provided for the active substance manufacturer. Additionally the applicant has provided information on control of the drug substance at the site of the drug product manufacturer in section 3.2.S. of the dossier. Full information in CTD format is provided for both proposed drug product manufacturers (FPMs). An overview on the assessment of the provided information is provided below.

3.1.2. Active Substance

Conflicting information on the nature of the API (Caffeine or Caffeine Citrate – which could potentially form *in situ* during the drug product manufacturing process) is provided by the MAH. In the application form it is stated that Caffeine Citrate is the API. Module 3 largely refers to Caffeine as API. Yet there are also sections of Module 3 which refer to Caffeine Citrate or even to both forms. The nature of the API (Caffeine or Caffeine Citrate) as actually present in the finished product should be discussed and supported by data, if not otherwise justified.
Anyway, a valid CEP (R1-CEP 1998-022) has been provided for Caffeine, which confirms that the quality of the substance is suitably controlled by the current versions of the monograph Caffeine no. 267 of the Ph. Eur., current edition including supplements. No additional controls are mentioned in the CEP. A retest period of 60 months is stated on the CEP, if the drug substance is stored in a container consisting of fibre drums or big bags lined with a low-density polyethylene bag. The applicant does not provide additional stability data.

Control of the drug substance at the site of the drug product manufacturer:
The provided drug substance specification complies with the Ph.Eur. monograph for Caffeine. Nevertheless several concerns have been identified: confirmation is requested that the presented drug substance specification is the consolidated version and is followed by both proposed FPMs; a test for bacterial endotoxins should be included; the limit for microbiological quality should be revised in line with Ph.Eur. 5.1.4; the acceptance criterion for parameter appearance is not in line with the Ph.Eur. monograph; acceptance criteria for specified parameter odour are missing the in-house methods for determination of particle size and chloroform content should be referenced; reference should be made that the results for parameter assay (by HPLC) should be expressed with respect to dried substance and information on reduced testing on receipt by the FPM should be eliminated from the dossier.

The applied analytical methods are basically those of the Ph.Eur. monograph for Caffeine. However, for determination of related substances a thin-layer chromatography method is described in the dossier whereas a HPLC method is described in the specification and Ph.Eur. 0267. Moreover, method descriptions for parameters assay (by HPLC), particle size, chloroform content and microbiological quality are missing. Most analytical procedures are performed according to Ph.Eur, thus it is not necessary to provide validation data on these methods. However, method validation data are requested for the analytical methods for determination of assay (by HPLC), particle size and chloroform content, which are assumed to be in-house methods.

In-house CoAs from one of the FPMs are provided for two drug substance batches. However, the specification indicated on the CoAs is not identical with the drug substance specification presented in dossier section 3.2.S.4.1. Moreover, the specification has been requested to be modified. Information on the reference standards used by the FPM is missing.
Drug substance characteristics relevant for the drug product:
Caffeine is sparingly soluble in water, freely soluble in boiling water and slightly soluble in ethanol (96 per cent). Its solubility is increased in the presence of citrates. Moreover, an acid pH increases its stability.

3.1.3. Finished Medicinal Product

Two drug product manufacturers are proposed. Stability data from both drug product manufacturers are provided. Confirmation that those parts of the full dossier which are only provided for one of the FPMs are also applicable for the other is requested.

Description of the product and Pharmaceutical Development

The finished product is a clear, colourless, sterile, aqueous solution and is intended to be administered intravenously (solution for injection) or orally (oral solution). However, considering the method of administration described in section 4.2 of the SmPC the dosage form should rather be “Solution for Infusion” and “Oral Solution”.

Composition:
Caffeine (API), Citric acid (for solubilisation of the API and pH adjustment), sodium chloride (to get an isotonic solution), WFI (solvent), diluted hydrochloric acid (q.s., for pH adjustment) and sodium hydroxide (q.s., for pH adjustment).
Qualitative and quantitative information on the used API and excipients are provided. However, the amounts of API and excipients should be described in mg/ml or mg/ampoule instead of % w/v. Moreover, Caffeine is referenced as active ingredient. This should be justified or changed in line with the response on the issue regarding the actual form of the API in the drug product. Further on, in order to be in line with the strength of the product contained in its name, it should be further explained in section P.1 that the 5 mg/ml of caffeine contained in the formulation is equivalent to 10 mg/ml of caffeine citrate. Finally, information on the used type of Citric acid (monohydrate or anhydrous) should be provided.

The chosen components are commonly used in comparable products. This can be seen from the British Pharmacopoeia which defines “Caffeine Citrate Injection” as a sterile solution of Caffeine citrate prepared by the interaction of Caffeine and Citric Acid Monohydrate in Water for Injections. Sodium chloride which is not mentioned in the BP is used to achieve an isotonic product, which is also common for injectable dose forms. HCL and Sodium Hydroxide are only used for pH adjustment, which is acceptable. It is confirmed that all excipients comply with Ph.Eur. No excipients of human or animal origin and no novel excipients are used. However, additional information on the manufacture of citric acid is requested as it may be manufactured by fermentation.

No bioequivalence or other clinical study has been performed as the MA procedure follows a well-established use application. Accordingly it is not necessary to provide information on the clinical formulation.

No overage is proposed. The pH of the drug product is within the range specified in the release- and shelf-life specification, which as indicated above increases stability of the drug substance. Osmolality of the solution is not discussed and should be demonstrated.

The manufacturing process is simple and the finished product is terminally sterilized according to the reference conditions of Ph.Eur.5.1.1. The finished product complies with Ph.Eur. 2.6.1 (sterility) and Ph.Eur. 2.6.14 (bacterial endotoxins). With regards to the acceptance criteria for microbiological purity of the API and excipients the information currently provided in dossier are inconsistent and need to be clarified. Moreover, it should be demonstrated how microbiological quality and endotoxin content on WFI produced in-house is monitored.

Clear type I hermetically sealed glass ampoules are used as container closure system. Compliance with Ph.Eur. 3.2.1 is confirmed. The name of the supplier(s), a technical drawing and an in-house specification specific for the actual packaging material of the drug product are missing and should be provided. Moreover, further details (colour, code rings, OPC etc.) of the ampoules should be given.

Compatibility/in-use stability data are provided for drug product diluted 1:1 in glucose 5%, glucose 4% with sodium chloride 0.18% and sodium chloride 0.9%. However, the provided information is not sufficient and additional data are requested.

The drug product development site should be indicated.

Manufacture of the product and process controls

Sites involved in the manufacture and control of the drug product were indicated. However, the information is not complete and needs to be updated.
The drug product is manufactured according to a standard process. The manufacturing process is simple: basically the compounds are mixed, pre-filtered, filled and terminally sterilised according to Ph.Eur. 5.1.1. There are no intermediate products proposed. The low API content (1%) is not considered critical as the drug product is a solution. Pre-sterilisation bioburden is critical for sterility of the drug product and is controlled as IPC with an acceptable limit of LT 100CFU/100ml.
Nevertheless, several concerns have been identified regarding the manufacturing process: operating parameters should be indicated; the pre-filtration step should be justified and additional information on the used filter/filtration step should be provided; acceptance criteria are missing for some of the described IPCs; the analytical methods applied for post-filtration bioburden and seal integrity testing should be described; additional information on the autoclave loads is requested; information on critical process steps and how they are controlled should be provided in the dossier.

Process validation data are provided for both proposed drug product manufacturers and principally support that the manufacturing process is appropriate. However, the currently provided process validation data are not sufficient for full validation of the manufacturing process (e.g. because batches are not consecutively manufactured, not of production scale or originate from one bulk product batch). Process validation protocols compliant with Annex 1 on the process validation guideline should be provided. Moreover, if the pre-filtration step is justified, then product specific filter validation data should be provided. Potential leachables from the pre-filter and adsorption of the product to the filter should be addressed.

Product specification

The proposed release and shelf-life specification complies with ICH Q6A, Ph.Eur. 2619 (“Pharmaceutical Preparations”), Ph.Eur. 0520 (“Parenteral Preparations”) and Ph.Eur. 0672 (“Liquid Preparations for Oral Use”). Following parameters are tested: appearance, identity caffeine, assay of caffeine, total impurities, pH, sub-visible particles, extractible volume, bacterial endotoxins and sterility. An identity test for citrate should be included additionally.

The dose to be administered is calculated on a per kg bodyweight basis. Accordingly neither “uniformity of dose units” nor “uniformity of mass of delivered doses from multidose containers”, which are principally referenced in above mentioned Ph.Eur. monographs, are relevant for this product.
The limit for parameter pH is compliant with the British Pharmacopoeia monograph for “Caffeine Citrate Injection” and is therefore accepted without further justification. No limits for individual impurities (known or unknown) are proposed. However, the limit for total impurities complies with the identification threshold according to ICH Q3B. Accordingly it is acceptable that individual impurities are not reported separately. It is not described in the dossier how the limit for bacterial endotoxins is calculated. However, the proposed limit complies with the result if calculated according to Ph.Eur. 5.1.10 and is therefore acceptable. Nevertheless, the calculation of the limit for bacterial endotoxins should be included in the dossier.
Assay is included in the release- and shelf-life specification of the finished product in relation to Caffeine. This should be justified or changed in line with the response on the issue regarding the actual form of the API in the drug product (see assessor´s comment on section 4.1 of this AR). Moreover, the

limit should not be expressed in %w/v, but in % nominal content.

With regard to the identification threshold for impurities and the limit for bacterial endotoxins the following should be noticed:
The maximum daily dose according to the SmPC is 20 mg Caffeine citrate (=2 ml drug product) per kg body weight, representing the loading dose. However, according to “Martindale: The Complete Drug Reference” a second loading dose may be given within 4 – 24 hours after the first. Accordingly a maximum daily dose of 40 mg Caffeine citrate (=4 ml drug product) per kg body weight has been assumed for assessment of the proposed limits.

Method descriptions are provided for parameters identity, assay and total impurities. For the other methods reference is made to Ph.Eur. Information on how the reported values for parameters “assay” and “total impurities” are calculated is missing and should be provided. Moreover, a system suitability test should be incorporated into the HPLC method for determination of identity (Caffeine), assay and total impurities (related substances).
The in-house method for determination of identity, assay and total impurities (related substances) described in dossier is applied and validated at different sites. The method was originally developed and validated at Burton on Trent Hospital, which is now not included in the marketing authorization application. A method validation report for this site is provided and is sufficient. Analytical method transfer reports should be provided for the other control sites. Moreover, the stability indicating character of the analytical method for determination of assay and related substances (total impurities) is not sufficiently demonstrated.
Sterility and bacterial endotoxins are tested applying compendial methods. Accordingly, method verification data should be provided.

Batch data are provided but are not sufficient. Batch data should be provided for 3 consecutively manufactured batches (at least of pilot scale) for each proposed drug product manufacturer and each presentation (1 ml and 2 ml / ampoule). Moreover, there are again inconsistencies regarding the nature of the drug substance: Assay is reported with regard to Caffeine citrate [mg/ml] in the table on the batch results, but with regard to Caffeine [% w/v] in the CoAs. Moreover, total impurities results should be given numerically (currently it is only stated that the results comply with the specification).
A discussion on elemental impurities is missing and should be provided in accordance with guideline ICH Q3D.

Appropriate information is provided on the reference standards used for the stability study.
Information on the reference standards used for other testing activities (e.g. release testing and method validation) taking into consideration the other proposed chemical quality control sites should be provided too. Moreover, the role of caffeine for system suitability CRS should be explained, as no such reference material is mentioned.

Stability of the product

Stability studies have been performed for drug product manufactured by both proposed drug product manufacturers.
However, several concerns have been identified. There are again inconsistencies regarding the nature of the drug substance (Caffeine Citrate vs Caffeine). Moreover, for one of the both manufacturers the selected stability batches have not been manufactured consecutively, are only of 1ml fill volume and only one of them is of production scale. Accordingly a post-approval stability commitment should be provided that two more industrial scale batches of 1 ml fill volume and 3 industrial scale batches of 2

ml fill volume will be put on long-term stability. Further on, it should be justified why batches some batcheshave been tested after 5 months instead of 6 months storage at accelerated conditions. Expression of endotoxin results should also be clarified. Finally, current stability results up to 36 months should be available and thus should be presented.
On the other hand, the stability results for the other drug product manufacturer are quite old and not all parameters of the shelf-life specification are controlled at accelerate conditions. These data are thus only considered as supportive information. However, principally the provided stability results support that both presentations (1 ml and 2 ml) of the drug product are stable over the tested period of time (up to 48 months).
The stability study performed at 2°C – 8°C is not sufficient as parameter “sub-visible particles” has not been considered. The same is true for the photostability study.
Overall, the proposed shelf-life of 36 months should be justified taking above addressed concerns into consideration. However, the currently provided data are sufficient to confirm that the drug product is stable at the tested temperatures. Nevertheless, considering the dose form following additional labelling statement should be made: “Do not freeze”.
Regarding in-use stability of solution for infusion it is stated in SmPC section 6.3 that it has been demonstrated for 10 days at 25°C. Respective in-use stability data supporting this statement are missing and should be provided. Moreover, it should be clarified what is meant by “solution for infusion” (it is assumed that un-diluted solution is meant).

Comparability exercise for Finished Medicinal Drug Product

N/A

Adventitious agents

N/A

GMO

N/A

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

There is a major objection regarding GMP compliance of a site responsible for stability testing of the finished product. Accordingly a GMP certificate covering this function should be provided. Moreover, this site should be included in application form section.

Conflicting information on the nature of the API (Caffeine or Caffeine Citrate – which could potentially form *in situ* during the drug product manufacturing process) is provided by the MAH. The nature of the API (Caffeine or Caffeine Citrate) as actually present in the finished product should be discussed and supported by data, if not otherwise justified. The complete dossier needs to be harmonised respectively.
Anyway, a valid CEP (R1-CEP 1998-022) has been provided for Caffeine. No additional controls are mentioned in the CEP. A retest period of 60 months is stated on the CEP, if the drug substance is stored in a container consisting of fibre drums or big bags lined with a low-density polyethylene bag. The applicant does not provide additional stability data.
Several other concerns are raised regarding the information provided on control of the drug substance at the site of the drug product manufacturers.

The finished product is a clear, colourless, sterile, aqueous solution and is intended to be administered intravenously (solution for injection) or orally (oral solution). However, considering the method of administration described in section 4.2 of the SmPC the dosage form should rather be “Solution for Infusion” and “Oral Solution”. The chosen components of the drug product are commonly used in comparable products. The information provided on pharmaceutical development is mostly sufficient. However, some other concerns are identified including insufficient data on compatibility of the drug product with the proposed diluents (glucose 4%/sodium chloride 0.18%, glucose 5% and sodium chloride 0.9%).

The drug product is manufactured according to a standard process: basically the compounds are mixed, pre-filtered (0.2µm filter), filled and terminally sterilized according to Ph.Eur. 5.1.1. The low API content (1%) is not considered critical as the drug product is a solution. However, the provided information on the manufacturing process is not sufficient and several other concerns are identified including justification of the proposed pre-filtration step and missing filter validation data.
It is confirmed that the used excipients comply with Ph.Eur. No excipients of human or animal origin and no novel excipients are used. However, it is requested to clarify if citric acid is manufactured from fermentation. If so, additional quality information is requested. Moreover, it should be clarified if citric acid monohydrate or anhydrous is used.
The proposed drug product release and shelf-life specification complies with ICH Q6A, Ph.Eur. 2619 (“Pharmaceutical Preparations”), Ph.Eur. 0520 (“Parenteral Preparations”) and Ph.Eur. 0672 (“Liquid Preparations for Oral Use”). The following parameters are tested: appearance, identity caffeine, assay of caffeine, total impurities, pH, sub-visible particles, extractible volume, bacterial endotoxins and sterility. An identity test for citrate should be included additionally. Analytical method descriptions and where relevant validation data are provided. However, the provided validation data are not sufficient including insufficient information on the stability indicating nature of the method applied for determination of assay and related substances. Batch data are provided but are not sufficient. A discussion of elemental impurities in line with the principles of ICH Q3D is missing. Insufficient information is also provided on the used reference standards.
Clear type I hermetically sealed glass ampoules are used as container closure system. Compliance with Ph.Eur. 3.2.1 is confirmed. However, other relevant information including an in-house specification specific for the actual packaging material is missing.

Stability studies have been performed for drug product manufactured by both proposed drug product manufacturers. However, several other concerns have been identified. The proposed shelf-life is thus currently not sufficiently justified by the provided data. Moreover, in SmPC section 6.3 it is stated that in-use stability of the solution for infusion has been demonstrated for 10 days at 25°C. Respective in-use stability data supporting this statement are missing. Moreover, it should be clarified what is meant by “solution for infusion” (it is assumed that un-diluted solution is meant).

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The provided quality documentation is insufficient. There is a major objection regarding GMP compliance of a control site responsible for stability testing. Moreover, a number of other concerns (including several sub-items) have been identified.

Overall, the present application for marketing authorisation is thus not approvable from a quality point of view.

3.2. Non clinical aspects

3.2.1. Pharmacology

Caffeine is a naturally occurring alkaloid, a member of the methylxanthine family and an unselective antagonist on A1, A2A, A2B and A3 adenosine receptors (Alexander et al., 2011). Besides, caffeine blocks phosphodiesterases and activates ryanodine receptors located predominantly in skeletal and cardiac muscle. The latter two mechanisms are observed at high caffeine concentrations, which are usually not obtained with alimentary caffeine applications, but play a crucial role in intoxications (Kua and Lee, 2016).

The bibliographic background on the pharmacology of caffeine is sufficient, and no further non-clinical studies are considered necessary. Unfortunately, however, the description of the non-clinical pharmacology of caffeine citrate is not based on a systematic approach to accumulate unbiased evidence supporting the use of caffeine citrate in the targeted indication, prevention of BPD. This conclusion is based on the following arguments:

A non-clinical model for BPD is not presented by the applicant and not available in the literature. The experimental settings share limitations regarding applicability and translatability for the targeted indication prevention of BPD: The documented animal models are based on tissue damage due to hyperoxia, lipopolysaccharide or bleomycin exposure. None of these conditions reflects the clinical situation of BPD. Thus, the aspired indication for Blectifor, prevention of BPD, is not suitably addressed by the non-clinical studies provided.

It is unclear why the applicant focused on A1 and A2A receptors only. The A2B and A3 receptors, which are related to bronchoconstriction and pro-inflammatory effects, are implicated in asthma and other patho-mechanisms of the lung. Thus, the role of A2B/A3 receptors in primary pharmacology of respiratory function should be implemented and discussed.

The applicant presents a small spectrum of studies and articles related to caffeine´s action outside the lung. There are much more published data on caffeine effects. Of special interest would be a systematic focus on the central nervous system, heart and the gastrointestinal system. In this context, apnoea treatment in premature infants with caffeine is well established and mainly attributed to central nervous system (CNS) stimulation. There may be potential similarity and a certain degree of overlap between the effects of caffeine in AOP and in prevention of BPD in premature subjects, therefore the primary pharmacology has to include data of caffeine action in the CNS with consequences on respiratory function. The applicant is therefore asked to discuss the role of caffeine in the CNS in order to clarify any therapeutic impact on BPD prevention. The discussion should also address any evidence (or lack thereof) for a difference in the mechanism of action of caffeine citrate in “prevention of BPD” (orphan designation granted for Blectifor) and in “apnoea of prematurity”, for which Peyona has orphan status.

There is no consistent evidence from non-clinical studies supporting an antifibrotic, antioxidant or anti-inflammatory action of caffeine citrate.

3.2.2. Pharmacokinetics

The non-clinical pharmacokinetic data of caffeine are inadequately presented. Although a full spectrum of relevant literature exists no PK parameters are presented (volume of distribution, plasma protein binding capacity, accumulation in specific organs etc.). PK data are not set into context with respect to species, age and dose/administration route.

Facing the clinical PK data achieved with caffeine citrate in neonates, evidence generated on the nonclinical level are considered of minor importance but may contribute to clinically raised concerns. I.e. to provide exposure data derived from nonclinical models in different species in comparison to clinical PK data. Thus the applicant is requested to present PK data in context to species, age and dose/administration route.

3.2.3. Toxicology

A literature based data convolute was submitted to describe neonatal toxicology of caffeine in various species. According to the longstanding experience and research on caffeine enough publications are available to allow evaluation of toxicological aspects. Single and repeat-dose toxicological studies were reported to obtain LD50 values.

Safety margins (NOAEL) for caffeine citrate are not provided and cannot be deduced from the submitted data. In vitro studies are not suitable to evaluate repeated dose toxicity. The studies are also not in full compliance with current guidelines for toxicological studies, in particular uncertain dosing weakens study data interpretation (study compound via drinking/food instead of IV or oral gavage). The applicant should calculate NOAELs for the drug substance from available literature aiming to strengthen safety evidence for the selected clinical posology.

According to the widely accepted IARC monograph caffeine is unlikely to be carcinogenic in humans. However the Applicant failed to provide and summarise the most relevant bibliographic data about the carcinogenic effect of caffeine.

Potential reproductive and embryofoetal toxicities were identified but are considered of limited relevance for the proposed indication and at therapeutic concentrations.

Growth retardation, altered behaviour and irregular control of respiration was reported and found to be more severe under conditions of malnutrition. In particular, increased physical activity was observed in rats, after postnatal caffeine exposure (Guillet et al., 1990). Elevated growth hormone and thyroid hormone levels may explain enhanced metabolism in the presence of caffeine.

The applicant does not provide a statement on toxicological effects on gut, related to necrotizing enterocolitis, which has been identified as a potential risk in caffeine treated infants (Cox et al., 2015). However, this risk is more appropriately explored within the clinical assessment and is discussed there.

Although different presentations of caffeine were used for toxicological studies this presents no limitation regarding interpretation of data.

3.2.4. Ecotoxicity / environmental risk assessment

In accordance with the “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use”, Blectifor (caffeine citrate), 10mg/ml Solution for Injection, is considered to have no environmental impact, since a) the active substance caffeine is widely used as foodstuffs, and b) Blectifor is comparable to extemporaneously prepared products containing the same API.

All ingredients are well-established with many years of use in pharmaceutical products. None of these ingredients have been shown to have an environmental impact. Caffeine Solution for Injection has been widely used for many years. It is anticipated that any increase in the sales of the proposed product will only substitute for caffeine administration from extemporaneously prepared solutions, and thus will have no impact on environmental exposure by these ingredients.

3.2.5. Discussion on non-clinical aspects

The pharmacological action of caffeine is well described by the existing literature. However, the demonstration of its efficacy in a BPD prevention model is lacking since no adequate BPD animal model exists. No safety concerns or toxicological concerns are raised justifying additional in vitro or in vivo studies.

3.2.6. Conclusion on non-clinical aspects

From a non-clinical perspective the dossier provides sufficient data for the application and no major objections are raised. However, some other concerns need to be addressed to appropriately cover this part of the dossier, whereas for other deficiencies reference to the clinical assessment report is made, where pivotal evidence may not be achieved at the non-clinical level and is of supportive value only.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Pharmacology studies

A tabular listing of Pharmacology studies can be found in Module 2.7.2 “Summary of clinical pharmacology studies”. 74 Studies were provided by the applicant dating from 1979 to 2015.

In vitro studies that provide PK and PD information including their relevant features and outcomes, preterm patient PK and initial tolerability studies, extrinsic factor PK studies and Population PK studies are included.

Safety and efficacy studies

A tabular listing of all studies submitted for efficacy and safety evaluations can be found in the clinical Assessment report or in Module 2.7.3 “Summary of Clinical Efficacy” of the dossier. Only the publications considered most relevant to this submission are included in the listing below.

Controlled studies

Table 2

Study reference	Aim of study	Subjects	Outcome
Placebo controlled studies			
Davis 2010	Post-hoc analysis of CAP trial (see below), to determine whether the benefits of caffeine vary in three subgroups of participants.	Subgroup 1: indication for treatment Subgroup 2: type of ventilation support; no positive pressure ventilation, non-invasive ventilation, endotracheal tube. Subgroup 3: timing of commencement of study drug; randomised <3 days n=783 vs randomised at ≥3 days n=1086 evaluable.	1. No differential treatment effect in subgroups defined by clinical indication for starting drug. 2. Caffeine was much more beneficial than placebo in infants having a higher level of respiratory support ie those with non-invasive ventilation or endotracheal tube. 3. Earlier initiation of caffeine is associated with significant improvement in primary and secondary outcomes. For BPD incidence early caffeine 111/396 placebo 190/426, late caffeine 239/567 placebo 257/528, OR 0.58 (CI 0.39-0.88)
Schmidt 2006, 2007, 2012 (the CAP studies)	Multicentre placebo-controlled randomised controlled trial, designed to investigate the short-term and long-term safety of caffeine citrate. Primary outcome of trial was death before a corrected age of 18-21 months, or survival with neurodevelopmental problems (cerebral palsy, cognitive delay, hearing loss, blindness) Secondary outcomes were incidence of other morbidities of prematurity; BPD, respiratory support, patent ductus arteriosus.	2006 premature infants GA 25-29 weeks, birthweights 500-1250 g, aged <10 days (mean age of randomisation 3 days). The clinical indications for caffeine therapy were treatment of AOP (n=830, 42%), prophylaxis against apnoea (n=454, 22.5%), as an aid to extubation (n=719, 36%) and other (n=3, <1%). Randomised to two groups: 1006 were assigned to the caffeine group and 1000 to the saline placebo group. Dose of caffeine; 20 mg/kg loading dose then 5 mg/kg/day maintenance, increased to 10 mg/kg/day if lack of efficacy suspected. Continued for at least 24 days, and finished at 35 weeks PMA.	Primary outcome: death or disability significantly better in caffeine group: caffeine 376/936, placebo 430/931. Secondary outcomes: Infants receiving caffeine had reduced rates of BPD (caffeine 349/961, placebo 447/953, OR 0.65 (95% CI 0.54-0.70); this was independent of initial indication for therapy. Infants receiving caffeine spent approx 1 fewer weeks with an endotracheal tube, any positive pressure ventilation, and supplemental oxygen. Caffeine group had improved incidence of patent ductus arteriosus. Post hoc analysis to determine mechanisms of neuroprotective effect of caffeine suggested early discontinuation of positive airway pressure as main variable, accounting for approx 50% of effect. Five year follow up shows no morbidity attributable to caffeine, confirming long term safety.

No-treatment controlled studies N/A			
Dose-response studies (without placebo)			
(Steer 2004)	Randomised double-blind controlled study. To evaluate two different caffeine dosing regimens to facilitate extubation of preterm infants. Incidence of BPD in treatment groups included in outcomes.	234 premature infants <30 weeks GA, undergoing mechanical ventilation >48 hours. Treatment started ≤ 24h before or ≤ 6h after extubation. Study group 1, n=116: high dose caffeine citrate 80 mg/kg loading dose, 20 mg/kg/day maintenance. Study group 2, n=122: normal dose caffeine citrate load 20 maintenance 5	High dose caffeine patients more successful extubation. High dose 15% failure to extubate, normal dose 30%. BPD outcomes: According to 28 day definition high dose 66%, normal dose 74%. According to 36 weeks definition high dose 34%, normal dose 48% (p=0.06)
Mohammed 2015	To compare two dosage regimens for treatment of apnoea and success in extubation. Randomised double-blind controlled trial. Safety and efficacy, with incidence of BPD in treatment groups included in outcomes.	120 preterm neonates <32 weeks GA, diagnosed with AOP and receiving on ventilation support, randomised into two treatment groups. High dose caffeine n=60, load caffeine citrate 40 mg/kg, maintenance 20 mg/kg/day. Low dose caffeine n=60 load 20 maintenance 10. Duration of treatment 27-30 days.	Primary outcome; successful extubation more frequent in high dose caffeine p<0.05. BPD outcome no statistically significant difference: high dose 13/60 (21.6%), low dose 19/60 (31.7%).
Active control (without placebo) N/A			

Uncontrolled studies

Study reference	Aim of study	Subjects	Outcome
(Chavez-Valdez 2011)	BPD outcome recorded in study of cytokines in tracheal washings and plasma of caffeine-treated neonates. Cohort study.	26 preterm infants GA≤30 weeks, intubated and given surfactant for RDS during first 24 hours of life. All received caffeine treatment at standard dosage, started in first six days of life. Serum [caffeine] measured at 1 week. 11 of these infants subsequently developed BPD.	Infants who developed BPD had longer duration of intubation, and higher incidence of uterine infection. Also had higher plasma interleukin IL-1beta and IL-6 levels. Plasma [caffeine] levels were compared with BPD outcomes; BPD infants had same median [caffeine] as non-BPD infants, but with a different distribution.
(Kumral 2012)	BPD outcome recorded in study of genetic susceptibility to AOP and response to treatment. Cohort study.	Cohort of 115 consecutive premature infants born at GA 24-34 weeks. 60 without AOP and 55 with AOP, who were treated with caffeine at standard dosage. 30 responded to caffeine, 25 didn't. 26 patients in total developed BPD; 6/60 in non-apnoea group, 20/55 in apnoea group (p=0.001).	Genetic characteristics of caffeine responders and BPD developers described, related to adenosine receptor polymorphisms.. BPD developed in 8/30 caffeine responders and 11/25 caffeine resistant (p=0.006) ie caffeine responsiveness associated with decreased risk of developing BPD.
Observational, cohort studies			
Dobson 2014	To compare respiratory outcomes on early (<3 days of life) caffeine vs late (≥3 days of life) caffeine. Retrospective cohort analysis of a multicentre dataset covering 13 years. Trends in caffeine use over time also described.	Cohort of 69,056 VLBW premature infants who received caffeine therapy for any indication. 29,070 receiving early caffeine propensity score-matched (ie risk factors of developing BPD) with 29,070 infants receiving late caffeine. Caffeine dosage not specified.	Early caffeine 27.6% died or developed BPD. Late caffeine 34% died or developed BPD. (OR 0.74, 99% CI 0.69-0.8). Early caffeine associated with shorter duration of mechanical ventilation, mean difference 6 days (p<0.001).

Lodha 2015	To compare respiratory outcomes on early (<3 days of life) caffeine vs late (≥3 days of life) caffeine. Retrospective cohort analysis of a multicentre network dataset.	From a cohort of 7274 premature neonates <31 weeks GA, 5517 received caffeine therapy for any indication: n=5101 early, n=1295 late. Caffeine dosage not specified, but "usually" standard dosage in participating centres.	Mortality same in both groups. Early caffeine associated with lower BPD rates. Early 27.8%, late 27.7%, but when adjusted for BPD risk factors, OR 0.79 (95% CI 0.64-0.96). Early group had shorter duration of mechanical ventilation. Late group had higher incidence of patent ductus, but other outcomes comparable between groups.
Patel 2012	To compare death rates, respiratory outcomes of early (<3 days of life) caffeine vs late (≥3 days of life) caffeine. Other outcome PDA rates. Retrospective cohort analysis of a single institution.	140 consecutive neonates <1250g birthweight received caffeine for any indication: 83 early (and 57 late. Caffeine dosage not specified.	Death or BPD rate better in early group: 21/83 early, 30/57 late caffeine (adjusted OR 0.26, 95% CI 0.1-.0.73) Duration of ventilation better in early group: early 6 days, late 22 days, p<0.01. PDA requiring treatment early caffeine 10%, late caffeine 36% (adjusted OR 0.28 95% CI 0.1-0.73)
Taha 2014	To compare respiratory outcomes on early (<3 days of life) caffeine vs late (≥3 days of life) caffeine. Retrospective cohort analysis of a multicentre network dataset.	2951 infants weight ≤1250g, treated with caffeine within first 10 days of life for any indication. Early caffeine n=1986. Late caffeine n=965. Caffeine dosage not specified.	Mean birth weight and gestational age were slightly lower in late caffeine group, otherwise risk factors for BPD were similar. Outcome BPD, BPD or death, age of first extubation, duration of respiratory support, age achieving room air, all significantly better in early caffeine.

Reports of analyses of data from more than one study

Study reference	Aim of study	Subjects	Outcome
Beam 2014	Systematic review of randomised controlled trials for the prevention of BPD.	47 RCTs encompassing 21 drugs met inclusion criteria.	13 RCTs for 5 drugs were identified as having reduced the incidence of BPD: 2 for vitamin A, 1 for caffeine citrate (the CAP trial), 9 for dexamethasone, 1 for inositol and 1 for clarithromycin.
Jensen 2015	Evidence-base analysis of pharmacological therapies for prevention of BPD. Application of the GRADE methodology.	Analysis of evidence from trials for dexamethasone, vitamin A and caffeine.	For caffeine, 1 RCT and five observational studies identified and analysed GRADE analysis level of evidence of efficacy "high"; authors strongly recommend use of caffeine soon after birth for prevention of BPD.
Park 2015	Evidence-based review of early caffeine therapy in VLBW infants and neonatal outcomes. Meta-analysis.	1 RCT, 4 retrospective cohort studies, and one abstract reviewed.	Total of 59,136 participants in trials identified, data extracted. Meta-analysis suggests that early caffeine use has beneficial effects on neonatal outcomes, including mortality and BPD, without increasing the risk of necrotising enterocolitis (NEC). Risk of death (odds ratio [OR], 0.902; 95% confidence interval [CI], 0.828 to 0.983; P=0.019), bronchopulmonary dysplasia (BPD) (OR, 0.507; 95% CI, 0.396 to 0.648; P<0.001), and BPD or death (OR, 0.526; 95% CI, 0.384 to 0.719; P<0.001) were lower in the early caffeine group.

This application includes more than 140 literature references dated 1967-2016 to support caffeine citrate for prevention of BPD in terms of its pharmacology, efficacy and safety profile. The lists of literature references in the individual documents (Clinical Overviews and Summaries) are not consistent and many full-texts are missing. The literature search is not traceable and no information on the search strategy is provided.

Whereas key publications on the concerned topic have been identified (i.e. those on the CAP dataset), the Applicant has not explained on which basis data/studies were screened and considered relevant for inclusion in the qualitative synthesis. Search criteria, selection criteria and the respective selection process (e.g. via a PRISMA flow diagram) have not been outlined, which leaves open the question whether the referred-to studies indeed represent the overall published data and the risk of a selection bias (on a publication level) cannot conclusively be ruled out. The potential for publication bias and the availability of 'grey literature' (e.g. data from prematurity registries) as potentially relevant data source have not been addressed. Whereas it is agreed in principle that in the context of a bibliographic application certain data sources will bear more weight than others for B/R assessment (i.e. following an arguable consensus on 'levels' and 'quality' of evidence, depending on the research question(s), respective outcomes and trial designs), the comprehensiveness and adequacy of the initial search and subsequent identification of candidate data sources is an independent, yet important consideration for judging the quality of a literature review and the conclusions drawn thereupon. It should also be clear that questions as to the efficacy of caffeine (citrate) in BPD prevention would in principle mandate different search/selection criteria than questions pertaining to the safety of the compound and the proposed posology in the concerned population.

The systematic identification of scientific literature research should be outlined, taken the abovementioned into account. Literature not already included in the dossier should be summarized and contextualized with the currently available data. Literature deemed relevant should be graded and discussed regarding their quality and importance for this application. The clinical summaries (pharmacology, efficacy and safety) should reflect this accordingly.

As an exemplary side note, recent systematic reviews by e.g. Beam et al. 2014, Picone et al., 2012 in principle support the use of caffeine (citrate) for BPD prevention and base their findings primarily on the results obtained from the CAP trial, in line with the Applicant's approach. In a meta-analysis from 2016, Kua & Lee cite (among others) a placebo-controlled trial by Armanian et al., 2016 and a controlled trial (comparing different caffeine (citrate) treatment initiation time points) by Saeidi et al., 2014 have not been referred to by the Applicant in the presented literature. This does not necessarily imply that high-impact publications have been missed but highlights one the one hand the need to further elaborate on the search/inclusion strategy for published articles but also hints at the fact that it might not be straightforward to devise such criteria, depending on the research question(s) asked. It should also be clear that questions regarding the efficacy of caffeine (citrate) in BPD prevention would in principle mandate different search/selection criteria than questions pertaining to the safety of the compound and the proposed posology in the concerned population.

The Applicant's case for a positive benefit/risk of caffeine (citrate) in premature infants is built mainly upon the CAP trial, a placebo-controlled RCT (Schmidt 2006, Schmidt 2007, Davis 2010) where BPD was prospectively considered a secondary outcome measure. This approach is supported and trial details are discussed in depth in later sections of this assessment report. Controlled trials without placebo comparison but evaluating different doses or treatment initiation time points, as well as single arm studies were also included and are considered relevant insofar as they might inform recommendations regarding posology, optimal treatment timing and duration, as well as serve as data sources to judge upon consistency across trials.

The array of trials investigating methylxanthine use in respiratory NICU, thus not focusing on caffeine citrate is considered of limited relevance.

3.3.1. Pharmacokinetics

The pharmacokinetic properties of caffeine in adults are widely known. The substance is broadly used also in neonatal medicine since decades for several indications. There are some publications on caffeine PK in the anticipated target population available. The preparation of the clinical pharmacology part of the submitted dossier was done in a rather superficial way, however. Although many relevant publications are submitted as full texts, several aspects of caffeine PK (and PD) relevant to this application are not sufficiently discussed. Consequently, there are some gaps in the knowledge of PK, PK/PD relationship and the optimal dose in the target population which need to be further addressed.

Absorption

Oral administration of caffeine citrate 20 mg/kg (equivalent to 10 mg/kg of caffeine) to premature neonates produced peak plasma concentrations (Cmax) of caffeine ranging from 6 to 10 mg/L within 30 minutes to 2 hours (tmax). Bioavailability of orally and IV administered caffeine in premature newborns is comparable for a single dose.

Food effect: Food did not significantly affect Cmax, AUC (0-120h) indicating that oral caffeine could be administered either with or without food. However, during the treatment of apnea of prematurity, the elimination of caffeine has been found nearly three-fold faster in the formula-fed than in the breast-fed infants (Le Guennec & Billon, 1987; Blake et al., 2004), the underlying mechanism(s) of which is still

debated. There are two proposals. First, enhanced in vitro CYP1A expression via an AhR-mediated pathway by infant formula but not human milk provides a potential mechanistic basis for the increased caffeine elimination in formula-fed infants (Xu et al. 2005). Alternatively, formula may affect maturational events independently from the known induction mechanisms by accelerating the maturational expression of CYP1A2 or CYP3A4. The proposed SmPC does not give any recommendation in this regard.

Distribution

Caffeine is sufficiently hydrophobic to pass through most membranes in the body and is distributed into all body compartments. There is no placental barrier to the passage of caffeine from mother to foetus and caffeine passes into breast milk. Precautions have to be taken with this regard and the PI adequately reflects these concerns. Caffeine is readily distributed into the brain and, in neonates; the CSF levels are similar to the plasma concentrations. The apparent volume of distribution is between 0.8 and 0.9 L/kg and is higher than observed in adults (0.4 – 0.6L/kg). Caffeine is rapidly distributed into the brain, and caffeine levels in the CSF of preterm neonates approximate the plasma concentrations.

Transplacentally acquired caffeine levels ranged from 1.1 to 3.7µg/ml were measured in cord blood of preterm infants. Caffeine concentrations between 2 and 4.3 µg/ml were observed in breast milk of lactating women who consumed 100mg caffeine (about one cup of coffee), and measurable caffeine concentrations in sera of breast-fed infants whose mothers consumed 750mg caffeine daily (literature cited in clinical AR). It seems advisable to measure baseline caffeine levels in premature infants born to mothers who consumed caffeine prior to delivery (when caffeine (citrate) therapy is planned). Plasma concentrations should be monitored during caffeine (citrate) treatment of infants whose mothers consume caffeine while providing breast milk for feeding, as proposed by the Applicant (section 4.2 of the SmPC).

The extent of protein binding was not discussed for any age group (preterm neonates or others), therefore the statement in the SmPC “In adults, the mean plasma protein binding in vitro is reported to be approximately 36%.” needs to be further substantiated (see attached documents).

Elimination

Elimination of caffeine in neonates is much slower than in adults because of their immature hepatic and/or renal function. In premature newborns, caffeine is eliminated predominantly via renal excretion according to first order kinetics, and the fraction excreted unchanged in the urine (Ae) is approximately 86% (within 6 days), compared with less than 4% in adults. Mean half-life (T1/2) and Ae are inversely related to gestational age. T1/2 of caffeine in premature infants is about 100 hours (50 to 300 h reported). A dependency on GA or PNA/PMA could explain observed differences, but was not further discussed by the applicant. In the study by Pons, 1988, caffeine elimination half-life and clearance varied linearly with GA and exponentially with PNA/PMA, which could explain the observed differences to some extent. T1/2 of caffeine is approximately 5 hours in adults. The elimination half-life of caffeine deceases from birth until it reaches adult values at approximately 60 weeks post conception.

A number of high-quality POP-PK studies also identified postnatal age as a significant covariate of the Cl and characterized the time course of the process. But this information is not included into the current version of the SmPC. The SmPC speaks mostly about young and newborn infants, the only comment about premature neonates is that “Elimination half-lives may be in excess of 52-96 hours in premature neonates”. Among other studies, the POP-PK study of Charles (2008) seems to be one of the best sources to characterize the age-dependent increase of caffeine Cl in neonates. Therefore, the

Applicant is asked to update Section 5.2 of the SmPC and illustrate how the Cl and the half-life of caffeine changes with postnatal age.

The elimination of caffeine in infants with renal or hepatic impairment has not been studied, however, one post-marketing survey (Lista 2016) indicated that in the presence of renal and/or hepatic impairment, adverse events were encountered more frequently and it is advised that in such cases that plasma caffeine levels are monitored.

Metabolism

Caffeine is metabolised in the liver by cytochrome P4501A2 (CYP1A2); potential metabolic pathways include N-demethylation at positions 1, 3 or 7 of the molecule and/or hydroxylation of carbon 8. The predominant process of caffeine metabolism in the preterm infant is N7-demethylation which matures at about 4 months of age. N3- and N7-demethylation increase exponentially with post-natal age.

Interconversion between caffeine and theophylline has been reported in preterm neonates. Approximately 25% of theophylline is converted to caffeine via methylation and between 3-8% of caffeine is converted to theophylline. The conversion of theophylline to caffeine must be considered in infants previously treated with theophylline; an adequate precaution (measurement of caffeine concentrations prior to initiation of therapy) is included in the SmPC.

No information was provided on the PK of active and inactive metabolites. The Pharmacokinetics of the relevant caffeine metabolites paraxanthine (PX), theobromine (TB) and theophylline (TP) should be described.

There are some controversial statements in the literature concerning the impact of factors such as e.g. GA or birth weight on the levels of metabolic activity. A possible clinical consequence is not discussed.

Dose proportionality

Caffeine (citrate) is normally given as a single loading dose, followed 24 hours later by a daily maintenance dose. A single loading dose of 20 mg/kg caffeine citrate was given in ten studies. This resulted in predictable, stable caffeine plasma levels between 5 and 20 µg/ml in the great majority of cases according to the applicant.

The concentration in serum increases proportionately to the administered dose (Lee 1996, Zohra 2013, publications not included in the dossier). Progressively higher maintenance doses are associated with progressively higher plasma levels; there appears to be a linear relationship between dose and plasma levels.

In the PK study by Aranda (J Pediatr 1979) repeated dosing with a maintenance dose of 2.5mg/kg/day caffeine was carried out in 10 infants for a mean of 19 days, yielding steady state plasma concentrations between 7.4 and 19.4mg/L. Target levels for the claimed indication are not available and might be following target levels for treatment of AOP. However, this needs to be further discussed by the applicant taking into account possible differences between the populations and resulting caffeine need, respectively.

Intra- and inter-individual variability

Substantial inter- and intra-individual variability can be expected in the preterm neonate population due to rapid maturational changes in the post-natal period. Caffeine clearance depends predominantly on body weight and post-natal age. The described inter-individual variability (CV) was about 20-25% for clearance and 10-25% for volume of distribution. The extent of expected differences in PK (and PD) is unknown. The age range of patients included in PK studies was not outlined by the applicant. Cited

references are often more than 20 years old, they come from a time were intensive care differed markedly from nowadays' standards. Nowadays infants are surviving at considerably younger ages and extremely low birth weight children could be underrepresented in the provided literature. It is not known if caffeine PK differs to older infants.

Interactions

Pharmacodynamic drug interactions are mentioned in the preclinical dossier; no literature data on in-vivo interactions in humans were provided nor were possible interactions with medications used in the target patient population discussed.

However, the relevant background literature has not been provided and also, the list of interacting drugs seems rather outdated. Also, possible interactions with Pentoxifylline, Milrinone or Sildenafil, substances that are also used in the respective population, have not been discussed. Available data concerning possible drug interactions with caffeine (citrate) in neonates should be extracted from the literature and presented also in the Blectifor dossier to substantiate SmPC recommendations.

3.3.2. Pharmacodynamics

The pharmacodynamics effects of caffeine have been extensively studied and are well characterised.

The mechanism of action most likely to mediate effects relevant for the prevention of BPD, however, does not seem entirely clear, and could be a composite of several caffeine characteristics. Primary and secondary pharmacodynamic effects were not individually explained in the clinical part of the applicant's dossier. Animal models could be helpful to further explore this issue, but concerns on sensitivity of the provided models are raised (see preclinical AR). Histological lung studies in humans are not feasible as BPD is rarely fatal nowadays.

Mechanism of action

Caffeine (1,3,7 trimethylxanthine) has different properties at a cellular level. At therapeutic concentrations, it is an adenosine antagonist and it is this action which accounts for all of the physiological effects of caffeine; stimulation of the CNS and respiratory systems, cardiac stimulation, relaxation of smooth muscle and increased metabolism.

According to the applicant there are two types of adenosine receptor principally involved in the actions of caffeine, both widely distributed in body tissues; A1 and A2A. However, as outlined in the preclinical assessment, A2B and A3 receptors are implicated in the asthma and other patho-mechanisms of the lung. Their involvement in caffeine effect on BPD prevention was not discussed. However, the two receptors A1 and A2 have differing, often conflicting, roles and activation of each mediates separate actions. A1 activation activates potassium channels, inhibits intracellular adenylate cyclase, and inhibits neurotransmitter release. Physiologically, A1 activation by adenosine mediates sedation, bradycardia, vasoconstriction, bronchoconstriction, and decreased glomerular filtration. Conversely, A2A activation actually stimulates adenylate cyclase. This produces vasodilation, bronchodilation, central respiratory depression and peripheral respiratory stimulation, platelet inhibition, decreased locomotor activity and immunosuppression. If given repeatedly, caffeine seems to upregulate and increase the number of adenosine receptors, especially A1. At much higher (approx. twenty times higher) concentrations, caffeine inhibits phosphodiesterase and therefore delays the breakdown of intracellular cAMP. However, this only occurs at concentrations which would be toxic to the organism, and it is doubtful if this mechanism plays any part in mediating the clinical effects of therapeutic caffeine. It is possible that phosphodiesterase inhibition might have a role in the clinical manifestations of caffeine toxicity, for example seizures, although this remains speculative.

At even higher concentrations, caffeine binds to sites on intracellular calcium channels, releasing stored calcium thus interfering with neural transmission and muscular contraction. Again, this mechanism plays no part in the physiological effects of caffeine at therapeutic doses, but might have a role in cases of severe caffeine toxicity.

Even if the pathophysiology of BPD seems to be not fully understood to date, there appears to be agreement on a causal relationship between ventilatory support delivered as part of intensive care preterm neonate management (including different ventilation modalities as well as different levels of oxygen supply) and injury to the developing lung due to physical stress or oxygen toxicity, which in turn manifests in inflammatory response and tissue remodelling. Any effect of caffeine in terms of BPD prevention is therefore likely indirect, i.e. mediated via reducing the need for, duration or invasiveness of mechanical ventilation, positive pressure ventilation or oxygen support during the first weeks of life. This needs further discussion and might have consequences in terms of the wording of the indication.

The characterisation of specific caffeine PD effects relevant for the prevention of BPD is superficial in the provided dossier and the literature data seems not thoroughly investigated. Relevant publications, mostly from the 1980ies and 1990ies is submitted, however, important results are not outlined or discussed. **Laubsher** et al 1998 e.g. explored the compliance of the respiratory system and the strength of the Hering Breuer reflex after theophylline and caffeine use. It was concluded that theophylline and caffeine have similar effects on neonatal respiratory function but caffeine administration is associated with an earlier onset of action. **Murat** et al. 1981 found a significant decrease in the apnoea index in preterm newborns with idiopatic apnoea treated with caffeine. Other authors investigated the relationship between methylxantines and heart rate in comparable patient populations. It was concluded that heart rate alone cannot be used to predict toxic drug levels and high drug levels will not necessarily cause tachycardia.

Another publication not cited by the applicant, **Turmen** et al.; Relationship of dose and plasma concentrations of caffeine and ventilation in neonatal apnea. Semin Perinatol 1981; 5 (4): 326-31., explored the minimum and the safe effective dose and plasma concentration of caffeine which would elicit a significant ventilatory response in premature babies with apnoea. It is concluded that minimal effective dose and plasma concentration in neonatal apnoea are low, 2.5mg/kg and 2.9mg/L, respectively. From prolonged recordings, however, it is suggested that breathing patterns improve remarkably as plasma concentrations approach about 8mg/L.

These investigations were all undertaken with a focus on children with AOP. However, improvement of respiratory system compliance, effect on Hering Breuer reflex and oxygen requirements could certainly be relevant also for the prevention of BPD and should be adequately discussed. Caffeine effect on the myocardium, increasing ventricular output, stroke volume and mean arterial blood pressure in neonates should also be further discussed with regard to their possible tribute to prevention of BPD.

3.3.3. Discussion on clinical pharmacology

There are many gaps in the documentation of caffeine (citrate) pharmacology, also as regards the target indication “prevention of BPD”. Lack of knowledge on the exact aetiology of the disease and, consequently, the mechanism of caffeine action within the process, has consequences on the interpretability of clinical data. The underlying pathomechanisms and risk factors causing or contributing to BPD development and consequently the role of caffeine citrate pharmacology in a respective preventive setting is not entirely clear at the moment. Thus, an appropriate target population is currently not defined. This has consequences for the wording of the indication, which is presently not agreeable. The proposed SmPC states that Blectifor should be administered until the neonate is no longer dependent on oxygen or ventilator. From a clinical pharmacology viewpoint, the

relationship between the time since birth until this event (i.e. turning off the oxygen supply) and the descriptors of the caffeine concentration profile (Cmax, AUC or Cmin) would be the interest but seem not available.

Also, the provided dosing recommendations seem not sufficiently substantiated at the present time:

The selected dose of a 20mg/kg loading dose followed by 5mg/kg/d maintenance dose is the standard regimen for caffeine treatment in AOP and used in most of the provided historical studies (> 30.000 patients). It was approved also for Peyona on the basis of historic scientific literature. Steady state plasma levels of 5-20mcg/ml can be expected with the proposed regimen. The highest plasma caffeine level that has been recorded with standard doses was 43 µg/ml and the lowest level at which serious toxicity can occur is determined as 100 µg/ml according to the applicant. The SmPC of Peyona states that no safety concerns have normally been raised with plasma levels below 50 mg/l. This allows the conclusion that the dose could in general be appropriate from a safety point of view also in the prevention of BPD.

Although the proposed dose regimen might be appropriate from a safety point of view, no target range in which a positive benefit/risk profile can be assumed has been determined (see discussion on dose-response relationship in the sections below).

The same dosing scheme is recommended for all infants irrespective of their GA, PNA/PMA or weight. These factors are known to significantly influence caffeine pharmacokinetics due to maturation processes in the new-born body and caffeine requirement could differ between individuals and lead to under- or overexposure. Also, there also seems to be a genetic component relevant for caffeine response. Although the extent of the effect is unclear at the moment it could be worthwhile to include available information in section 5.1 of the SmPC.

Duration of therapy

The following recommendations are outlined in the SmPC "*Treatment should be continued until the child is no longer dependent on oxygen or ventilator assistance, which is usually at a gestational age of 37 weeks. This limit may, however, be revised according to clinical judgement in individual cases."*

The optimal duration of treatment for BPD prophylaxis seems inconclusive and might in the end need to be determined individually. However, keeping in mind the long half-life in the target population (approx. 100h), the potential for accumulation when treatment is prolonged remains a concern. The median duration of treatment stated in the PI of Peyona is reported as 37 days. There is no such statement available for caffeine (citrate) in the prevention of BPD, but the applicant states that the usual practice when using caffeine (citrate) for the prevention of BPD is to continue until 36 weeks PMA, which commonly involves at least four weeks of caffeine (citrate) therapy, which would more or less be comparable to Peyona. Furthermore, due to maturation of the organism and increasing metabolic and eliminating potential, older children might in general be less vulnerable to higher (accumulated) caffeine levels than younger children and could consequently be under dosed; however, this correlation needs to be further examined for the target population.

After weaning from respiratory support, continuing caffeine (citrate) treatment might still be prudent in order to prevent AOP or reintubation, according to the applicant. This would, however, not be within the scope of the anticipated target indication "prevention of BPD". It is important to note that there is no exact definition when "prevention of BPD" is not indicated anymore. It is not clear if BPD can still develop at a later time point (i.e. after a GA of 37 weeks) or after caffeine (citrate) therapy had been terminated.

Initiation of treatment

There is no prospectively conducted study evaluating the best time point for the initiation of caffeine (citrate) therapy to prevent BPD, however, there is a fair amount of retrospective literature data examining early vs. late caffeine with respect to several objectives and also BPD. Timing of caffeine therapy should be properly justified and clear recommendations should be given to the clinicians, if possible.

The data on the PK of caffeine was mainly derived from neonates treated for AOP. Differences between the AOP population and the target population for Blectifor (e.g. differences in respiratory support) could have an influence also on PK parameters; however, the actual impact on the validity of the provided information is unknown.

3.3.4. Conclusions on clinical pharmacology

The Applicant provided several publications, including in vitro studies, preterm patient PK and initial tolerability studies, extrinsic factor PK studies, population pharmacokinetics (PK) studies and pharmacokinetic data from phase III studies as well as in vivo studies that provide PD and dose-response or concentration-response studies with PD endpoints. The studies were conducted predominantly in premature infants

The pharmacokinetic properties of caffeine in adults are widely known. The substance is broadly used also in neonatal medicine since decades for several indications. Publications on caffeine PK in the anticipated target population are available. The preparation of the clinical pharmacology part of the submitted dossier was done in a rather superficial way, however. Although many relevant publications are submitted as full texts, several aspects of caffeine PK (and PD) relevant to this application are not sufficiently discussed.

Caffeine (citrate) is an extensively studied substance and many pharmacodynamic properties are described in the literature. The effects are mediated primarily via the antagonism of the actions of adenosine receptors in the CNS.

In ventilated neonates, caffeine increased respiratory system compliance and reduced supplementary oxygen requirements. Also effects on the cardiovascular system were observed. The exact mechanism for activity of caffeine in the prevention of BPD in the preterm neonate, however, remains unknown; a combination of several effects seems likely. The iatrogenic noxes ventilation support and/or oxygen supply have been indicated as the main drivers for BPD development. Any effect of caffeine in terms of BPD prevention is therefore likely indirect, i.e. mediated via reducing the need for, duration or invasiveness of mechanical ventilation, positive pressure ventilation or oxygen support during the first weeks of life. The role of caffeine citrate in BPD prevention is not clear at the moment, which impacts also on the wording of the indication.

Information on the relation between plasma concentration and effect is sparse. The PK/PD relationship between caffeine plasma levels and duration of respiratory support was not investigated. Most data submitted to describe Blectifor PD in the target setting were generated in the treatment of AOP. The overlap of the two indications/populations and its consequences on the interpretability of data for the present submission were not discussed by the applicant. The proposed dose recommendation seems mainly based on the standard regimen prescribed in the CAP trial, where up- and down titration was possible, however, according to the available reports. A 20mg/kg loading dose followed by a 5 mg/kg/d maintenance dose is also the standard regimen proposed in the PI of Peyona, however, up-titration is foreseen in certain cases and also the indication is different to what is intended for Blectifor. The proposed dose regimen needs to be justified with respect to the available (PK and) PD data relevant for the target indication. Also, the need for plasma level monitoring of caffeine in the

subgroup of infants in the lowest age/body weight range should be further discussed as there are indications that the therapeutic window might be narrow (see Chavez Valdez, 2011) and an individual response highly correlated with GA, PNA/PMA and weight can be expected.

Pharmacodynamic interactions with other medicinal products or substances were not addressed. In summary, there are some gaps in the knowledge of PK, PD, PK/PD relationship and the optimal dose regimen in the target population which need to be further addressed. The precise MoA of caffeine citrate in the prevention of BPD has not been fully elucidated.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

Dose response studies

No adequate studies dedicated to investigating the dose-response for caffeine (citrate) in the treatment of BPD seem to be available.

There is a fair amount of literature data reporting caffeine plasma levels after different doses summarised by the applicant. With the proposed regimen for Blectifor (20mg/kg loading dose followed by 5mg/kg/d maintenance) steady state plasma levels between approx. 5-20 mcg/mL can be expected, although the range was wider in some studies (approx. 4.8-43 mcg/mL). Higher doses lead to higher plasma levels and a linear relationship is suggested by the applicant. He claims that the concentration in serum increases proportionately to the administered dose with reference to Lee 1996 and Zohra 2013. Both publications were, however, not included in Module 5.4 of the dossier and also not included in the above tables for unknown reasons.

The optimal therapeutic dose range (plasma level target range) for prevention of BPD remains unknown. Although the proposed dose regimen might be appropriate from a safety point of view, no target plasma range in which a positive benefit/risk profile can be assumed has been conclusively determined. For other indications (treatment of AOP), a clinical effect has been noted at levels as low as 3 µg/ml. In the prevention of BPD, a lower limit of effective plasma levels of caffeine is not known, however. Main hurdles for the determination of such a target range might be that (i) for the prevention of BPD, the exact target mechanisms still seem unknown and (ii) most of the past investigations did not measure caffeine plasma levels to relate them to clinical effect (on BPD). There is one publication which was not cited by the applicant, by Turmen et al.; “Relationship of dose and plasma concentrations of caffeine and ventilation in neonatal apnea” (Semin Perinatol 1981; 5 (4): 326-31). The minimum and safe effective doses and plasma concentrations of caffeine, which would elicit a significant ventilatory response in premature babies with apnoea were explored. The authors concluded that the minimal effective dose and plasma concentration in neonatal apnoea are low, 2.5mg/kg and 2.9mg/L, respectively. From prolonged recordings, however, it is suggested that breathing patterns improve remarkably as plasma concentrations approach about 8mg/L. In how far the reported plasma levels could help defining a target level for BPD prevention is unknown.

Chavez Valdez, 2012, measured the incidence of BPD related to plasma caffeine levels in 26 preterm infants treated with the standard regimen for treatment of AOP (20mg/kg loading dose and 5 mg/kg/day maintenance dose) at 1 week. Median doses were not different between both groups (BPD/no BPD). The author emphasized the importance of maintaining plasma levels within the therapeutic range, which he determined as 10-20 ug/mL.

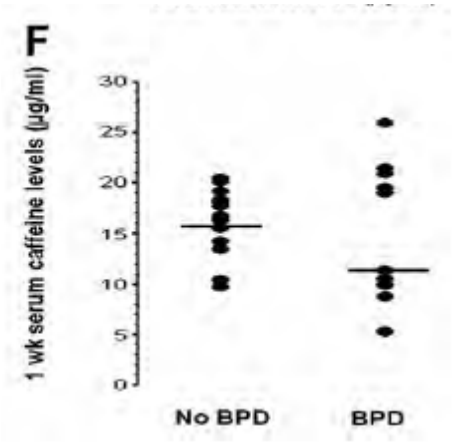
BPD developed in 11 patients. Although median caffeine levels at 1 week were not statistically different in infants with and without BPD (11.4 versus 16.5 mg/mL, respectively; P = 0.43), caffeine levels

showed a different distribution, with most of the extreme values observed in infants in whom BPD developed (Figure, F below).

Due to the low sample size, the lack of statistical analysis and based on visual inspection of data it is unclear whether the distribution of caffeine serum levels was indeed different between the BPD/non-BPD groups. The data indicate that infants in whom BPD developed showed higher plasma IL-1-beta and IL-6 and higher ratio to IL-10. This may suggests that the balance could have shifted to pro-inflammatory direction in infants with BPD. It is uncertain whether it was due to more extreme serum caffeine levels (as the authors speculate) or other factors.

One may also speculate that due to respirogenic effects of caffeine a shorter period of mechanical ventilation is needed, consequently traumatic effects to airways are also reduced. Therefore, the response to traumatic effects and systemic stress, e.g. inflammation is reduced both locally in the lung and systematically. Results show that those infants in whom BPD developed had a longer exposure to mechanical ventilation (medians: 26 vs. 2 days) and a higher incidence of confirmed infection (27 vs. 0%).

Figure F, Scatter plot of caffeine levels at 1 week stratified by BPD diagnosis, with solid line representing median.



Chavez Valdez, 2012, outlines that *"levels of caffeine outside of 10-20 ug/mL are potentially associated with a pro-inflammatory profile and may have significant clinical implications due to the increase of specific cytokines. Although studies have not definitively linked increase in TNF-α concentrations with the development of BPD, increases of other cytokines, such as IL-1b and IL-6, have been more closely linked. Impaired early IL-10 production by mononuclear cells has also been associated with BPD."* Plasma levels <10 mg/mL and >20 mg/mL can occur with the proposed dose scheme for Blectifor (20mg/kg loading dose followed by 5mg/kg/d maintenance).
Though the sample size was too small to derive statistically significant results, these data imply that individual response to standard doses has to be considered and suggest that plasma level monitoring could be worthwhile to optimise outcomes also in BPD prevention.

Also, incidences of BPD at different doses across available historical studies were investigated by the applicant. From the post-hoc analyses across different trials pictured in the below table no definite conclusion on a dose-response relationship can be drawn, however, results of the individual studies indicate that incidence of BPD declines in higher dose groups compared to lower doses. Thus, a positive dose response relationship could be assumed. Again, appropriateness of the recommended

Blectifor dosing algorithm, which is on the lower end of recommendations in the individual studies, needs to be discussed with this regard.

Steer et al. 2004 and Mohamed et al. 2015 each randomised premature infants to different caffeine regimens in two RCTs which provide some within-trial dose-response data. In an extubation trial Steer et al. compared 20mg/kg loading + 5mg/kg maintenance daily with an 80mg/kg loading + 20mg/kg maintenance regimen and as a secondary outcome report a pronounced lower BPD incidence in the high dose cohort (i.e. 34% vs. 48% at w36). Mohamed et al., in an AOP trial, compared 20mg/kg loading + 10mg/kg daily against 40mg/kg loading + 20mg/kg maintenance and as a secondary outcome report a lower incidence in the high dose cohort (22% vs. 32% at w36). Whereas indicative of a dose-response for caffeine in the treatment of BPD, these findings are not considered supportive of the dose regimen proposed by the Applicant at least in terms of efficacy. Of note, both trials refer to the outcome of oxygen supply at week 36 as 'chronic lung disease' and not as BPD.

It is also noteworthy that results of Chavez Valdez et al. 2012 who described that caffeine might have a pro inflammatory effect at high doses (>20 ug/ml) and results from Steer et al. 2003 as well as Mohamed et al 2015 who found BPD rates to be lower in higher dose groups, appear controversial. The hypothesized anti-inflammatory mode of action of caffeine in the respective indication might need to be questioned with this regard.

Table 1: Incidence of BPD related to caffeine dose in clinical studies.

Study reference	Dose of caffeine citrate (Load/ daily maintenance, mg/kg)	Incidence of BPD (numbers)	incidence of BPD as a percentage, (significance)
CAP trial (Schmidt 2006)	0 / 0 (placebo group)	447 / 953	46.9 % (compared with treatment group OR 0.65 (95% CI 0.54-0.70))
	20 / 5 (caffeine treatment group)	349 / 961	36.3%
Steer 2003	20 / 5 (standard dose group)		48%
	80 / 20 (very high dose group)		34% (high v standard dose group p=0.06)
Mohamed 2015	20 / 10 (high dose group)	19 / 60	31.7%
	40 / 20 (very high dose group)	13 / 60	21.6% (high vs very high dose group p=0.31)
Chavez-Valdez 2011	20 / 5	11 / 26	42.3%
Lodha 2015	20 / 5 was "usual practice"	1339 / 5101	27.8%

McPherson et al. (A pilot randomized trial of high-dose caffeine therapy in preterm infants; Pediatr Res. 2015 Aug; 78(2): 198-204., literature not included in Module 5.4) randomly assigned seventy-four preterm infants (≤30 weeks gestational age) to either a high (80 mg/kg IV) or standard (20 mg/kg IV) loading dose of caffeine citrate in the first 24 hours of life. MRI and neurobehavioral testing were undertaken at term equivalent age. Infants returned at 2 years of age for developmental testing. They found an increased incidence of cerebellar haemorrhage in infants randomized to high-dose caffeine

(36% vs. 10%, p=0.03). Infants in the high-dose caffeine group also demonstrated more hypertonicity (p=0.02) and more deviant neurologic signs (p=0.04) at term equivalent age. Diffusion measures at term equivalent age and developmental outcomes at two years of age did not differ between groups. Thus, a dose response relationship as regards safety outcomes could also be assumed which has to be considered in the discussion of appropriateness of the proposed dose recommendations.

The proposed dose algorithm for Blectifor follows recommendations as outlined in the PI of Peyona, caffeine citrate approved for preterm infants with AOP. According to the proposed PI of Blectifor "doses adjusted according to clinical judgement" are possible. It should be specified by the applicant when and how these adjustments shall be performed and the literature supporting this statement should be outlined (see attached SmPC and PI). It is noted that for AOP an escalation of maintenance dose up to 10mg/kg/d is approved (see PI Peyona). In how far this could be beneficial (or detrimental) also for patients in prevention of BPD was not discussed by the applicant and will need to be further explored.

In the pivotal CAP trial the maintenance dose could also be escalated to 10mg/kg/d if AOP persisted. However, no dose adjusted outcomes were reported and the number of patients where dose escalation was performed is unknown. This makes also for interpretation of results reported for BPD incidences in this study somewhat difficult.

The dose recommendations for Blectifor need to be further substantiated, addressing both efficacy and safety considerations and with respect to the claimed target indication.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 3 Summary of efficacy for the CAP trial (Schmidt 2006, 2007, Davis 2010)

Title: Caffeine for Apnoea of Prematurity		
Study identifier	unknown	
Design	2006 infants with birth weights of 500 to 1250 g were randomly assigned to receive either caffeine (citrate) or placebo until therapy for apnea of prematurity was no longer needed. The following reasons why clinicians intended to use caffeine (citrate) were documented: to prevent apnea, to treat apnea, or to facilitate the removal of an endotracheal tube. The primary outcome was a composite of death, cerebral palsy, cognitive delay deafness, or blindness at a corrected age of 18 to 21 months. Bronchopulmonary dysplasia was prospectively defined as secondary outcome measure and defined by the need for supplemental oxygen at a postmenstrual age of 36 weeks.	
	Duration of main phase:	18-21 month
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	Follow-up up to 5 years reported
Hypothesis	Superiority	

Treatments groups	Caffeine (citrate) group		Caffeine citrate 20mg/kg loading dose once, 5mg/kg/d maintenance dose (could be increased to a max of 10mg/kg/d or reduced at investigators discretion). It was recommended to continue therapy with the study drug until the infant had tolerated at least five consecutive days without the use of positive airway pressure. median 37 days , 1006 randomized
	Placebo group		An equivalent volume of normal saline (dosing modalities see above for verum), median 36 days, 1000 randomised
Endpoints and definitions	Primary endpoint	No label intended	a composite of death, cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18 to 21 months
	Relevant Secondary endpoint	Target indication Prevention of BPD	Bronchopulmonary dysplasia defined by the administration of supplemental oxygen at a postmenstrual age of 36 weeks.
	Relevant Secondary endpoint	No label intended	Mortality before a corrected age of 18-21 months;
	Secondary other: specify endpoint	No label intended	Short term: ultrasonographic signs of brain injury, necrotizing enterocolitis, retinopathy of prematurity, and growth. Long term: death, cerebral palsy, cognitive delay, deafness, or blindness
Database lock	Not specified. Recruitment Oct 11, 1999 - Oct 22, 2004. Short term data published in 2006, 18-21 month data published in 2007. 5-year FU data published in 2012. It is unclear if analyses published in 2006 were made only after database lock for the 18-21 month FU time point.		

Results and Analysis

Analysis description	**Secondary outcomes BPD and Mortality**			
Analysis population and time point description	BPD: All patients alive at week 36 were analysed. Mortality: death before a corrected age of 18 months was evaluated			
Descriptive statistics and estimate variability	Treatment group	Caffeine	Placebo	
	Nr of subjects available for BPD EP	963	954	
	BPD	350 (36.3%)	447 (46.9%)	
	Nr of subjects available for mortality EP	974	970	
	Mortality	62 (6.4%)	63 (6.5%)	
Effect estimate per comparison	BPD	Comparison groups	Caffeine vs. Placebo	
		Unadjusted OR	0.65	

		Odds Ratio Adjusted for Center and Patient Characteristics (95% CI)*	0.64 (0.52–0.78)
		P-value	<0.001
	Mortality	Comparison groups	Caffeine vs. Placebo
		Unadjusted OR	0.98
		Odds Ratio Adjusted for Center and Patient Characteristics (95% CI)*	0.99 (0.65 – 1.50)
		P-value	0.87
Notes	*Important additional analyses:* -) The median postmenstrual age at last oxygen use was 33.6 vs. 35.1 weeks (IQRs: 30.6-36.9 vs. 32-37.6; p<0.001) for caffeine citrate and placebo (approximately 10 days shorter duration of oxygen supply). -) The median PMA at last use of endotracheal tube was 29.1 vs. 30 weeks (IQRs: 28-31 vs. 28.7-31.9; p<0.001) and the median PMA at last use of positive airway pressure was 31 vs. 32 weeks (IQRs: 29.4-33 vs. 30.3-34; p<0.001) for caffeine (citrate) and placebo. -) In subjects not receiving positive pressure ventilation BPD incidence was 22.5% vs. 21.1% (OR 1.08, 95% CI: 0.64-1.82) for caffeine citrate vs. placebo. The current analyses of secondary outcomes were adjusted according to study center and patient characteristics with the use of a logistic-regression model that included terms for treatment, center and baseline patient characteristics. The proposed logistic regression model for the analysis of BPD is considered generally appropriate. The analysis methods are not described in great detail in the paper, assessment is limited with this regard.		

Additional important findings, reported as 'trial conduct' by study authors:

The median postmenstrual age at last **oxygen use** was 33.6 vs. 35.1 weeks (IQRs: 30.6-36.9 vs. 32-37.6; p<0.001) for caffeine (citrate) and placebo respectively. This could also be expressed as an approximately 10 days shorter duration of oxygen supply.

As additional findings, the median PMA at last use of **endotracheal tube** was 29.1 vs. 30 weeks (IQRs: 28-31 vs. 28.7-31.9; p<0.001) and the median PMA at last use of **positive airway pressure** was 31 vs. 32 weeks (IQRs: 29.4-33 vs. 30.3-34; p<0.001) for caffeine (citrate) and placebo, respectively.

Clinical studies in special populations

No clinical studies in other populations than pre-term neonates have been provided which is acceptable for this well-established use procedure.

There is a considerable current interest in the genetic background of caffeine response and BPD, and this is likely to be the subject of future research.

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

The Applicant himself has not performed analyses across trials and only discusses the individual trial findings (see also "supportive studies" below) on a very high level. Issues of consistency or discrepancies in findings and/or populations studied across trials have not been addressed in a

structured or reproducible manner, which complicates any comprehensive and integrative assessment of the overall database.

According to the Applicant the study populations were broadly homogeneous across studies, which is not easily agreed on as this statement will evidently depend on the level of granularity applied when describing them, but also based on the variable incidence BPD rates reported by individual trials. Substantial heterogeneity already within studies was evident for important baseline characteristics, which could on the one hand improve generalisability of results, but, based on subgroup analyses performed on the CAP sample and non-negligible differences in BPD incidences between trials, raises questions as to the uniformity of caffeine benefit across relevant subgroups.

Different, varying or insufficiently described caffeine (citrate) regimens were used across and within trials, and based on available signals suggesting dose-response, the pragmatic adoption of 20mg/kg loading + 5mg/kg maintenance dose as 'standard regimen' for a BPD label cannot readily be endorsed. Regarding the optimal timing of therapy onset, i.e. chronological age (or potentially the temporal relationship to ventilation/oxygen initiation) there are data suggesting that this might play an important role.

The "negative" Dobryansky RCT referred to seems to be available as conference abstract only and did not show any benefit in terms of death and BPD or severe BPD associated with caffeine use (i.e. 43% vs. 45% for caffeine vs. not further specified SOC in n=60 vs. 60 for the composite EP). It is agreed that it is difficult to draw firm conclusions based on the insufficient documentation (e.g. on blinding, SOC definition) that is available.

It would have been expected from the Applicant to formally contextualise the CAP data with other data sources, particularly the large scale cohorts (Dobson et al., 2014, Lodha et al., 2015, Taha et al., 2014, see below) to ascertain the estimated caffeine effect in the caffeine arm, but also with natural history datasets or the placebo arms from other RCTs testing different candidate compounds for the prevention of BPD (e.g. Vitamin A) to ascertain the natural course incidence. This should still be done to "confirm" CAP findings independently but also with an eye on potentially identifying (1) temporal shifts in outcome due to changes in clinical practice, (2) key baseline characteristics that could guide the definition of an appropriate target population and (3) co-interventions that either mitigate or pronounce any caffeine effect.

The focus of most publications after the Schmidt et al., 2006 publication apparently shifted from the fundamental question about whether caffeine (citrate) is at all efficacious in BPD prevention to how/when and, to a lesser degree, in whom it should be used.

It is furthermore referenced to three recent systematic reviews (shortly summarised in table 2) that have addressed the question of BPD prevention, not exclusively focusing on caffeine, which is endorsed as relevant data source (notwithstanding the previously made comments on the apparent lack of a systematic approach to literature identification):

Park et al., 2015 screened for RCTs, case-control studies and prospective/retrospective matched cohort studies in VLBW infants comparing 'early' vs. 'late' caffeine use (3-day threshold) and reporting death, BPD or both combined. The research question is considered of limited relevance as it does not encompass a comparison of caffeine vs. other interventions or placebo. The authors conclude that based on Patel et al., 2013, Taha et al., 2014, Dobson et al., 2014 and Abbasi et al., 2010 and Davis et al., 2010 (with the exception of the Abbasi data, all being referenced by the applicant) that 'early' treatment with caffeine seems to convey greater benefit in terms of death/BPD than 'late' treatment.

Beam et al., 2014 exclusively screened for RCTs on pharmacological candidate interventions for the prevention of BPD. For caffeine, the authors identified only the CAP trial as sole eligible source of evidence and describe the findings as stated above. A comprehensive and critical discussion on the problems surrounding BPD definition and the weaknesses of the 'oxygen supply at 36weeks PMA definition' is also provided. The level of evidence in the publication by Dobson was classified as "moderate" and the others ranged from "low" to "very low" based on their observational design.

Jensen et al., 2015 screened broadly for studies that assessed BPD (oxygen supply at 36weeks PMA definition) across different interventions as primary or secondary outcome. The CAP trial was selected as data source for the comparison caffeine vs. placebo, the publications by Dobson, Lodha, Patel, Taha and Davis (see above) were referred to concerning the question about 'early' vs. 'late' treatment initiation. Schmidt et al., 2006 was considered as "high" level of evidence according to GRADE. The authors recommend the treatment of extremely preterm infants with caffeine for BPD prevention and suggest that early initiation may confer additional benefit.

Overall, it is considered reassuring that the cited systematic reviews identify by and large the same data sources as also referred to by the Applicant. The CAP trial was considered high quality evidence and is considered pivotal for this application. The reviews came up with rather similar high-level conclusions as to the benefit or benefit/risk associated with caffeine (citrate) use as the Applicant. At the same time, a number of open questions were repeatedly raised pertaining to the optimal caffeine (citrate) regimen, time point of initiation of therapy, identification of a target population and overall role in the multimodal perinatal respiratory management.

It is worth noting that an additional very recent review focusing on 'early' caffeine therapy in preterm neonates (Kua & Lee, 2016) has been identified that was not referenced by the applicant possibly due to its publication date. Primary outcomes of interest were stated as BPD and mortality, but a broad range of secondary outcomes was also considered. This likely explains why more data sources were identified for synthesis than in the other cited reviews. Of note, meta-analysis of 3 retrospective cohort studies contributing 30.000+ patients showed that the use of 'early' caffeine was associated with an increased mortality compared to 'late' use (which was not confirmed in a meta-analysis for 2 RCTs) (see clinical assessment report for further details). Whereas this finding does not necessarily raise concerns as to a potentially detrimental effect in terms of increased mortality of caffeine compared to placebo, they contradict a perceived consensus on early administration being preferred over late initiation of caffeine (citrate) treatment.

The retrospective study of Hand et al (2016) revealed no influence of timing of caffeine on BPD within the first seven DoL which emphasizes the need of further data. However, as a majority of the studies shows benefit of early start of caffeine, it should be explored if further guidance could be provided in the SmPC.

Supportive studies

The referred-to studies (shortly summarised in table 2) are based on premature neonate cohorts from the US (**Patel 2012/Dobson 2014, Taha 2014**) and Canada (**Lodha 2015**). All report lower BPD incidence (as well as "BPD or death" incidence) among patients who received early caffeine treatment compared to 'late' recipients, but rates vary considerably between studies as described above.

Dobson defined BPD as the "need for any respiratory support at postmenstrual age 36 0/7-36 6/7 weeks if <32 weeks gestational age (GA) at birth or at 28-34 postnatal days if 32 weeks GA at birth". Furthermore propensity matching was used and it is worth noting that among matched patients (for several baseline variables including: GA, BW, sex, race, Apgar at 5 min, centre and others, as well as

DOL1 variables of respiratory support, apnoea and others) the difference between 'early' and 'late' more than halved compared to the unmatched comparison and the difference in mortality was inversed (i.e.4.5 vs. 3.7% in favour of 'late' administration). This could be interpreted as the early/late discrimination also separating different patient populations. An additional finding was that in a subgroup analysis by GA strata, the effect on BPD odds caused by early caffeine was consistent across strata but in infants below 24 weeks GA who received early caffeine an increased mortality was observed. The authors considered this finding as potentially caused by survival bias which could indeed serve as an explanation.

Lodha used a BPD definition of "supplemental oxygen at week 36 PMA or at discharge from NICU". They also report that a small group (n=416) did not receive caffeine. It is not clear why that was the case, but provided these infants were similar to the caffeine recipients in key characteristics, the BPD incidence in these children would have been of particular interest but has not been stated. Differences between early/late caffeine in terms of BPD incidence were only seen in analysis adjusted for GA, antenatal steroid exposure, small for GA, site, intubated on d2, SNAP-II score and surfactant administration, but not in unadjusted analysis. The mortality pattern observed by Dobson was not confirmed.

Neither caffeine (citrate) regimens used nor overall exposure have been reported for either trial (instead it has been required as a yes/no variable) so no information on dose-response could be derived.

Overall, the debate about whether or not caffeine (citrate) treatment should, if at all, be initiated early after birth (i.e. prior to day 3) seems not conclusively settled. In a reaction to the Dobson findings, the author of the CAP study agree in an interesting editorial (Schmidt et al., 2014, Journal of Pediatrics) that the debate about the optimal time point might rather be one about whether the post-hoc demarcation at 3 days divided two distinct populations.

In the context of this application, the 4 cited studies are in principle considered relevant for their size and the fact that they could serve as a basis for a comprehensive discussion on the applicability of a broad BPD prevention indication in preterm neonates without further restrictions or specifications, trends in SOC that could have affected BPD incidences over time and/or caffeine's therapeutic benefit thereupon and on the consistency of findings with other data sources (i.e. CAP), all of which yet have to be provided by the Applicant.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

This is an application based on Article 10a of Directive 2001/83/EC for an orphan indication, with inherent limitations regarding the availability and accessibility of (primary) study data. However, this does not obviate the need to conclusively justify a positive benefit/risk for caffeine citrate for the intended indication in a clearly defined target population and well defined modality of use.

Based on a not further specified literature search (that can therefore not be commented on as regards the criteria applied and its comprehensiveness), the applicant has identified (among others) four key publications reporting data from one single, reportedly double-blind, placebo-controlled randomised trial investigating the effects of caffeine citrate in roughly 2000 infants with a birth weight of 500-1250g recruited during the first 10 days of life in a hospital setting (i.e. the CAP trial). Infants were eligible "if caffeine treatment was considered appropriate by the treating physician" and were randomised 1:1 to receive caffeine (citrate) or placebo. Patients were recruited internationally between

1999 and 2004. A total of 2006 infants were enrolled - 994 in Canada, 58 in the United States, 520 in Australia, and 434 in Europe and Israel. Neither study protocol nor study report is available.
The primary objective was to investigate the benefit of caffeine citrate over placebo in terms of a composite of death, cerebral palsy, cognitive delay, deafness or blindness at a corrected age of 12-18 months. Bronchopulmonary dysplasia was stated as a pre-specified secondary outcome and defined as the "need for supplemental oxygen at a postmenstrual age of 36 weeks".
The included patient population indirectly reflects the proposed target population of "preterm neonates" via the eligibility criterion of an upper birth weight limit of 1250g, but inclusion and exclusion criteria have not been outlined in detail and, as discussed below, there are open questions as to the adequacy of such a broad definition. In how far the included study centres and respiratory protocols are reflective of current SOC in NICU management is not clear. It should be noted that respiratory management of preterm infants is inevitably multimodal, involving perinatal pharmacological interventions as well as ventilation and oxygen support of varying invasiveness and intensity. Some of these interventions have been plausibly linked to BPD development (e.g. mechanical ventilation) others have, similar to caffeine citrate, been explored regarding their potential to prevent BPD (e.g. steroids, CPAP).

The comparison against placebo is considered informative and, in light of no approved therapy for the prevention of BPD being available, also the preferred one to enable conclusions on the efficacy of caffeine citrate.

'Mortality' and 'BPD incidence' are seen as the key endpoints in this frail population and have to be considered competing outcomes. No composite combining these two has been devised however.

The main study duration, stated as 18-21 months for primary outcome assessment, is considered acceptable as it encompasses a PMA of 36 week for the BPD outcome and sufficient follow-up for the mortality endpoint. 5-year follow-up data are also available for a considerable proportion of study participants. No long-term lung outcomes have been reported from the CAP trial which is an important shortcoming for the interpretation of the BPD incidence at 36 weeks, which has to be considered a surrogate endpoint for long-term pulmonary sequelae, even more so in light of the severe deficiencies that have been identified with the adjudication of BPD:

Several BPD definitions have been proposed and investigated since the 1980s (the progression is nicely outlined in a key publication by Maitre et al., 2015, not provided by the Applicant) including attempts to differentiate severity levels/grades. The apparently mostly used definition of BPD, i.e. 'supplemental oxygen at 36 weeks postmenstrual age' (the 'Shennan definition' based on the seminal Shennan et al., 1988), has been criticized in the past for being subjective, not formally addressing the actual need for oxygen support, not further specifying 'oxygen supply' and moderate performance in terms of predictive properties for long-term outcomes of such a definition. It is also worth noting that this definition stems from a time were intensive care differed markedly from nowadays' standards. Inclusion of physiologic criteria (i.e. weaning attempts, saturation targets) to determine the need for oxygen has been stipulated but such have obviously not been used frequently, at least in caffeine (citrate) trials. It should be noted, however, that depending on the definition used, the BPD incidences were found to vary substantially in given datasets and the magnitude of difference between disease definitions has been likened to the reported effect sizes for putative BPD-preventive agents over placebo. Whereas the Applicant has briefly and theoretically addressed the issue of BPD adjudication it appears that more elaborate BPD definitions have either not been considered during study selection and compilation/interpretation of results or such have never been applied in caffeine (citrate) trials.

As regards trial conduct, it is noted that of the 5000+ infants who were candidates for trial inclusion, only ~2000 were allocated to either treatment arm, and of those who were not randomized, 667 were excluded due to bad prognosis and 681 were not approached for unclear reasons. As a result, the generalisability of the results obtained in the trial sample to the target population could be questioned. It was left at the treating physicians' discretion to increase or decrease the maintenance caffeine or placebo dose during the trial as deemed necessary either based on lack of efficacy or AEs/toxicity. Actual (total) exposure and regimens used remain unclear. Accordingly, dose-exposure-response data are also not available. More generally, adherence to and deviations from the protocol appear to have not been recorded/reported systematically.

The sample size (which was justified on the basis of the primary composite variable) was apparently sufficient to demonstrate a significant reduction in BPD incidence between treatment groups. BDP incidence was one of several secondary outcomes and multiplicity was not accounted for in the analysis, which may increase the risk of a false positive finding. However, given the observed p value of <0.001 (for the comparison between treatment arms of BPD incidence in infants who were alive at a PMA of 36 weeks), the difference would still be considered statistically significant if a conservative multiplicity adjustment method was applied taking all reported endpoints into consideration. Furthermore, it has not been reported whether early discharged infants were reliably defined as having no BPD, how children discharged on oxygen support where considered and whether there were missing values (and how these have been dealt with in analyses).

In Schmidt et al., 2006 it is stated that with the exception of an external safety monitoring committee and study pharmacists (presumably at study sites) nobody involved in study or care of patients was aware of study arm assignment. Davis et al., 2010 state that caregivers and outcome assessors were "masked to assignment". Measures to assure masking of treatment (e.g. dedicated study nurse to administer caffeine orally, appearance of placebo IV injection etc.) were not described in the publications, however, and it cannot fully be excluded that e.g. the preparation of the IP at the study site led to some information flow concerning the allocation and it is not clear whether blinding was sufficiently maintained throughout the relevant observational period. As the BPD definition employed is subjective, appropriate blinding is considered important for the internal validity of results. Potential differences in overall NICU management in case of knowledge about treatment allocation can also not be fully excluded and respective information seems to be lacking (e.g. switch in or newly introduced respiratory support during trial).

Overall, the CAP study is considered the centrepiece of evidence for efficacy of caffeine citrate in BPD prevention in this application due to its design, size and relevance for the concerned research question. Among referenced studies, most weight is accordingly given to its results but, importantly, also to the critical interpretation of its findings that entailed subsequently.

In a side note, the Applicant refers to a 'negative' RCT (i.e. Dobryansky et al., 2012) which seems to be available as conference abstract only and did not show any benefit in terms of death + BPD or severe BPD associated with caffeine (citrate) use. It is agreed with the Applicant that it is difficult to draw firm conclusions based on the insufficient documentation (e.g. on blinding, SOC) that is available. However, if additional information was available on this trial, this would be of interest for its design and the placebo control.

Controlled trials without placebo comparison but comparing different doses or treatment initiation time points, as well as single arm studies were also included in the dossier and are considered relevant insofar as they might inform recommendations regarding posology, optimal treatment timing and duration as well as target population definition. They were also considered to judge upon consistency of findings between trials.

It is furthermore referenced to three recent systematic reviews that have addressed the question of BPD prevention, not exclusively focusing on caffeine (citrate) as intervention and not necessarily focusing on the question "if" caffeine (citrate) conveys benefit but rather "when" or "for whom". These are in principle agreed as relevant data sources (the previously made comments on the apparent lack of a systematic approach to literature identification notwithstanding).

Efficacy data and additional analyses

Whereas there is a fair amount of data on the dose-exposure relationship for caffeine (citrate) in the target population, exposure-response and dose-response relationships in BPD prevention specifically have not been studied extensively and firm conclusions cannot be drawn. Exposure-response data are ambiguous in the studied range of serum caffeine, and whereas some dose-dependency for caffeine and BPD development has been observed, the respective studies would, from an efficacy perspective, suggest considerably higher induction and maintenance doses than those suggested by the Applicant and used in the CAP trial.

As stated above, accounting for the vulnerability of the target population of preterm infants and the intended label claim, the outcomes "mortality" and "BPD incidence" are considered of primary interest for efficacy assessment.

In the CAP trial, mortality rates did not significantly differ between treatment arms, i.e. 5.2% vs. 5.5% (caffeine citrate vs. placebo) prior to first discharge home, 6.4% vs. 6.5% before 18 months corrected age and 6.8% vs. 6.9% before 5 years corrected age, at least indicating a non-detrimental effect of caffeine-citrate on overall survival.

BPD incidence prior to first discharge home differed significantly between treatment arms: 36.3% vs. 46.9% (caffeine citrate vs. placebo) with an OR adjusted for centre of 0.63 (95% CI: 0.52-0.76; $p<0.001$) and an OR of 0.64 (95% CI: 0.52-0-78) if adjusted for additional baseline characteristics (i.e. GA, sex, presence of antenatal steroids, multiple birth, endotracheal tube at randomisation).

To better understand the observed caffeine citrate-related effect on BPD, it seems more straightforward to express this effect as reducing the need for oxygen supply (of unknown intensity in terms of e.g., h/day or FiO_2) by approximately 10 days rather than arguably overstating this results as a reduced BPD incidence that simply relies on 'oxygen use at week 36' as defining element. More specifically, the median PMA at last oxygen use was 33.6 vs. 35.1 weeks (30.6-36.9 vs. 32-37.6 IQRs) in the caffeine (citrate) and placebo groups, respectively. It is not to disregard the clinical value of complete weaning from oxygen, but it seems warranted to consider e.g. 'time to oxygen weaning' or 'time on oxygen support' as continuous outcome rather than assuming that the time point of week 36, and dichotomisation for this threshold, is definitive for acute BPD and even more so, predictive for subsequent related risks. The additional finding that infants were one week younger (median values) at the time of last use of intubation and last use of positive airway pressure ventilation in the caffeine (citrate) arm is considered supportive of caffeine's purported role as weaning support.

BPD has been related to long-term pulmonary sequelae such as lower-respiratory tract infections, reduced lung function, airway hyperresponsiveness, etc. (e.g. Eber & Zach, 2001) and prevention of such late morbidities would be considered the main therapeutic benefit of BPD prevention. Unfortunately, neither the 18-21 month follow-up publication on the CAP dataset, nor the 5-year follow up provide any information on long-term pulmonary outcomes which might have allowed to further substantiate the clinical relevance of the findings at a PMA of 36 weeks, which is an important uncertainty for understanding the study results.

A label claim for caffeine citrate of “preventing BPD” as currently proposed, suggests that there will be no tissue damage in ‘responders’ and, following from that, no long-term respiratory sequelae. In fact, based on the discussion above, a graduation might be necessary to describe the actual effect observed and for benefit/risk assessment. This has also been reflected by Maitre et al., 2015 who mandate an understanding of “*lung disease in preterm infants as pathophysiological continuum that may have lasting effects independent of the current oxygen-based definition*”. The applied BPD definition arguably blurs the actual treatment effect, and even if this definition has been applied uncritically in the past by some study authors, it has been fundamentally criticised by others. This shall not be ignored when interpreting the reported benefit of caffeine (citrate) as prophylactic treatment.

A number of subgroup analyses on the CAP data, as well as several studies on independent datasets have raised questions regarding the consistency of the reported caffeine citrate effect across the spectrum of BPD-related, key baseline characteristics of the infants studied. These are considered important, as the CAP trial recruited very broadly among preterm infants and without focusing on BPD risk. For example, in subjects not receiving positive pressure ventilation, the BPD incidence was 22.5% vs. 21.1% (OR 1.08, 95% CI: 0.64-1.82) for caffeine citrate vs. placebo, indicating preterm neonates are at risk of BDP only if they have been ventilated. The risk of BDP could be considerably low with non-invasive respiratory support. Also the publication by Davis 2010 concluded that there was no benefit of caffeine in patients NOT receiving respiratory support.

Apart from apparent large differences in baseline risk for BPD development depending on the degree of prematurity, ventilation modality (i.e. intubation, positive airway pressure) and time point of caffeine (citrate) treatment initiation postpartum have been found as potential marker of response to caffeine (citrate). The applicant has not addressed these issues with a view on a potential indication wording. Limitations as to the access to primary data are acknowledged in the present case. That being said, the available data suggest that the definition of a target population as well as devising an optimal caffeine citrate regimen need further consideration to really understand the benefit of caffeine in BPD prevention.

The applicant has not performed analyses across trials and only discusses the individual trial findings on a very high level. Issues of consistency or discrepancies in findings and/or populations studied across trials have not been addressed in a structured or reproducible manner which complicates any comprehensive and integrative assessment of the overall database regarding efficacy data. It would have been expected from the Applicant to formally contextualise the CAP data with other identified data sources.

In this context it is worthwhile noting that spurred by the results of a very recent, large retrospective cohort study, investigating the optimal timing of caffeine (citrate) therapy initiation in 60000+ infants, the authors of the original CAP study stated in a reaction that “*healthy VLBW infants with GA >29 weeks not requiring respiratory support should not be enrolled in a trial of early caffeine prophylaxis to reduce BPD or death because their risk of both outcomes is very low*” and even recommend against treating these infants with caffeine at all, “*unless they develop apnoea*” in a request for further research in this population (Schmidt et al., 2014).

Furthermore, based on the currently provided data there might be an overlap of the populations covered by the indication applied for in the context of this application, "prevention of BPD," and "treatment of apnoea of prematurity" (AOP).
The CHMP asked the applicant to provide an estimate of the extent of overlap of the target populations covered by the two indications. It should be clarified how the prescribing neonatologist should decide which caffeine product to use in preterm infants at risk of BPD but also requiring treatment of AOP. The discussion should also address the mechanism of action of caffeine citrate in the treatment of AOP

versus in the prevention of BPD, where the claimed MoA has not been substantiated by the submitted data.

3.3.7. Conclusions on clinical efficacy

Based on the data provided, caffeine citrate appears to convey benefit as a supportive measure in the respiratory NICU management of premature infants but the interpretation of efficacy findings in the context of the intended label needs further discussion.

Based on remaining uncertainties pertaining to the underlying pathomechanisms and risk factors causing BPD or contributing to its development, the exact role of caffeine citrate in the prevention of BPD is not clear. There are questions pertaining to the definition of a most appropriate target population where a positive benefit/risk is to be expected. Apart from that, the used definition of BPD (i.e. need for continued 'oxygen supply at a PMA of 36 weeks') has important weaknesses.

In addition, a number of open questions pertaining to the anticipated long-term benefit, optimal caffeine (citrate) and adequate dosing regimen have been identified.

Overall, the compiled data do not support the rather broad indication wording for "prevention of BPD" in premature infants, and the population where a positive B/R ratio could be expected needs to be further characterised.

3.3.8. Clinical safety

Caffeine therapy in premature neonates, at the dose recommended in this application (and higher) has been used in clinical practice for over 35 years. There is a considerable body of clinical data from short-term clinical trials, long-term safety studies and reports of toxicity, which allow a comprehensive view of caffeine's safety profile in this age group.

The applicant has submitted an overview of publications providing information on the safety of caffeine (citrate) therapy irrespective of the indication for use. The dosing regimen proposed in this application is at the lower limit of the dose regimens as reported in the literature. As stated in the previous sections, the population as defined by the indication wording as well as the optimal dose regimen for Blectifor remain to be defined yet. No specific safety data in the target indication/population has been provided. The patient population in need for BPD prevention might differ somewhat from neonates treated for AOP, which is the population in whom most of he provided data was generated. It is e.g. unknown if for BPD prevention a longer treatment duration can be expected or if the timing of initiation of treatment differs compared to AOP treatment. The applicant should discuss if the safety profile of caffeine (citrate) could differ in BPD prevention and if the provided literature is applicable and relevant with this regard.

Patient exposure

Overall extent of exposure

The number of premature infants exposed to caffeine (citrate) treatment in the various different clinical studies, described in the preceding section, is summarised as follows.

Numbers of premature infants exposed to caffeine:

• Placebo or no-treatment controlled studies: 1,634

• Observational or active comparator studies: 2,189

• Case reports of caffeine accidental toxicity: 13

• Long-term neurodevelopmental and growth studies: 2374

• Single dose studies: 167

The applicant has not provided details on the search terms used and on criteria for including publications other than the following statement: “The clinical studies which recorded adverse events, and the plasma [caffeine] levels associated with AEs….” The literature research and selection of studies is not clear. A systematic literature search is requested and details concerning search strategy and study selection shall be provided.

The numbers of the summary table stratifying the exposed infants by study types do not agree with the numbers in the tables listing the individual studies. (The applicant refers to the CAP study with different numbers concerning the study population in different tables.) Since these numbers serve as basis for the frequency allocation, the applicant is requested to clarify the numbers.

Concerning the characteristics of study population the applicant states that all of the subjects in these safety studies were premature infants in intensive care, being treated with caffeine (citrate) in the first ten days of life as (i) treatment for AOP, (ii) to assist in extubation or (iii) to prevent AOP. However, homogeneity of the population across studies is questioned in the efficacy sections of this report.

Since it can be assumed that over the years the population has changed with regard to the gestational age of the exposed infants, the applicant is requested to elaborate on the effect of the degree of prematurity on the safety outcomes under caffeine (citrate) treatment and on the limitations of the safety database concerning the very premature infants, considering the limited number of recent publications. As mentioned above it can be assumed that over the years the population has changed with regard to the gestational age of the exposed infants. Nowadays more and more children < 500g birth weight will survive. These infants are considered candidates for caffeine (citrate) treatment, however, an underrepresentation of this cohort in the provided studies can be assumed. Unlike in utero, the preterm neonate metabolises caffeine very slowly (mean half-live 100 h compared to approx. 5h in the adult). Caffeine is an adenosine antagonist and very early exposure could influence (i) development of adenosine receptor patterns and (ii) alter the development of the individual receptors with potential consequences on receptor sensitivity. The clinical relevance of this uncertainty remains unaddressed. The applicant is requested to discuss if the degree of prematurity could have an influence on safety outcomes and discuss the limitations of the safety database concerning the very premature infants considering the limited number of recent publications. This is considered necessary also in the light of the need to better characterise the population of preterm neonates eligible for caffeine for prevention of BPD. A discussion of safety outcomes for different cohorts based on gestational age shall be provided, if possible.

Adverse events

Table 4

Table: Studies using standard dosage ie 20 mg/kg loading, then 5 (increasing to 10 if required) mg/kg/day as maintenance, or lower.

Adverse Event	Number	Percent	Frequency
Placebo controlled or no-treatment controlled studies (n caffeine = 1099)			
Tachycardia >180 bpm	approx 7	0.63	Uncommon
Irritablity / jitteriness	approx 5	0.45	Uncommon
Observational or active control studies (n caffeine = 1063)			
Tachycardia >180 bpm	approx 47	4.27	Common
Irritablity / jitteriness	6	0.54	Uncommon
Gastric stasis / feed intolerance	76	6.92	Common
Hypoglycaemia	0	0	Unknown (cannot be estimated)
Hyperglycaemia	8	0.72	Uncommon
Diuresis	5	0.45	Uncommon
Enteral bleed	1	0.09	Rare
Seizure	1	0.09	Rare
Plasma [caffeine] > 50 µg/ml	0	0	Unknown (cannot be estimated)

Table 5

Table: Studies using higher dosages of caffeine

Adverse Event	Number	Percent	Frequency
Placebo controlled or no-treatment controlled studies (n caffeine = 145)			
Tachycardia >180 bpm	0	0	Unknown (cannot be estimated)
Irritablity / jitteriness	0	0	Unknown (cannot be estimated)
Observational or active control studies (n caffeine = 274)			
Tachycardia >180 bpm	37	13.5	Very common
Irritablity / jitteriness	approx 18	6.56	Common
Gastric stasis / feed intolerance	66	24.1	Very common
Hypoglycaemia	1	0.36	Uncommon
Hyperglycaemia	0	0	Unknown (cannot be estimated)
Diuresis	0	0	Unknown (cannot be estimated)
Enteral bleed	0	0	Unknown (cannot be estimated)
Seizure	0	0	Unknown (cannot be estimated)
Plasma [caffeine] > 50 µg/ml	4/5 studies	All where daily dose is ≥20 mg/kg	Common

According to the applicant other methylxanthines do not have a qualitatively different spectrum of adverse effects or toxicity; they differ from caffeine only quantitatively. Literature supporting this statement has not been provided. Due to the large safety database for caffeine this is acceptable, however.

Under the heading of other significant adverse events the applicant lists safety findings from scientific literature without further discussing their relevance or the need to include them in the SmPC. The Applicant is requested to provide a discussion concerning the relevance of adverse events detected in the literature for the SmPC wording.

Central nervous system

In this section the applicant refers to a possibly altered sleep pattern (among other adverse reactions), according to Brandon, 2005. In addition, a publication titled “Apneic preterms and methylxanthines: arousal deficits, sleep fragmentation and suppressed spontaneous movements (Hayes 2007)” has been provided, but not discussed in the summary of clinical safety. This issue is reflected in the SmPC as sleep disturbance. Long term follow up regarding this issue is reassuring (Marcus 2014).

In the light of the fact that a CNS stimulant like caffeine (citrate) could lower the seizure threshold the applicant has referred to several publications reporting the occurrence of seizures which are listed in the proposed SmPC (Davis 1986, Lista 2016).

According to Vesoulis et at. (2016) seizure incidence and duration appear to increase with high dose caffeine (80mg/kg) as compared to standard dose (30 mg/kg). According to Chavez Valdez (2011), caffeine at serum levels >20 mg/mL, was associated with a pro-inflammatory profile after 1 week of treatment in a cohort of preterm infants; the cytokine profile appears to be dose dependent. Adverse event incidence is higher when higher doses were applied. This needs to be taken into account for the final decision on the dose regimen which is currently under discussion.

The applicant has also made reference to a non-clinical study concerning the exposure of neonatal glial cells to methylxanthines and the reduction of cholesterol synthesis to 65% compared with controls after 24 hours of culture (Allan and Volpe 1979). With cholesterol being the major lipid constituent of myelin, caffeine therapy could have a theoretical risk of inhibiting myelination in the developing nervous system. But since according to Schmidt et al, 2006, no increased incidence of brain injury was noted via ultrasonographic evidence (13% in caffeine group, 14.3% in controls) the applicant did not further pursue this issue. Given the large number of infants in the placebo controlled CAP trial and the reassuring observations on neurologic development in a later follow up trial in the same population this is acceptable.

Metabolism, glucose and mineral balance, growth

The applicant summarised information from literature for the listed adverse events of increased urinary sodium and calcium loss, hyperglycaemia and hypoglycaemia.

According to Erenberg (2000) no changes in blood liver function tests were noted in 45 caffeine treated infants. However, the publication only refers to the fact that no clinically significant difference has been observed concerning laboratory values between the caffeine and placebo groups. The second study (Huon1998) confirming the absence of liver function test abnormalities refers to low-dose doxapram treatment following a caffeine loading dose.

The CAP authors report a statistically significant negative effect of caffeine (citrate) versus placebo on weight gain during the first 3 weeks of life (i.e. -16g after w1, -23g after two weeks and -13g after 3

weeks) that were, however, no longer manifest during weeks 4 to 6 of life. The need to reflect short term effects on weight gain in the SmPC should be discussed by the applicant.

Gastrointestinal

Information concerning mainly listed effects on the upper gastrointestinal tract has been provided. Three publications (Skopnik 1990, Kentrup 2000 and Sacré et al 1987) on caffeine effects (without a control group) reporting the occurrence of gastro-oesophageal reflux verified by pH probes from the oesophagus are presented. According to Sacré et al the pH normalised 2 weeks following caffeine treatment cessation. According to Khalaf et al, 2001, there was no correlation between the days on methylxanthine treatment and the degree of gastro-oesophageal reflux. Occurrence of gastrointestinal bleeding (Autret 1985, Lee 2002), although a possible consequence of hyperacidity, has not been put into perspective or discussed with regard to the SmPC wording. This discussion needs to be provided.

Cardiovascular

According to the applicant no adverse effects of caffeine directly on the myocardium have been recorded in humans. Caffeine increases cardiac output, stroke volume and arterial blood pressure. In addition the application gives an overview of literature findings mainly concerning the occurrence of tachycardia (based on definitions of HR>160 up to >200), which is a common event according to the proposed SmPC.

Caffeine has effect on the cerebral blood flow, so it might influence the rate and the incidence of intraventricular haemorrhage (IVH) which is a severe and not uncommon complication in preterms. The applicant refers to a study by Steer, 2004, comparing high versus low dose caffeine. Of 234 infants given caffeine as prophylaxis before extubation, 67 infants developed intraventricular haemorrhage (IVH). It is stated that this was not thought to be related to caffeine therapy as it is not infrequent to occur in premature infants. It has to be noted, however, that 5 out of 6 intraventricular grade 3 or 4 haemorrhages occurred in the high dose caffeine group. The provided studies (Steer et al, Taha et al.) and data are insufficient to assess this aspect.

Data concerning cerebral and intestinal perfusion are conflicting according to the applicant (Dani 2000, Van Bel 1989, Saliba 1989, Hoecker 2002, Lane 1999).

Apparently few, observational studies have investigated the cardiovascular effects of caffeine in the neonate. Some have demonstrated transient decreases in cerebral and intestinal blood flow after a caffeine dose with no change in cardiac output (Tracy 2010). The applicant is requested to discuss available information regarding the influence of caffeine on cerebral and intestinal circulation in order to further elucidate any potential consequences thereof (periventricular leukomalacia, haemorrhage and necrozing enterocolitis, respectively). In addition the influence of the doses used and other variables influencing the outcome shall be summarized and discussed for the already presented publications as well as for any further articles.

According to McPherson (2015) early high-dose caffeine (80 mg/kg load versus 20 mg/kg load) was associated with increased incidence of cerebellar haemorrhage (36% vs. 10%, OR 5.0 [95% CI 1.2–20.7], p=0.03) and cerebellar hemorrhage or death (49% vs. 23%, OR 3.2 [95% CI 1.1–8.9], p=0.03), The applicant is requested to discuss the influence of high dose caffeine on adverse events and the implications for the SmPC.

Haematological

Fang (1998) studied the influence of caffeine and theophylline treatment on erythropoietin levels. Although according to the Applicant the effect they noted was indeed due to methylxanthine therapy

seemed a reasonable assumption since adenosine regulates erythropoietin production no discussion on the need to reflect this information in the SmPC has been provided by the Applicant.

Endocrine

The applicant presents a study by Williams et al in 2005 (multicentre, 780 premature infants) trying to correlate thyroid function from blood tests at 7, 14 and 28 days with the medical status and drug therapy of the infant; approximately a quarter of children treated with caffeine during the study period. The study found no consistent effect of caffeine therapy on the levels of thyroid hormone and TSH in the blood samples. Due to the important influence of thyroid hormones on the developing brain (Aleid G. van Wassenaer 2008, Maria Cristina Vigone, 2014) the applicant is requested to discuss the relevance of this information together with any further information on the influence of caffeine treatment on the thyroid function with special emphasis on the children with very low gestational age (<27 week).

Renal

The applicant summarised information from literature for the listed adverse events of increased urinary sodium and calcium loss as well as on diuresis.

Skin and musculoskeletal adverse effects

No adverse skin or musculoskeletal events have been reported in clinical practice, according to the summary of clinical safety. Caffeine extravasation causing local skin necrosis was reported in one case where an accidental overdose was given (clinical overview). As caffeine citrate is acidic, this would be expected to cause harm. The applicant is requested to discuss the need to reflect skin necrosis in the SmPC in the light of the reported case and the plausible mechanism.

Overall, a dose dependent increase of safety findings can be assumed for caffeine.

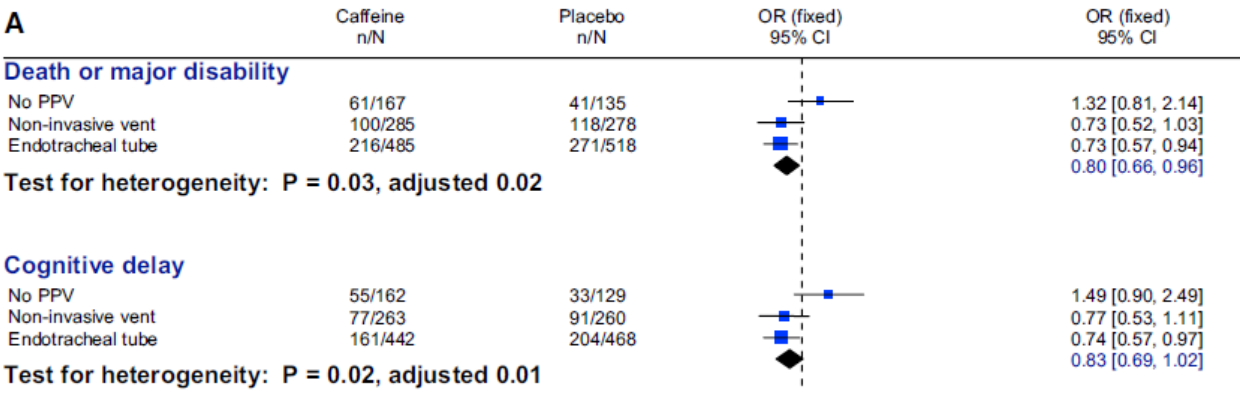
The applicant should thoroughly discuss adverse events (also serious events such as NEC and at least cerebral haemorrhage, brain injury and neurological development) with consideration to the potential influence of the factors gestational age and early versus late treatment initiation and the dose used on the incidence of these serious adverse events.

Serious adverse events and deaths

Death

The Applicant has provided information on mortality only in relation to caffeine overdose and states that no such events have been reported for human neonates.

Of note, Davis et al. 2010 did subgroup analyses on the basis of the CAP dataset and found a trend for a detrimental caffeine effect on death and major disability in those patients, who did not receive any positive pressure ventilation at baseline (compared with placebo).
The influence of the mode of respiratory support on BPD development and the anticipated caffeine regimen has extensively been discussed in other parts of this report from an efficacy perspective. Even if the reported outcome was a composite endpoint combining “death” and “major disability” and the contribution of either of the two is not clear, this is considered an alarming outcome. The same trend was observed for cognitive delay.



With regard to the pertaining uncertainties on the definition/further characterisation of an eligible population for caffeine treatment in the targeted indication, these findings are of interest and need to be taken into account. The Applicant is asked to explore the influence of patient characteristics and treatment modalities (level of respiratory support) on severe AEs such as death and major disabilities (including cognitive delay).

Dobson et al. 2014 investigated the effect of "early" vs "late" caffeine using a multicentre database of a cohort of 62,056 VLBW babies. They analysed the data to see if the incidence of BPD or death was associated with the timing of caffeine initiation. Their secondary outcome was to see if there was an association between timing of caffeine initiation and CNS damage e.g. brain haemorrhage or periventricular leucoplakia. 30,891 babies that had received "early" (first dose before third day of life) caffeine, and 23,816 babies that had received later caffeine were identified. Although the "3 day" cut off seems to be arbitrary and was not scientifically substantiated, results showed differences between both groups: Of infants receiving early caffeine therapy, 3681 (27.6%) died or developed BPD, compared with 4591 infants (34.0%) receiving late caffeine therapy (OR, 0.74; 99% CI, 0.69-0.80). Infants <24 weeks GA receiving early caffeine had a higher incidence of death. This finding is of potential concern, however, the authors claim that the lower mortality observed in the late caffeine group may be related to a survival bias. Mortality at this GA is high, and most deaths occur early after birth; for instance, an infant who received early caffeine (day of life (DOL) 0-2) was at risk of dying on DOL 4. In contrast, an infant included in the late caffeine cohort who received caffeine on DOL5 obviously could not have died on DOL4. However, it needs to be noted that infants who died within the first 3 days of life (n= 208) were excluded from the analyses.

Other serious adverse events

Lower gastrointestinal tract: necrotising enterocolitis (NEC)

The applicant states that the background incidence for necrotising enterocolitis is approximately 10% of neonates weighing less than 1500g.

Following the summary of early case reports of NEC in the context of caffeine treatment, the applicant indicates that Taha et al's 2014 retrospective database analysis of 2,951 premature infants treated with caffeine during the first ten days of life showed that early use of caffeine was associated with an increase in the risk of necrotizing enterocolitis: early 144/1986 (7.2%), late 57/965, (5.9%), OR 1.41, 95% CI 1.04-1.91, p = 0.027. Other large-scale similar studies (Lodha 2015, Dobson 2014) failed to replicate this finding and a meta-analysis of the combined data (Park 2015), including Taha's, showed

no deleterious effect of caffeine on NEC incidence overall. Further reassurance comes from the placebo controlled trial of caffeine in over 2000 premature infants (Schmidt 2006), where the incidence of NEC was similar in both groups.

Apparently, the timing of treatment initiation does not affect the incidence necrotising enterocolitis. Therefore the information on the potential influence of caffeine on the development of necrotising enterocolitis (NEC) based on a possible mechanism of action reflected in the SmPC seems appropriate.

The high background incidence makes it difficult to obtain any meaningful information from post marketing surveillance.

Overdose

The Applicant has provided a compilation of overdose case reports detailing the following additional adverse events not reflected in the proposed SmPC: heart failure, compromised circulation, gastric stasis, gastric dilatation, metabolic acidosis, hyponatraemia. In addition the following reactions have been reported in children at the age of 2.5 and 4.5 months: hypertension and in a 12 year old child: abnormal eye movements. The relevance of the above mentioned adverse reactions for inclusion in SmPc section 4.9 needs to be discussed.

Laboratory findings

The effect on haemoglobin, haematocrit, plasma electrolytes, plasma glucose and plasma liver function tests has been described by the applicant in the summary of clinical safety under the heading “Other significant adverse events”. The influence on haemoglobin, haematocrit and the relevance of this information for the SmPC needs to be further discussed, as mentioned above. The influence of caffeine on plasma electrolytes and glucose is reflected in the SmPC and there appears to be no evidence for changes in liver function tests.

Safety in special populations

Preterm infants have immature hepatic and renal systems and specifics of caffeine PK in this subgroup are of interest.

The Applicant has provided 2 publications with information on hepatically and/or renally impaired premature neonates:

The survey by List, 2016 specifically aimed to include neonates with renal and/or hepatic impairment. The number of infants with organ impairment included was unfortunately very limited (From the 381 neonates with GA <32 weeks, 31 (8.1%) presented with hepatic and/or renal impairment. Twenty-

three (6%) suffered hepatic impairment, 5 (1.3%) showed renal impairment, and 3 (0.8%) suffered both hepatic and renal impairments.), therefore results have to be interpreted cautiously. A distinction between renally and hepatically impaired children was not performed and does not seem meaningful due to the low numbers.

In comparison to the other infants, a higher number of ADRs was observed in the group with hepatic and/or renal impairment. Consequently a statement in the PI that *a reduced daily maintenance dose of caffeine may be required in the case of renal impairment and the dose should be guided by blood caffeine measurements* is included. This is also in line with the Peyona SmPC recommendations. However, more specific guidance and target dose levels would be helpful (see attached documents SmPC and PIL).

Natarajan (2007) performed an observational study with the goal to determine the value of measuring plasma caffeine levels in preterm neonates treated with caffeine for apnea. Of 101 premature infants in, 23 had raised creatinine and 13 raised hepatic enzyme levels. The incidence of AEs was not recorded, but they noted that blood caffeine levels in response to treatment were no different from other neonates.

