15 June 2022
EMA/602372/2022
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for DogStem (EMEA/V/C/005829/0000)

Common name: equine umbilical cord mesenchymal stem cells

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

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Introduction

The applicant EquiCord S.L. submitted on 19 May 2021 an application for a marketing authorisation to the European Medicines Agency (The Agency) for DogStem, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 10 December 2020, as DogStem contains an active substance (equine umbilical cord mesenchymal stem cells – EUC-MSCs) that was not authorised as a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004.

At the time of submission, the applicant applied for the following indication: Reduction of pain and lameness associated with mild to severe osteoarthritis in dogs.

The active substance of DogStem are equine umbilical cord mesenchymal stem cells, a biological, cell-based product, with immunomodulatory and anti-inflammatory properties attributed to their paracrine activity, e.g. prostaglandin E_2 (PGE_2) secretion. The target species is dog.

DogStem suspension contains approximately 7.5 million equine umbilical cord mesenchymal stem cells in 1 ml and is presented in packs containing 1 vial of 1 ml.

The rapporteur appointed was Cristina Muñoz Madero and the co-rapporteur was Andrea Christina Golombiewski.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

On 15 June 2022, the CVMP adopted an opinion and CVMP assessment report.

On 30 November 2022, the European Commission adopted a Commission Decision granting the marketing authorisation for DogStem.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system, which fulfils the requirements of Directive 2001/82/EC, as amended. Based on the information provided, the applicant has the services of a Qualified Person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Union or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the dosage form, including batch release, takes place at EquiCord S.L., C/ Loeches 103 D, