25 June 2020
EMA/372967/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gencebok

International non-proprietary name: caffeine citrate

Procedure No. EMEA/H/C/005435/0000

Note

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

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List of abbreviations

API	Active Pharmaceutical Ingredient
BET	Bacterial endotoxins
CEP	Certificate of Suitability of the European Pharmacopoeia
CRS	Chemical Reference Substance (official standard)
ELBW	Extremely Low Birth Weight
GMP	Good manufacturing practice
HPLC	High Performance Liquid Chromatograph
INN	International Nonproprietary Name
IPC	In-process control test
IR	Infra red
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
RRT	Relative retention time
SmPC	Summary of Product Characteristics
USP	United States Pharmacopoeia
UV	Ultraviolet
VLBW	Very Low Birth Weight

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gennisium Pharma submitted on 12 October 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Gencebok, through the centralised procedure under Article 3(3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2019.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 10a of Directive 2001/83/EC.

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

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a biowaiver on bioequivalence study with the reference medicinal product Peyona instead of non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Peyona 20mg/ml solution for infusion and oral solution
- Marketing authorisation holder: CHIESI Farmaceutici S.p.A, Italy
- Date of authorisation: 02 July 2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/09/528/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Peyona 20mg/ml solution for infusion and oral solution
- Marketing authorisation holder: CHIESI Farmaceutici S.p.A, Italy
- Date of authorisation: 02 July 2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/09/528/001-002

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur : Alar Irs

The application was received by the EMA on	12 October 2019
The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	03 February 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 Mars 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	04 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	30 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 June 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 June 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to	25 June 2020

Gencebok on	

2. Scientific discussion

2.1. Introduction

This centralised marketing authorisation application concerns Gencebok, solution for infusion, 10 mg/ml, in 1ml ampoule. This application has been submitted in accordance with article 10(3) of Directive 2001/83/EC as amended (hybrid application). The originator and reference product is Peyona, solution for infusion and oral solution, 20 mg/ml, 1 and 3 ml ampoules. The difference between Gencebok and Peyona is the pharmaceutical strength. Gencebok is proposed with a lower concentration (caffeine citrate 10mg/ml corresponding to 5mg caffeine base) as compared to Peyona the reference medicinal product (caffeine citrate 20mg/ml corresponding to 10mg caffeine base). The lower concentration formulation in a single use ampoule (1ml) has been developed to respond to an increasing population of VLBW/ELBW newborns.

Both medicinal products contain the same active substance, caffeine citrate, which is a well-known drug substance and belongs to the pharmacotherapeutic group of psychoanaleptics and is a methylxanthine derivate (ATC code N06BC01). It is structurally related to methylxanthines theophylline and theobromine. Compared to theophylline, caffeine has a wider therapeutic index, fewer peripheral adverse effects and longer half-life, enabling once daily administration. Most of caffeine`s effects have been attributed to antagonism of adenosine receptors, both A_1 and A_{2A} subtypes, demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically in this indication.

The main action of caffeine is acting as a CNS stimulant. This is the basis of using caffeine for short-term treatment of apnoea of prematurity, for which several mechanisms have been proposed for the actions including: (1) respiratory centre stimulation, (2) increased minute ventilation, (3) decreased threshold to hypercapnia, (4) increased response to hypercapnia, (5) increased skeletal muscle tone, (6) decreased diaphragmatic fatigue, (7) increased metabolic rate, and (8) increased oxygen consumption.

The applicant claimed the same indication as the one currently approved for Peyona, the reference medicinal product which has been centrally authorised since 2009. Caffeine citrate aqueous solution is indicated in premature newborns for the treatment of primary apnoea and is intended for intravenous infusion and for oral administration.

The proposed posology is:

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

* Beginning 24 hours after the loading dose

In preterm newborn infants with insufficient clinical response to the recommended loading dose, a second loading dose of 10-20 mg/kg maximum may be given after 24 hours. Higher maintenance doses of 10 mg/kg body weight could be considered in case of insufficient response, taking into account the potential for accumulation of caffeine due to the long half-life in preterm newborn infants and the progressively increasing capacity to metabolise caffeine in relation to post-menstrual age. Although a therapeutic plasma concentration range of caffeine has not been determined in the literature, caffeine levels in studies associated with clinical benefit ranged from 8 to 30 mg/l and no safety concerns have normally been raised with plasma levels below 50 mg/l. More detailed dosage adjustments and monitoring requirements are described in the Product Information.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for infusion containing 10 mg caffeine citrate (equivalent to 5 mg caffeine) as active substance.

The solution for infusion is a clear, colourless, aqueous solution with a pH of 4.8 and osmolality of 65-95 mOsmol/kg.

Other ingredients are citric acid monohydrate, sodium citrate and water for injections.

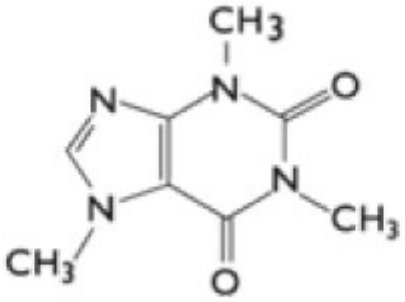
The product is available in type I clear glass 1 ml ampoule coded by 2 blue rings, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of caffeine is 1,3,7-trimethylpurine-2,6-dione, corresponding to the molecular formula $C_8H_{10}N_4O_2$. Caffeine has a relative molecular mass of 194.2 and the following structure:

Figure 1: Caffeine structure



As described in the active substance specification, caffeine is a white or almost white, crystalline powder or soft crystals; it is sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol (96 per cent).

As there is a monograph of caffeine in the European Pharmacopoeia (Ph. Eur.), the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for caffeine which has been provided within the current Marketing Authorisation Application. No information has been provided on the characterisation of the active substance and on its polymorphism. This is acceptable as the active substance is supported by CEP and it is present in solution in the finished product.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the CEP. In the CEP it is stated that the water is used in the last steps of synthesis; the quality of water is adequately controlled.

The active substance is packaged in a container consisting of fibre drums or big bags lined with low-density polyethylene bag, as described in the CEP.

Specification

The active substance specification includes tests for appearance, colour, identification (melting point, IR, loss on drying), appearance of solution, acidity, sulfates, related substances (HPLC), loss on drying, sulfated ash, assay on dried substance and bacterial endotoxins (BET). All the test methods are pharmacopoeial.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Since the finished product is sterile, the finished product manufacturer has included the test for bacterial endotoxins (BET) (as per Ph. Eur. 2.6.14) in the specification of the active substance.

The CEP holder specification includes a test for particle size distribution; since the active substance is in solution in the finished product, this test is not included in the specification as applied by the finished product manufacturer, this is acceptable.

The BET has been adequately validated and described according to ICH Q2.

Batch analysis data of 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

A retest period of 60 months, if stored in the named container, is stated in the CEP.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product Gencebok is a clear, colourless, sterile solution for infusion containing 10 mg/ml of caffeine citrate equivalent to 5 mg/ml of caffeine base.

Gencebok pharmaceutical form is stated in the PI as "solution for infusion" which differs from the pharmaceutical form stated in the PI of the reference product (solution for infusion and oral solution). "Solution for infusion and oral solution" has been deprecated from the EDQM Standard terminology database since 2014 for safety reasons. In line with the reference product, the finished product can be administered orally (including by nasogastric tube), as stated in the respective sections of the SmPC.

The aim of the pharmaceutical development was to obtain a sterile solution for infusion (and oral administration) with the same qualitative composition of the reference product and the USP respective monograph. The proposed strength of the active substance is half the strength of the reference product to allow the maintenance daily doses of 5 mg per kg body weight in the treatment of premature newborns without requiring a dilution of the finished product to obtain the needed concentration.

The applicant has studied appearance, impurity profile, assay, pH and osmolality of the reference product and confirmed comparability with the proposed product for the named attributes. In order to assure the targeted pH value 4.2 to 5.2 (as per USP monograph and EPAR of the reference product), the use of 0.1N sodium hydroxide was considered, however, it was concluded to be not necessary.

The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The specification of both citric acid monohydrate and sodium citrate (dihydrate) includes the pharmacopoeial BET. Nitrogen is an inerting gas used during the manufacture of the bulk solution, filtration and filling of the finished product. Its specification complies with Ph.Eur..

The finished product is for single use only, hence neither preservatives nor antioxidants are included in the formulation. It can be either used without dilution or diluted in sterile solutions for infusion such as glucose 50 mg/ml (5%), or sodium chloride 9 mg/ml (0.9%) or calcium gluconate 100 mg/ml (10%).

As the formulation is qualitatively the same as the one of the reference product, with the concentration of the active substance being half of the concentration of the reference product, no compatibility or in-use differences are expected after the optional dilution in the mentioned diluents. Nevertheless, the applicant has provided compatibility studies data for up to 24 hours after dilution, confirming the compatibility with the three named solutions for infusion, the results of the in-use compatibility studies have been reported in the Stability section. The applicant has used the same statement in the SmPC as the reference product in reference to the nasogastric administration of the product via an enteral feeding tube without providing supporting data. This is considered acceptable since the finished product is a solution, it has the same qualitative composition and pH of the reference product and it requires relatively short administration time.

From a manufacturing development perspective, the applicant employs terminal sterilisation, performed on the filled ampoules as per Ph. Eur. requirements. As per guidance, terminal sterilisation at Ph. Eur. conditions is the preferred sterilisation method; hence its use does not require further justification. Product compatibility with the filters used during manufacturing has been demonstrated based on the contact period of 5 days. Extractables from the filters have also been evaluated and do not pose concern. Manufacturing development studies are considered adequate.

As detailed in the clinical section of the report, a bioequivalence study is not required for either routes of administrations (intravenous and oral) as the both the reference and the proposed product have the same salt form of the active substance and qualitative composition, are aqueous solutions, the excipients are not known to have any interaction with the active substance or to adversely affect the GI transit, absorption, *in vivo* solubility or the solubility of the active substance; hence the reference product meets the requirements as outlined in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr).

The primary packaging is Type I clear glass 1 ml ampoule coded by 2 blue rings. The material complies with Ph.Eur. requirements. The same container is used for the reference product. The filling volume of the proposed finished product is 1 ml (compared to 1 ml and 3 ml of the reference product). The applicant sufficiently justified the development of the smaller ampule size based on maintenance daily doses of the product. The results of performed breakage tests provided during the procedure demonstrate that the risk of glass fragments entering the ampoule is very low. Hence, special precautions (filtering before use) are deemed not necessary. This is also in line with the reference product. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

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

The process has been described in sufficient details. Exceptions to the general practice (autoclave failure, weekends) are managed under GMP. The in-process controls are adequate for this type of manufacturing process.

Although the manufacturing process is a standard manufacturing process, satisfactory validation data on three commercial scale batches has been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of the ampule, including ring colour (visual), appearance of solution (clarity and colour, Ph. Eur.), identification of caffeine (by HPLC and UV), identification of citrate (USP), extractable volume (Ph. Eur.), particulate contamination subvisible and visible particles (Ph. Eur.), assay (caffeine citrate, HPLC), related substances (HPLC), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The specification includes a test for osmolality. The solution is hypo-osmolar (65-95 mOsml/kg) which has no impact for the oral administration route. A syringe infusion pump or other metered infusion devices are used for the slow intravenous infusion administration over 10 minutes; this prevent the risks of haemolysis observed with classic infusion. Batch data confirms the consistency of the osmolality also through supportive stability studies on 3 validation batches and 1 pilot batch for up to 6 months both under long-term and accelerated storage conditions. pH and osmolality are stated in the PI.

The in-house analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, assay and impurities testing has been presented and it is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 2 batches using validated analytical ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE (option 3 of ICH Q3D). Based on the risk assessment and the presented batch, data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

To address a major objection raised during the procedure, the applicant has performed a risk assessment in line with the requirements as outlined in information on nitrosamines for marketing authorization holders (EMA/189634/2019) and questions and answers on "Information on nitrosamines for marketing authorization holders" (EMA/CHMP/428592/2019 Rev.2) and it is concluded that no risk has been identified.

The reference standard for identification, assay and related substances has been adequately characterised.

Batch analysis results are provided for on three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

In response to a second major objection, stability data from four commercial scale batches of finished product stored for up to 6 months under long term conditions (30 ºC / 75% RH) and accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines have been provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance of solution (clarity and colour, Ph. Eur.), particulate contamination subvisible and visible particles (Ph. Eur.), pH (Ph. Eur.), assay (caffeine citrate, HPLC), related substances (HPLC), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). Osmolality is also tested in the primary stability batches. The analytical procedures used are stability indicating.

No significant changes have been observed for the tested parameters.

Data from the ongoing stability protocol will be provided as variation once the 36-month long term data will be available.

In addition, one batch was exposed to light, as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The data provided confirm that the finished product is not light sensitive.

In-use stability studies assessed compatibility with glucose 5%, sodium chloride 0.9% and calcium gluconate 10% for up to 24 hours for two commercial batches. The worst-case scenario (i.e. highest dilution) was investigated; the parameters tested were assay, related substances and pH, all results were within the proposed specification, confirming compatibility with the named media. Data from new in-use stability study, performed in order to meet the requirement of CPMP/QWP/2934/99, where it is stated that at least one of the two batches should be chosen towards the end of its shelf life, will be provided with the updated stability data.

Two additional studies (double freeze-thaw cycle and storage under high temperature conditions: 60°C ± 5°C for 4 days) were performed on one commercial scale batch. Samples were tested for appearance of the solution (clarity and colouration), visible particles and subvisible particles, assay, related substances and pH. A slight variation in clarity and subvisible particles was detected but the results stay within specifications, confirming the good stability of the finished product.

Based on available stability data, the proposed shelf-life of 12 months (without special storage conditions) as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Two major objections regarding the finished product stability and lack of risk assessment for nitrosamines have been sufficiently addressed. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The Pharmacodynamic, pharmacokinetic and toxicological properties of caffeine citrate are well known.

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

Caffeine is a natural substance and therefore in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) is exempt of the need for an environmental risk assessment (ERA). No additional ERA is thus needed for this hybrid marketing authorisation application in accordance with the applicable guideline.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetic and toxicology data.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considered that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required. Gencebok is considered to be approvable from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is a Marketing Authorisation Application under Article 10(3) hybrid application of Directive 2001/83/EC (as amended) for Gencebok, 10 mg/ml (equivalent to 5 mg of caffeine) solution for infusion. Gencebok has a different strength (10 mg/ml) than Peyona, the reference medicinal product (20mg/ml).

The qualitative composition in terms of excipients is the same as for Peyona, based on literature. The routes of administration, pharmaceutical form and the therapeutic indication applied as well as the recommended dose regimen are the same as for the reference product Peyona.

Caffeine is (1,3,7-Trimethylxanthine) a heterocyclic organic alkaloid compound with purine base called xanthine, consisting of pyrimidine ring linked to an imidazole ring, structurally related to theophylline and theobromine. Most of its effects have been attributed to antagonism of adenosine receptors, both A_1 and A_{2A} subtypes, demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically in this indication.

Caffeine citrate is indicated for the treatment of primary apnoea in premature newborns.

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

No clinical studies were submitted. Since the product is administered intravenously, the applicant claimed a biowaiver. Furthermore, similar to the reference product, the maintenance dose could be administered *per os.* As the concentration of the proposed drug product is different from the concentration of the reference product, a justification for the biowaiver has been provided by the applicant.

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate. There is no new clinical efficacy or safety data provided. The clinical sections of the SmPC of Gencebok are in accordance with the reference product Peyona.

Exemption

The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Corr**) states that a bioequivalence study is not required for parenteral solutions:

"*Bioequivalence studies are generally not required if the test product is to be administrated as an aqueous solution containing the same active substance as the currently approved product*."

Based on the intravenous route of administration of this medicinal product, a bioequivalence study is therefore not required. Bioequivalence can be concluded without further studies and as the qualitative composition of the two products is the same, no differences in non-clinical or clinical effects are expected as a result of different concentration of the drug product.

The maintenance dose can be administered either by intravenous infusion or *per os* (including nasogastric tube), in line with the reference product. As the concentration of the proposed drug product is different from the concentration of the reference product, a justification for the biowaiver has been provided by the applicant according to the general requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**):

- Both products contain the same active substance in the same salt form - caffeine citrate – and both products contain the same excipients, qualitatively. The excipients used are not known to have any interaction with the drug substance and to affect the gastrointestinal (GI) transit, the absorption, *in vivo* solubility or the stability of the active substance.
- Caffeine has a wide therapeutic index;
- The drug product is an aqueous solution with the active substance and the excipients fully dissolved.
- The pharmacokinetics of the caffeine is well-known and linear within the range of the two strengths, according to the EPAR for Peyona.
- There are no changes in the routes of administration, pharmaceutical form, therapeutic indication and recommended dosage regimen;
- The clinical sections of the SmPC of Gencebok are in line with the reference product Peyona; according to the section 5.2 of the SmPC, the caffeine citrate readily dissociates in aqueous solution. The citrate moiety is rapidly metabolized on infusion or ingestion.
- The EPAR of the reference product Peyona states that the comparison of the PK parameters obtained in studies where IV and oral doses of caffeine citrate were administered suggests that oral and IV pharmacokinetics of caffeine citrate are similar and absolute bioavailability of orally administered caffeine citrate is nearly 100%". This is considered to be also applicable to the

proposed hybrid medicinal product since the composition of two products can be essentially considered similar. It is not expected that the manufacturing process, different concentration of the drug product or different volume to be administered affect the drug release and absorption. In addition, similar to the reference product no effect of feeding formula on the extent of absorption of caffeine citrate in premature infants is expected.

- To achieve the same dose per kg body weight, the volume of the proposed product to be administered is double the volume of the reference product to maintain the same amount of caffeine citrate. The different concentration of the proposed product in the proposed formulation is not expected to impact the pharmacokinetics as the dose to be administered is the same.

Considering the composition of the final drug product, the applicant considered that the justification provided are adequate and sufficient to support the biowaiver claims.

Clinical studies

No clinical studies were submitted. Since the product is administered intravenously as well as orally, the Applicant applied for a biowaiver.

2.4.2. Pharmacokinetics

No pharmacokinetic studies have been conducted to support this application. A literature overview has been provided.

Pharmacokinetic properties of the reference product Peyona (source SmPC): caffeine citrate readily dissociates in aqueous solution. The citrate moiety is rapidly metabolized on infusion or ingestion.

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

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

Caffeine metabolism in preterm newborn infants is very limited due to their immature hepatic enzyme systems and most of the active substance is eliminated in urine. Hepatic cytochrome P450 1A2 (CYP1A2) is involved in caffeine biotransformation in older individuals. Inter-conversion between caffeine and theophylline has been reported in preterm newborn infants; caffeine levels are approximately 25% of theophylline levels after theophylline administration and approximately 3-8% of caffeine administered would be expected to convert to theophylline. In young infants, the elimination of caffeine is much slower than that in adults due to immature hepatic and/or renal function. In newborn infants, caffeine clearance is almost entirely by renal excretion. Mean half-life ($t_{1/2}$) and fraction excreted unchanged in urine (Ae) of caffeine in infants are inversely related to gestational/postmenstrual age. In newborn infants, the $t_{1/2}$ is approximately 3-4 days and the Ae is approximately 86% (within 6 days). The available limited data on the dose proportionality suggests the dose linearity for the investigated dose-range (2.5 - 3mg/kg to 30mg/kg).

2.4.3. Pharmacodynamics

No new pharmacodynamic or efficacy studies were presented, and no such studies are required for this application. Literature review has been submitted and the SmPC text is based on the reference product.

Mechanism of action

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

Pharmacodynamic effects

Caffeine's main action is as a CNS stimulant. This is the basis of caffeine's effect in apnoea of prematurity, for which several mechanisms have been proposed for its actions including: (1) respiratory centre stimulation, (2) increased minute ventilation, (3) decreased threshold to hypercapnia, (4) increased response to hypercapnia, (5) increased skeletal muscle tone, (6) decreased diaphragmatic fatigue, (7) increased metabolic rate, and (8) increased oxygen consumption.

Clinical efficacy and safety

The clinical efficacy of caffeine citrate was assessed in a multicentre, randomised, double-blind study that compared caffeine citrate to placebo in 85 preterm infants (gestational age 28 to <33 weeks) with apnoea of prematurity. Infants received 20 mg/kg caffeine citrate loading dose intravenously. A maintenance daily dose of 5 mg/kg caffeine citrate was then administered either intravenously or orally (through a feeding tube) for up to 10-12 days. The protocol allowed infants to be "rescued" with open-label caffeine citrate treatment if their apnoea remained uncontrolled. In that case, infants received a second loading dose of 20 mg/kg caffeine citrate after treatment day 1 and before treatment day 8.

There were more days without any apnoea under caffeine citrate treatment (3.0 days, versus 1.2 days for placebo; p=0.005); also, there was a higher percentage of patients with no apnoeas for ≥ 8 days (caffeine 22% versus placebo 0%).

A recent large placebo-controlled multicentre study (n=2006) investigated short-term and long-term (18-21 months) outcomes of premature infants treated with caffeine citrate. Infants randomised to caffeine citrate received an intravenous loading dose of 20 mg/kg, followed by a daily maintenance dose of 5 mg/kg. If apnoeas persisted, the daily maintenance dose could be increased to a maximum of 10 mg/kg of caffeine citrate. The maintenance doses were adjusted weekly for changes in body weight and could be given orally once an infant tolerated full enteral feeding. Caffeine therapy reduced the rate of bronchopulmonary dysplasia [odds ratio (95% CI) 0.63 (0.52 to 0.76)] and improved the rate of survival without neurodevelopmental disability [odds ratio (95 %CI) 0.77 (0.64 to 0.93)].

The size and direction of caffeine effect on death and disability differed depending on the degree of respiratory support infants needed at randomisation, indicating more benefit for the supported infants [odds ratio (95%CI) for death and disability, see table below].

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

Subgroups	**Odds ratio (95% CI)**
No support	1.32 (0.81 to 2.14)
Non-invasive support	0.73 (0.52 to 1.03)

Endotracheal tube	0.73 (0.57 to 0.94)

Only Literature data on clinical safety was provided by the applicant, which is acceptable for this type of application. The data are considered adequate and in line with the reference medicinal product.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

This is a Marketing Authorisation Application under Article 10(3) hybrid application of Directive 2001/83/EC (as amended) for Gencebok, 10 mg/ml (equivalent to 5 mg of caffeine) solution for infusion.

The reference product is Peyona 20mg/ml (equivalent to 10 mg of caffeine) solution for infusion and oral solution, centrally approved on 02/07/2009.

The qualitative composition of Gencebok, in terms of excipients, is the same as for Peyona, based on literature. The routes of administration, pharmaceutical form and the therapeutic indication applied as well as the recommended dose regimen are the same as for the reference product Peyona.

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

Caffeine citrate is indicated for the treatment of primary apnoea in premature newborns.

No new pharmacokinetic data have been presented, a literature review and a discussion along the lines of the assessment of the reference product have been submitted by the applicant and is considered to be acceptable.

An exemption for conducting a bioequivalence study has been proposed by the applicant and has been found acceptable by the CHMP. No further requests for the demonstration of similarity of the two drug products is considered to be needed. The biowaiver with regard to oral administration has been accepted as well based on provided justification and taking into account the composition of the final drug product.

The clinical overview on the clinical pharmacology, efficacy and safety of the product has been provided and is considered adequate. No new pharmacodynamic, efficacy or safety studies were presented, and no such studies are required for this application type.

The recommended posology is 20mg caffeine citrate per kg body weight (loading dose) and the maintenance dose is 5mg caffeine citrate per kg body weight.

The clinical sections of the SmPC of Gencebok are mainly similar to the reference product Peyona with very minor adjustments made in connection with the lower concentration of the current product, where necessary.

The dose of caffeine citrate is calculated per body weight; thus, the lower concentration of the proposed drug product increases the final volume to be administered but is not considered to impact the dosage regimen. The final solution to be administered has the same amount of caffeine citrate.

The product is intended to be marketed only in single 1 ml ampoule. The suitability of the proposed ampoule size of 1ml has been sufficiently justified as the lower concentration solution is more suitable for the better match with the maintenance dose (more commonly used over loading dose) in the treatment of premature newborns. The Applicant has addressed the issue of potential risk of glass

fragments entering the ampoule by conducting a breakage test on 10 ampoules. The results demonstrate that the risk is low and special precautions (e.g. filtering before use) are therefore not deemed necessary.

The most common side effects are hyperglycaemia, tachycardia, phlebitis and inflammation at the site of infusion.

The difference in concentration with the reference medicinal product does not pose any safety (in terms of Adverse Events) or efficacy concerns as the dose to be administered as final infusion solution is calculated as the amount of caffeine citrate per kg body weight. Nevertheless, some concerns were raised about potential medication errors due to the differences in concentration between the two products. Therefore, medication errors is listed as an important potential risk in the RMP summary of safety concerns. In order to further address this important potential risk, additional risk minimisation measures in the form of a healthcare professional card containing key elements about the risk of medication error was agreed (see RMP and Annex II.D of the Product Information).

The pharmaceutical form of Gencebok ("solution for infusion") is different from Peyona, the reference product ("solution for infusion and oral solution"). The term 'solution for infusion and oral solution' is no longer recommended to be used as a standard term and it has been deprecated by EDQM since 2014 due to safety reasons. Therefore, during the evaluation of this hybrid application, the applicant was requested to replace the pharmaceutical form 'solution for infusion and oral solution' with 'solution for infusion'. As Gencebok can still be orally, similarly to Peyona, reference to the oral administration use remains covered in the relevant sections of the Product Information.

2.4.6. Conclusions on clinical aspects

Since the product can be administered intravenously and *per os*, the Applicant submitted biowaiver together with justification for not performing bioequivalence studies. Furthermore, no clinical studies were submitted. The clinical data in the summary of product characteristics are based on the reference product. Overviews of clinical pharmacology, efficacy and safety literature have been provided.

This was considered acceptable by CHMP.

2.5. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Toxicity due to maternal caffeine ingestion; • Increase in caffeine plasma levels in premature infants with cholestatic hepatitis; • Increase in caffeine plasma levels in premature infants with clinically relevant renal insufficiency; • Cardiac disorder in infants with pre-existing cardiac disease, including arrhythmias; • Treatment-related convulsions/seizures
Important potential risks	• Decrease in weight gain / failure to thrive; • Caffeine withdrawal; • Necrotising enterocolitis; • Medication errors.