In view of the target population the absence of safety data in the elderly population is acceptable.

Immunological events

Allergy to caffeine has not been recorded so far, according to the applicant.

Safety related to drug-drug interactions and other interactions

According to the SmPC higher Blectifor doses may be needed following co-administration of active substances that increase caffeine elimination (e.g. phenobarbital and phenytoin). In addition, the SmPC refers to concurrent use of caffeine and doxapram that might potentiate their stimulatory effects on the cardio respiratory and central nervous system. If concurrent use is indicated, cardiac rhythm and blood pressure must be carefully monitored.

However, the fact that clearance of caffeine tended to be enhanced in 17 patients who were being treated with dexamethasone (Thomson, Kerr et al. 1996) is not reflected in the proposed SmPC and should therefore be discussed by the applicant; this has already been discussed and indicated in the clinical pharmacology section.

As already indicated in the clinical pharmacology section possible interactions with Pentoxifylline, Milrinone or Sildenafil, substances that are also used in the population of preterm neonates, have not been discussed. Available data concerning possible drug interactions with caffeine in neonates should be extracted from the literature and presented also in the Blectifor dossier to substantiate SmPC recommendations. Any safety outcomes concerning the concomitant use of Pentoxifylline, Milrinone or Sildenafil with caffeine shall be presented.

Discontinuation due to AES

The applicant has not provided information on discontinuation or dose reduction due to adverse events across trials. The topic should be further investigated.

3.3.9. Discussion on clinical safety

Caffeine (citrate) has been used in neonatal intensive care since decades. There have been many clinical studies over the last 40 years, involving more than 4,000 children treated with caffeine, which have contributed to a picture of the safety of this medication. However, only a minority of the provided literature includes details on safety monitoring and or safety outcomes.

AEs encountered during caffeine therapy in neonatal medicine are considered as an augmentation of caffeine's pharmacodynamic effects. No specific remedial measures, apart from withholding or reducing a dose, have been found necessary for these AEs. The common side effects reported in studies using the recommended dosages are tachycardia and gastric stasis / feed intolerance. Hyperglycaemia, diuresis, and irritability / jitteriness are encountered uncommonly. Enteral bleeding and seizure are rare. Two studies have shown evidence of sleep disturbance as a consequence of CNS arousal in caffeine-treated children, although the actual numbers of affected children were not stated.

In placebo-controlled trials, the only AEs reported as occurring more frequently than placebo are tachycardia, irritability / jitteriness or delayed weight gain. In Erenberg et al's smaller placebo-controlled study, no increased incidence of any AEs was seen in the treatment group.

Caffeine therapy has been shown to temporarily reduce splanchnic arterial flow in some studies; it provokes gastric stasis and increased intestinal secretions. These factors combined might constitute a risk for NEC development, like it was suspected in Erenberg's placebo-controlled trial. However, other, larger studies showed no evidence of this suspicion. Reassurance was provided by the larger CAP trial, which showed no increased incidence of NEC in caffeine-treated infants.

Similarly, caffeine has been implicated as potentially aggravating ischaemic neural injury, however the placebo-controlled trials provided important reassurance. The CAP trial found no increased incidence of brain injury in caffeine-treated infants, but they had a lower incidence of cerebral palsy and cognitive delay when assessed at 18 months. Assessments at corrected age of 18 months and 5 years showed no long-term adverse neurodevelopmental effects attributable to caffeine.

Systematic and comprehensive safety reporting is often underrepresented in publications appearing in journals where the main focus rests on illustrating and discussing the efficacy findings. Whereas caffeine (citrate) has been used in neonatology for decades and approved products and accordingly pharmacovigilance measures are in place, the target population, duration of treatment, the impact of the disease and sequelae to be prevented and its expected incidence need to be accounted for.

The Applicant provided a compilation of safety findings in the context of caffeine (citrate) treatment from scientific literature over the last 4 decades, but overall has not meaningfully discussed the presented issues, with a few exceptions. The findings should have been put into perspective providing for example background incidences derived from historical data. Also potentially underlying pathomechanisms are not further discussed.

Information on mortality was provided only in relation to caffeine (citrate) overdose and it is stated that no such events have been reported for human neonates. This is somewhat in contrast to the publication by Davis et al. 2010, who found a trend for a detrimental caffeine (citrate) effect in those patients of the CAP study, who did not receive any positive pressure ventilation at baseline compared to placebo. With regard to the pertaining uncertainties on the definition/further characterisation of a population eligible for caffeine (citrate) treatment in the sought indication, these findings are of interest and need to be taken into account.

No specific safety data according to the target indication/population has been provided. The patient population in need for BPD prevention could differ somewhat from infants treated for AOP, which is the population in whom most of the provided data was generated. It is e.g. unknown if for BPD prevention a longer treatment duration can be expected or if the timing of initiation of treatment differs compared to AOP treatment.

Chavez Valdez, 2012, outlines that "levels of caffeine outside of 10-20 ug/mL (which can easily occur with the suggested dose regimen for Blectifor of 20mg/mL loading dose and 20mg/mL maintenance dose) are potentially associated with a pro-inflammatory profile and may have significant clinical implications due to the increase of specific cytokines. McPherson et al. and other authors found higher AE rates in high-dose caffeine groups when compared to a more conservative dosing approach. A dose response relationship as regards safety outcomes could be assumed, which has to be considered in the requested discussion of appropriateness of the proposed dose recommendations.

It can be assumed that over the years the population in need for BPD prevention has changed with regard to the gestational age of the exposed infants. Nowadays more and more children < 500g birth weight will survive. While these infants might be considered candidates for caffeine (citrate) treatment, an underrepresentation of this cohort in the provided studies in historical cohorts of neonates can be assumed.

The preterm neonate metabolises caffeine very slowly (mean half-live 100 h compared to approx. 5h in adults). Caffeine is an adenosine antagonist and very early exposure could influence (i) development of adenosine receptor patterns and (ii) alter the development of the individual receptors with potential consequences for receptor sensitivity. The safety profile of this cohort cannot be estimated from the provided data.

3.3.10. Conclusions on clinical safety

The Applicant has reviewed the literature and has provided a thorough review of the safety of caffeine. Since it has been used for neonatal treatment for over 40 years, and became the second most often prescribed drug after antibiotics in the NICUs, a comprehensive picture of the safety profile is available. Based on the data provided by the Applicant the majority of the studies with safety endpoint do not report serious adverse events at the standard dose (20/5 mg/kg) of caffeine citrate. Some mild and transient alterations in the heart rate i.e. tachycardia are reported. Other relevant but mild AEs are jitteriness, transient mild hyperglycaemia and feeding intolerance. None of these has been reported as severe, they resolve after discontinuation of the therapy.

However, there are well known limitations of the safety reporting in publications and external validity of data cannot be claimed, also taking into account the target condition.

In the CAP trial comparable low numbers of infants in both groups (2.3% in the caffeine group and 1.4% in the placebo group) had doses of study drug withheld or reduced due to suspected toxicity. There are signals, however, that caffeine (citrate) safety could depend on intrinsic and extrinsic factors such as e.g. respiratory support modalities or GA.

The need for further characterising and defining an eligible target population remains a concern, also from a safety perspective. Since the dosing regimen is still under discussion also safety in higher dose ranges need to be discussed further.

3.4. Risk management plan

Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 6: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Tachycardia Gastric stasis, feed intolerance Increased urinary sodium and calcium Jitteriness, irritability, sleep disturbance Seizure Diuresis Overdose

Summary of safety concerns	
	General increase in metabolism Hyperglycaemia
Important potential risks	Necrotising enterocolitis (NEC) Hypersensitivity reaction Sepsis Gastro-oesophageal reflux disease
Missing information	none identified

As disease concept and mode of action are under discussion in the clinical assessment this part could be subject to updates. The co-medication used is not reflected thoroughly and other treatment options are not discussed at all. These aspects have to be covered in the RMP Part II: Module SI - Epidemiology of the indication(s) and target population.

As detailed also in section 4.10 of the clinical AR the Applicant has already marketed a caffeine product although in a different indication, safety related information as well as sales data shall be provided also in the RMP.

Overall MedDRA terms as proposed by the applicant shall be updated in order to capture all case reports in relation to the important identified and potential risks.

All possible interactions of the everyday NICU pharmacotherapy of preterm and very preterm infants (i.e. antibiotics, adenosine, heparine, epinephrine, ibuprofen, fluconazole pentoxifylline, milrinone or sildenafil etc.) with caffeine shall also be presented in the RMP. The need to reflect these interactions as a safety concern shall be discussed.

As discussed in the clinical assessment the safety effects of early treatment initiation, exposure of preterm neonates at increasingly low gestational ages the influence of potentially higher doses used as well as potentially longer treatment durations shall be further discussed and there could be considerable knowledge gaps concerning the safety impact regarding this subpopulation and different usage patterns which should then be included as missing information.

The Applicant has mainly reflected adverse events that have been reported in the context of caffeine treatment regardless of their importance. The Summary of safety concerns shall not be a list of adverse reactions in line with SmPC section 4.8.

The Applicant is therefore requested to remove the following adverse events from the list of important identified and potential risks:

- Gastric stasis, feed intolerance
- Increased urinary sodium and calcium
- Jitteriness, irritability, sleep disturbance
- Diuresis
- General increase in metabolism
- Hyperglycaemia
- Hypersensitivity reaction
- Sepsis
- Gastro-oesophageal reflux disease

Tachycardia shall be modified to better reflect the importance for the at risk population:

- Cardiac disorders in infants with pre-existing cardiac disease

Premature infants with renal and hepatic impairment have been shown to be affected by adverse drug reactions more frequently than others (Lista 2016). This shall be reflected adequately in the RMP.

Enteral bleeding, Caffeine withdrawal and Medication errors shall be included as potential risks.

Since the Applicant has presented information concerning elevated caffeine plasma levels in the context of maternal caffeine ingestion which is only relevant if extremely and unusually high caffeine intake has taken place this is not considered an important risk for Blectifor although it is for the already approved caffeine product, Peyona. Long term safety has been described in the follow up trials concerning the CAP population and no additional concern regarding long term effects has been detected.

The outcome of the discussion on the knowledge gaps concerning early treatment initiation, exposure of preterm neonates at increasingly low gestational ages the influence of potentially higher doses used as well as potentially longer treatment durations shall be included as missing information if applicable.

Adverse event frequencies are usually not part of the safety specification and should be removed.

Conclusions on the safety specification

Having considered the data in the safety specification

The CHMP considers that

Cardiac disorders in infants with pre-existing cardiac disease, increased vulnerability of premature infants with renal and hepatic impairment, enteral bleeding, caffeine withdrawal and medication errors should also be safety concerns

The CHMP considers that the following should not be safety concerns

Gastric stasis, feed intolerance, Increased urinary sodium and calcium, Jitteriness, irritability, sleep disturbance, Diuresis, General increase in metabolism, Hyperglycaemia, Hypersensitivity reaction, Sepsis, Gastro-oesophageal reflux disease and Tachycardia

Pharmacovigilance plan

The applicant proposes only routine pharmacovigilance activities for all the listed safety concerns. We consider that no additional pharmacovigilance activities are deemed necessary for those safety concerns that are proposed.

The target population at risk has changed in the last decade towards increasingly vulnerable children due to extreme prematurity, potentially in need for more invasive or prolonged respiratory support. The target population has been defined by the applicant as “preterm neonates”. However, this is a too broad definition, including extremely low birth weight neonates (<1000g) and extremely preterm (<28 weeks), based on WHO definitions. This may raise additional safety concerns that have not been addressed by the applicant, with possible consequences on the pharmacovigilance plan and risk minimisation measures.

So far, no potential for dependence or abuse, as well as no rebound phenomenon, have been recorded in premature infants. The extremely premature population may, however, need further monitoring, as defended by the CHMP.

Therefore, after the agreement on the safety specifications, the need to develop further activities may be considered.

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Nevertheless, after the agreement on the safety specifications, the need to develop further activities may be considered.

The PRAC Rapporteur considered that routine PV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

The applicant presents the planned routine risk minimisation activities for each safety concern in a tabular format as per guideline requirement.

The Applicant addresses the important identified risk “tachycardia” as “cardiac disorder, tachycardia” and part of the wording proposed for the SmPC also suggests that the risk is not only tachycardia but cardiac disorders, particularly where there is pre-existing cardiac disease. There are also other discrepancies regarding this safety concern throughout the RMP. The Applicant should therefore clarify this and amend table V.3 if necessary. All the relevant sections of the RMP should be updated accordingly.

For each safety concern, the applicant refers only to the key messages intended to be included in the PI. According to the upcoming RMP template (planned to be published in January 2017), although not necessary to mention the proposed text to be implemented in the PI to minimise each safety concern, the applicant should make reference to the concerned SmPC/PL section.

Routine risk minimisation measures proposed for the safety concerns, are in our view adequate.

No additional risk minimisation measures are proposed by the applicant, which is considered acceptable for the majority of the currently proposed safety concerns.

Nevertheless, regarding the important identified risk of overdose, the applicant is requested to comment about the need for additional risk minimisation measures to address this safety concern, due to its severity and potential to increase the risk of other adverse reactions.

Also, it is known that there is already one centrally authorised product containing caffeine citrate (Peyona), for which an educational material for HCPs is foreseen in the form of a card suitable for display in neonatal intensive care units, containing a group of key elements. Peyona has the double caffeine concentration comparing to Blectifor and therefore the risk of medication errors is a concern, as also proposed by the CHMP. Based on these assumptions, the applicant is requested to comment the need for additional risk minimisation measures to address the risk of medication errors (different caffeine concentration of Peyona) as well as other key elements as determined for Peyona, such as cardiac disorders.

After the agreement on the safety specifications, the need to develop further risk minimisation measures may be considered.

The PRAC Rapporteur having considered the data submitted, was of the opinion that the proposed risk minimisation measures are not sufficient to minimise the risks of the product and supplementary risk minimisation measures may be required relating to the risks of overdose and medication errors.

It should also be noted that it is foreseen that the Summary of safety concerns will be subject of discussion and therefore the risk minimisation measures may need to be adapted accordingly.

Conclusion

The CHMP and PRAC Rapporteur considered that the risk management plan version 1.0 dated June 2016 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance system

The MAH submitted the summary of the pharmacovigilance system (dated: 29th May 2016) which fulfils the requirements of GVP Module II, in the scope of this procedure in principle.

The summary includes the following elements:

-Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance
-The Member States in which the qualified person resides and carries out his/her tasks
-The contact details of the qualified person
-However the current document under 1.8.1 needs to be corrected so that the statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC refers to Directive 2001/83/EC and not to Directive 2010/84/EU.

The Pharmacovigilance System Master File (PSMF) is located in Gwent, UK.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance system at this time. See list of questions.

Based on the fact that the Applicant is a rather small company with no centrally authorised product so far and since apparently no pharmacovigilance inspection has taken place so far, the PRAC, having considered the data submitted in the application was of the opinion that a pre-authorisation pharmacovigilance inspection is required.

4. Orphan medicinal products

According to the conclusion of the COMP (Opinion dated 05/06/2014) the prevalence of “patients at risk of bronchopulmonary dysplasia” is between 1 and 3 people per 10000 individuals in the EU (EMA/COMP/89532/2014).

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

Bronchopulmonary dysplasia is a form of chronic lung disease that occurs in premature neonates. It is characterised by interruption of normal alveolar development as a consequence of the immature lung being exposed to the extrauterine environment and respiratory support as part of the NICU management with positive pressure ventilation and/or oxygen therapy.

BPD has been related to long-term pulmonary sequelae such as lower-respiratory tract infections, reduced lung-function, airway hyperresponsiveness, etc. and prevention of such late morbidities is considered an important therapeutic goal.

The definition of BPD applied by the applicant is '**use** of supplemental oxygen at 36 weeks postmenstrual age'. It is criticized for being subjective, not formally addressing the actual need for oxygen support, not further specifying 'oxygen supply' and for its unclear performance in terms of predictive properties for long-term outcomes (see section 2.1.1)

5.1.2. Available therapies and unmet medical need

There is no authorised product available in the community to prevent (or treat) BPD and an unmet medical need can be assumed.

The pathological changes of BPD are largely irreversible once they have occurred. Treatment of BPD is confined to mitigation of damage, and trying to minimise further damage or infection while waiting for new alveoli to develop during the first months of postnatal life.

Following the assumption that the pathomechanism underlying the development of BPD seems to be mainly driven by iatrogenic noxes, i.e. ventilation support and/or oxygen supply, reduction thereof or optimisation of respective regimens should be the main approach to prevent the condition. Resulting from this questions arise whether BPD could also be expected in premature children without respiratory support, and regarding the respective baseline incidences and expected benefit of treatment/prevention.

There is a limited number of drug therapies being developed or used to prevent BPD. E. g., Vitamin A has been reported to reduce the incidence of BPD by approximately 10%. Other drugs such as (perinatal) steroids, surfactant, inositol have also been used/tested.

5.1.3. Main clinical studies

This is a bibliographic application relying entirely on published literature documenting the effects of caffeine (citrate) in preterm neonates. The CAP trial ("Caffeine Therapy for Apnea of Prematurity", Schmidt 2006, Schmidt 2007) is considered the pivotal trial for this application. The multicentre international study was conducted in a hospital setting between 1999 and 2004 and had a double blind, placebo-controlled design.

2006 preterm infants with birth weights of 500 to 1250 g were randomised to receive caffeine citrate or placebo during the first 10 days of life. Infants were eligible if they were considered candidates for caffeine therapy based on physicians' judgement, either to prevent apnoea, to treat apnoea or to facilitate the removal of an endotracheal tube.

The primary objective was to investigate the benefit of caffeine citrate over placebo in terms of a composite of death, cerebral palsy, cognitive delay, deafness or blindness at a corrected age of 12-18 months. Bronchopulmonary dysplasia was a pre-specified secondary outcome and defined as the 'use of supplemental oxygen at a postmenstrual age of 36 weeks'.

5.2. Favourable effects

In the CAP trial, the median postmenstrual age at last oxygen use was 33.6 vs. 35.1 weeks (IQRs: 30.6-36.9 vs. 32-37.6; $p<0.001$) for caffeine (citrate) and placebo respectively. This could also be expressed as an approximately 10 days shorter duration of oxygen supply.

Accordingly, 'BPD incidence' (defined as supplemental oxygen use at a PMA of 36 weeks) prior to first discharge home differed significantly between treatment arms: 36.3% vs. 46.9% (caffeine citrate vs.

placebo) with an OR adjusted for centre of 0.63 (95% CI: 0.52-0.76; p<0.001) and an OR of 0.64 (95% CI: 0.52-0.78) if adjusted for additional baseline patient characteristics.

Mortality rates did not significantly differ between treatment arms, i.e. 5.2% vs. 5.5% (caffeine citrate vs. placebo) prior to first discharge home, 6.4% vs. 6.5% before 18 months corrected age and 6.8% vs. 6.9% before 5 years corrected age, at least indicating a non-detrimental effect of caffeine-citrate on overall survival.

As additional findings, the median PMA at last use of endotracheal tube was 29.1 vs. 30 weeks (IQRs: 28-31 vs. 28.7-31.9; p<0.001) and the median PMA at last use of positive airway pressure was 31 vs. 32 weeks (IQRs: 29.4-33 vs. 30.3-34; p<0.001) for caffeine (citrate) and placebo, respectively.