Missing information	• Rare adverse drug reactions; • Drug interaction with the most commonly used drugs in the NICU; • Long-term effects of caffeine therapy

Pharmacovigilance plan

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted.

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

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Toxicity due to maternal caffeine ingestion	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.6 and 5.2 PL section 2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of toxicity due to maternal caffeine ingestion.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Increase in caffeine plasma levels in premature infants with cholestatic hepatitis	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and 5.2 PL section 2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of increase in caffeine plasma levels in premature infants with cholestatic hepatitis.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Increase in caffeine plasma levels in premature infants with clinically relevant renal insufficiency	Routine risk minimisation measures: SmPC sections 4.2, 4.4 ,4.8 and 5.2 PL section 2 Legal status: Prescription Only Medicine and reserved for hospital use	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of increase in caffeine plasma levels in premature infants with clinically relevant renal insufficiency.	Additional pharmacovigilance activities: none
Cardiac disorder in infants with pre-existing cardiac disease, including arrhythmias	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of cardiac disorder in infants with pre-existing cardiac disease, including arrhythmias	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Treatment-related convulsions/seizures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of treatment-related convulsions/seizures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Decrease in weight gain / failure to thrive	Routine risk minimisation measures SmPC section 4.8 PL sections 2 and 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of decrease in weight gain / failure to thrive	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Caffeine withdrawal	Routine risk communication: SmPC sections 4.2 and 5.2 Legal status: Prescription Only Medicine and reserved for hospital use	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of caffeine withdrawal	Additional pharmacovigilance activities: none
Necrotising enterocolitis	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of necrotising enterocolitis.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Medication errors	Routine risk minimisation measures: SmPC section 4.2 Labelling about caffeine citrate/base Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of medication error.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Rare adverse reactions	Routine risk communication: SmPC sections 4.8 PL section 4 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: A Healthcare Professional card containing key elements about the risk of rare adverse reactions	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Drug interaction with the most commonly used drugs in the NICU	Routine risk communication: SmPC sections 4.2, 4,4 , 4.5 and 5.2 PL section 2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	A Healthcare Professional card containing key elements about the risk of drug interaction with the most commonly used drugs in the NICU;	
Long-term effects of caffeine therapy	Routine risk communication: SmPC sections 4.2 and 5.2 Legal status: Prescription Only Medicine and reserved for hospital use Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none

Conclusion

The CHMP considered that the risk management plan version 0.4 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Peyona 20 mg/ml solution for infusion and oral solution. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

Caffeine is widely used in the neonatal intensive care unit to treat apnoea of prematurity (AOP) but also to prevent apnoea-related symptoms and facilitate weaning from mechanical ventilation.

This application concerns a hybrid medicinal product, Gencebok (caffeine citrate, 10 mg/ml solution for infusion). The reference product Peyona (caffeine citrate, 20 mg/ml solution for infusion and oral solution) is indicated for Treatment of primary apnoea of premature newborns.

The quality of the product is considered to be acceptable and consistent. The differences in concentration between Gencebok and Peyona are in general fully and satisfactorily characterized by the published literature and comparative quality data required, and those differences are expected to have no adverse impact on the efficacy and safety of the proposed drug product.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The exemption from the necessity to conduct bioequivalence studies has been adequately justified.

A positive benefit/risk ratio can therefore be concluded.

Due to concerns about potential medication errors additional risk minimisation activities are required beyond those included in the product information. A healthcare professional card containing key elements about the risk of medication error was agreed (see RMP and Annex II.D of the Product Information).

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Gencebok is favourable in the following indication:

Treatment of primary apnoea of premature newborns.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

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

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

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

* Beginning 24 hours after the loading dose

- That the medicinal product should be used immediately after opening the ampoule and unused portions left in the ampoule should be discarded
- That baseline plasma levels may need measuring because of an increased risk of toxicity if
    - The neonate has been previously treated with theophylline

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