Based on subgroup analyses by 'ventilation support at baseline', the BPD effect observed in the overall should be further differentiated as follows: for subjects receiving non-invasive ventilation 25.2% vs. 36.5% (OR 0.58, 95% CI: 0.41-0.83), for subjects with endotracheal tube 48.1% vs. 60.5% (OR 0.60, 95% CI: 0.47-0.78) but for subjects not receiving any positive pressure ventilation 22.5% vs. 21.1% (OR 1.08, 95% CI: 0.64-1.82).

5.3. Uncertainties and limitations about favourable effects

Whereas key publications on the concerned topic have been identified (i.e. those on the CAP dataset), the applicant has not explained on what basis data/studies were screened and considered relevant for inclusion in the qualitative synthesis. Search criteria, selection criteria and the respective selection process (e.g. via a PRISMA flow diagram) have not been outlined, which leaves open the question whether the referred-to studies indeed represent the overall published data and the risk of a selection bias (on a publication level) cannot conclusively be ruled out. Apart from that, the potential for publication bias and the availability of 'grey literature' as potentially relevant data source have not been addressed.

The key outcome data stem from a single pivotal trial and have not been replicated independently. BDP incidence was one of several secondary outcomes and multiplicity was not accounted for in the analysis, which may increase the risk of a false positive finding. However, given the observed p<0.001 a conservative multiplicity adjustment method accounting for the range of outcomes would still yield a significant result. High quality randomized double blind prospective studies designed for the claimed indication of prevention of BPD have not been provided.

The main data sources are 4 peer-reviewed publications on the same dataset with inherent limitations regarding completeness and reproducibility of reporting. No study protocol and no study report are available for the CAP study. Consequently, trial conduct, adherence to the protocol, and accordingly, nature and potential impact of deviations on study outcomes cannot comprehensively be assessed. There is some concern stemming from the weak endpoint definition and the lacking adjudication of respective criteria, together with uncertainties as to the blinding of study personnel. Relevant co-interventions (e.g., switching between ventilation modalities, other candidate drugs for BPD prevention) have not been recorded/reported comprehensively, and the participant flow leaves open questions as to a potential preselection of trial participants and thus representativeness of effect for the target population.

Consistency of background BPD incidences as well as BPD incidences on caffeine (citrate) treatment (rather than treatment effect) across studies/datasets has not been addressed adequately by the applicant, but would be an important consideration to contextualise the findings for placebo and active arm from the CAP trial and to substantiate the external validity of CAP findings. Variability in BPD rates seems to be substantial which arguably reduces the external validity of CAP results and raises

questions regarding the uniformity of SOC and added benefit of caffeine (citrate) as well as the general understanding of the disease (definition).

The definition of BPD used as basis for this application, i.e. 'oxygen supply at 36 weeks postmenstrual age' has been fundamentally criticized in the past for being subjective, not formally addressing the actual need for oxygen support, not further specifying 'oxygen supply', and importantly, being of unclear value for predicting long-term (pulmonary) outcomes. It is also worth noting that this definition stems from a time were intensive care differed markedly from nowadays' NICU standards. Depending on the definition used, BPD incidences were found to vary substantially in given datasets of premature infants.

The Applicant has not addressed the longer-term health impact of BPD in quantitative terms. None of the 3 follow-up publications on the CAP trial report long-term pulmonary outcomes. Whereas BPD in premature infants has been associated a variety of untoward late effects on e.g., lung function, the primary findings have not been discussed in this regard. Whereas a short-term effect of accelerated weaning from mechanical ventilation and/or oxygen support attributable to caffeine-citrate is likely beneficial, a better understanding of its value as surrogate for long-term sequelae would be helpful for interpreting the observed effect sizes in the range of 7-10 days reduced duration (depending on the modality of respiratory support). An indication for caffeine citrate 'preventing BPD' as currently proposed, suggests that there will be no tissue damage in 'responders' and, following from that, no long-term respiratory sequelae.

Dose recommendations for Blectifor correspond to the basis regimen proposed for Peyona and for the CAP trial without considering differences in indication or population. Also, no guidance for up- or down titration is provided and no basis on which such a recommendation could be justified seems available. Caffeine citrate's therapeutic target range for BPD prevention is unknown. Exposure-response data are ambiguous in the studied range of serum caffeine levels. Whereas some dose-dependency for caffeine (citrate) and BPD development has been observed, the respective studies would, from an efficacy perspective, suggest considerably higher induction and maintenance doses than those used in the CAP trial and proposed by the applicant. In the CAP study, investigators were free to increase or reduce the IP dose for lack of efficacy or toxicity at their discretion and actual exposure data are not available.

The optimal timing of caffeine therapy ("early" within in the first three days of lives or "late") seems not determined yet although a difference in outcomes could be expected from available literature data.

At the moment, it is doubtful if caffeine (citrate) can be expected to exert its effect in preventing BPD in all preterm neonates. Besides ventilation support, other important baseline characteristics, above all degree of prematurity (i.e. GA/birth weight) are likely to impact either prognosis of BPD development and/or predict the likely pharmacologic response to caffeine (citrate) treatment. Based on subgroup analyses on the CAP dataset, which recruited a very heterogeneous sample in terms of immaturity and respiratory management, it appears that a broad indication in "premature infants" seems not justified for caffeine citrate in 'BPD prevention' and might need further refinement taking into account large variations in baseline risk depending on GA/weight at birth and the key role iatrogenic damage caused by ventilation support plays in BPD pathophysiology.

The studies show favourable effects of caffeine in premature and very premature (22-28 wk) newborns regarding AOP, prevention of reintubation, and several of them report decrease of BPD. Clear distinction between the populations considered for treatment of AOP and BPD prevention has not been made.

5.4. Unfavourable effects

Unfavourable effects are exaggeration of the normal physiological effects of caffeine; tachycardia, hyperexcitabilty, jitteriness, seizure. Vesoulis et al. 2016 reported that seizure incidence and duration appear to be increased with high dose caffeine (80mg/kg) as compared to what he defined as standard dose (30 mg/kg). In addition caffeine (citrate) treatment is known to influence the gastro- intestinal tract (gastric stasis, feed intolerance, hyper-secretion), glucose, sodium and calcium metabolism and diuresis. They occur in some individuals at standard dosages of caffeine, and settle if a dose is withheld or reduced. They are especially associated with higher dosages of caffeine and higher plasma levels of caffeine. Plasma levels of $\leqslant$ 30 µg/ml are generally well tolerated; plasma levels of 30-100 µg/ml are associated with a high incidence of jitteriness, tachycardia and feed intolerance.

Serious adverse effects are not encountered below 100 µg/ml, which would be considered a toxic level of caffeine. Levels of $\leqslant$ 100 µg/ml have not been encountered in clinical studies, but only in cases of overdose. Above 100 µg/ml, serious adverse effects include tachycardia, gastric dilatation, vomiting, seizures, heart failure, hyperglycaemia, hypoglycaemia, electrolyte disturbances and pyrexia. Provided supportive care can be given, these all return to pre-treatment states once the plasma caffeine levels drop to therapeutic range. Hyperglycaemia has been reported in one study where infants were receiving standard dosages of caffeine, but plasma levels were not recorded in these studies.
Very high doses may interfere with brain development with possible later outcomes like cerebellar dysfunction .

The influence on cerebral and enteral perfusion, which has been established in some publications, might play an important role in the development of necrotising enterocolitis and cerebral bleeding. Overall, serious adverse events appear to be rarely reported in scientific literature. Necrotising enterocolitis and sepsis reported in a small, placebo-controlled trial have not been observed in the CAP study.
Other investigations, amongst them some large cohort studies, investigating caffeine (citrate) safety were conducted since the authorisation of Peyona and indicated that the safety profile of caffeine (citrate) in preterm neonates could be dependent on both, intrinsic and extrinsic factors:

Davis et al. 2010, who did subgroup analyses on the basis of the CAP dataset, found a trend for a detrimental caffeine effect in those patients who did not receive any positive pressure ventilation at baseline compared to placebo. The reported outcome was a composite endpoint combining “death” and “major disability” and the contribution of either of the two is not clear, however. The same trend was observed for cognitive delay.

Dobson et al. 2014 investigated the effect of “early” vs “late” caffeine using a multicentre database of a cohort of 62,056 VLBW babies. Of these, 30,891 had received “early” caffeine (first dose before third day of life) and 23,816 had received later caffeine. Of infants receiving early caffeine therapy, 3681 (27.6%) died or developed BPD, compared with 4591 infants (34.0%) receiving late caffeine therapy (OR, 0.74; 99% CI, 0.69-0.80). Infants receiving early caffeine had a lower incidence of BPD (23.1% vs 30.7%; OR, 0.68; 95% CI, 0.63-0.73) and a higher incidence of death (4.5% vs 3.7%; OR, 1.23; 95% CI, 1.05-1.43). Infants <24 weeks GA receiving early caffeine had a higher incidence of death. These finding were also supported by Kua & Lee, 2016, who concluded that the use of ‘early’ caffeine was associated with an increased mortality compared to ‘late’ use in preterm neonates.

Necrotising enterocolitis had been associated with caffeine treatment in the past (Erenberg et al 2000). NEC is life-threatening and can result in long-term consequences, such as strictures and short bowel syndrome due to intestinal resection.

5.5. Uncertainties and limitations about unfavourable effects

Systematic and comprehensive safety reporting is often underrepresented in publications where the main focus often rests on illustrating and discussing the efficacy findings. Whereas caffeine (citrate) has been used in neonatology for decades and approved products and accordingly pharmacovigilance measures are in place, it is not appropriate to assume caffeine (citrate) being 'safe' in general without accounting for e.g. the target population and duration of treatment.

The alarming results by Dobson et al 2014, who reported that infants <24 weeks GA receiving early caffeine had a higher incidence of death, might be explained by the lower mortality observed in the late caffeine group being subject to survival bias. Mortality at this GA is high, and most deaths occur early after birth. For instance, an infant who received early caffeine (day of life (DOL) 0-2) was at risk of dying on DOL 4, while an infant in the late caffeine cohort, who received caffeine on DOL5, obviously could not have died on DOL4. However, it needs to be noted that infants who died within the first 3 days of life (n= 208) were excluded from the analyses.

The pronounced trend for a detrimental caffeine (citrate) effect in CAP patients who did not receive any positive pressure ventilation at baseline compared to placebo (reported by Davis et al. 2010) is not understood as regards biological plausibility.

NEC is a relatively common serious emergency event occurring in approximately 10% of very low birth weight infants (<1500g). It had been associated with caffeine treatment in the past (Erenberg et al 2000) and there are studies indicating reduced splanchnic blood flow in newborns who received 25mg/kg of caffeine (Lane 1999, Hoecker 2002), which would provide a pathophysiological rationale for this finding. However, a definite relationship could not yet be confirmed nor was a higher incidence of NEC seen for caffeine (citrate) in the larger, placebo controlled CAP study.

Theoretical concerns regarding neurodevelopmental outcomes based on a possible hypo-perfusion as hypothesised in the literature have not been observed in the long-term follow-up of the CAP study population (Schmidt 2007, 2012).

Caffeine has effect of the cerebral blood flow, so it might influence the rate and the incidence of intraventricular haemorrhage (IVH) which is a severe and not uncommon complication in preterms. The provided studies (Steer et al, Taha et al.) and data are insufficient and controversial to assess this aspect.

It can be assumed that over the years the population in need for BPD prevention has changed with regard to the gestational age of the exposed infants. Nowadays more and more children of < 500g birth weight might survive. These extremely low birth weight infants might be candidates for caffeine (citrate) treatment, however, an underrepresentation of this cohort in the provided studies in historical cohorts of preterm infants can be assumed. The safety profile of this cohort cannot be estimated from the provided data and remains uncertain at the present time.

It is unknown if the proposed dose regimen could lead to relevant under- or overexposure in certain individuals. Intrinsic factors such as weight, GA, PNA/PMA have an influence on caffeine metabolism and adequacy of the proposed dose across the broad range of preterm neonates remains uncertain.

Based on the fact that there is already a centrally authorised caffeine (citrate) product (Peyona) with a different caffeine concentration (double), medication errors (with the risk of underexposure/lack of efficacy of the product with the lower concentration, Blectifor) cannot be excluded.

5.6. Effects Table

Table 5. Effects Table for Blectifor

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PMA at last O_2 use	Age at weaning	weeks	33.6	35.1	RCT, db, plc; no formal outcome; reported as part of study conduct	CAP trial
"BPD incidence"	Oxygen use at PMA of 36 weeks	%	36.3	46.9	RCT, db, plc; concerns regarding internal and external validity; weak definition of BPD	CAP trial
PMA at last PPV use	Age at weaning	weeks	31.0	32.0	RCT, db, plc; no formal outcome; reported as part of study conduct	CAP trial
PMA at extubation	Age at weaning	weeks	29.1	30.0	RCT, db, plc; no formal outcome; reported as part of study conduct	CAP trial
Unfavourable Effects						
Tachycardia	Incidence of Tachycardia	%	21	41,3 Active control	Actively recorded HR	e.g. Larsen 1995
CNS excitability (Irritability/jitteriness)	Incidence of CNS excitability	%	1.65 low dose	1.77 high dose	No placebo control	Steer 2004
NEC	Incidence of NEC	%	4.3	2.6 placebo	Not observed in a larger RCT	Erenberg 2000
Death or major disability	Incidence of death or major disability	%	36,5	30,4 placebo	subgroup without PPV	CAP trial (Davis 2010)
Death	Incidence of death	%	4.5 "early caffeine (<3d of life)"	3.7 "late caffeine"	No comparison against placebo, potentially subject to "survival bias"	Dobson 2014

Abbreviations: db: double blind, NEC: necrotizing enterocolitis, PPV: positive pressure ventilation, RCT: randomised controlled trial

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

There is no product currently approved in the EU to prevent BPD and an unmet medical need can be assumed. The apparent key drivers of disease development (i.e. ventilatory NICU support) are indispensable in the target population and reversibility of tissue damage, once occurred, is apparently limited.

The observed effect of caffeine citrate in terms of "preventing of BPD in preterm neonates" cannot easily be interpreted due to the identified shortcomings associated with the endpoint definition. The

observation of accelerated weaning from mechanical ventilation attributable to caffeine (citrate) therapy is an acknowledged therapeutic goal, but its surrogacy value for long-term pulmonary outcome, which should be considered an important therapeutic objective, needs further justification, also accounting for the observed effect size (i.e. 7-10 days less ventilator support). Caffeine-related improvement in long-term outcomes attributable to BPD (including mortality rates but also respiratory endpoints) has not been addressed by the Applicant. Respective outcomes would clearly rank higher in importance than short-term weaning goals.

An appropriate target population among the very heterogeneous study sample included in the main trial(s) yet needs to be further defined; there are data indicative of important risk factors for BPD development. The benefit-risk ratio of a preventive agent will vary depending on the background rate of the condition to be prevented.

Overall, the beneficial effect of caffeine (citrate) is credible, yet not easily understood in terms of "BPD prevention" as the assumption of 'responders' to caffeine (citrate) becoming disease-free seems highly unlikely.

The unfavourable effects are mainly the adverse events which are not common, and usually mild and well tolerated at the proposed dosing regimen. Seizures, tacycardia, blood pressure should be monitored if persistent.

Regarding the risk of IVH, the provided data appear insufficient and controversial. Extreme prematurity but also very high doses of caffeine may lead to IVH. This may interfere with brain development and possibly trigger later outcomes like cerebellar dysfunction.

The population of preterm neonates is one with a high baseline risk of mortality as it is. Any measure taken in a NICU setting primarily aims to increase survival rates. Although caffeine (citrate) is in principle considered a safe agent, some literature data suggest that in certain subgroups harmful effects could be possible. Davis et al. 2010, who did subgroup analyses on the basis of the CAP dataset, found a trend for a detrimental caffeine (citrate) effect in those patients who did not receive any positive pressure ventilation at baseline compared to placebo. The reported outcome was a composite endpoint combining "death" and "major disability" and the contribution of either of the two is not clear, however. The same trend was observed for cognitive delay. Also, Dobson et al. 2014 report that infants <24 weeks GA receiving early caffeine (compared to later caffeine) had a higher incidence of death.

Another important safety concern pertains to the subpopulation of extremely pre-term infants < 500g that might be underrepresented in the provided literature data, due to progress made in neonatal intensive care in recent years.

Careful consideration of an appropriate target population that benefits from caffeine (citrate) treatment without being put at increased risk remains the main task for further steps in this application.

5.7.2. Balance of benefits and risks

BPD occurs in preterm infants and the prevalence of "patients at risk of bronchopulmonary dysplasia" has been estimated between 1 and 3 people per 10000 individuals in the EU. Respiratory problems are part of the increased mortality in preterm infants, but the precise level to which BPD contributes to this is uncertain, partly because prematurity is associated with multiple pathologies.

As clinical practice has changed over the last forty years, the pattern, severity and incidence of BPD has also changed. Successive improvements in treatment and ventilation strategies have improved survival of premature infants and decreased BPD severity. Nowadays, fatalities attributed to BPD are

rare. Literature derived from these times and submitted to support this submission has to be evaluated thereupon.

Arguably the main caffeine citrate-related finding in the provided literature is a reduction in time on different modalities of respiratory support (oxygen supply as well as PPV and intubation) as part of NICU management. There is no information on what caffeine (citrate) therapy could achieve in terms of improved long-term pulmonary outcomes as such data were not provided and might not exist. Important doubts as to the consistency of beneficial effects within the target population further reduce the weight of benefits compared to potential and known risks in a preventive setting where the mean baseline risk is substantially below 100%.

The safety of caffeine (citrate) in preterm infants has been defined previously since there is an approved caffeine citrate product for the treatment of apnoea of prematurity, and pharmacovigilance has been in place for several years now. Risks include: (1) the known AE profile of caffeine (citrate) in premature neonates, (2) signals indicating that caffeine (citrate) might have a detrimental effect on major outcomes such as survival or cognitive function in certain subgroups of the target population for BPD prevention and (3) uncertainties regarding the safety in particularly vulnerable subgroups (lower end of GA spectrum).

The weight assigned to particular benefits and risks of caffeine (actual and potential) might differ whether considering treatment of an existing condition (apnoea of prematurity) or prevention of a disease (BPD) that might occur.

The product information does not reflect the information provided in the clinical dossier and needs to be revised in several sections. Importantly, the wording of the indication is not supported at the present time and may need to be revised/restricted pending further discussion.

There is a major objection on the quality regarding GMP compliance and many other concerns regarding the provided quality documentation have been identified.

There are many uncertainties regarding the benefit associated with caffeine citrate in the intended indication that need to be further elucidated before a final conclusion can be drawn. At the moment, the anticipated favourable effects do not outweigh the potential and factual risks.

5.7.3. Additional considerations on the benefit-risk balance

The legal basis for this MAA has not been fully justified and further discussion on several requirements for demonstrating the “well established use” of caffeine citrate in the prevention of BPD has to be provided.

Due to the nature of the application no further studies can be requested to improve the evidence base. Interpretability of data is hampered as there is no primary literature available, no study reports or protocols are submitted. Overall, the information provided is fragmentary and poorly structured. A more systematic review/compilation of the literature and an improved integrative consideration of results across the different data sources could advance the knowledge on the role of caffeine citrate in the targeted indication.

5.8. Conclusions

The overall B/R of Blectifor 10 mg/ml solution for injection and oral solution is currently negative.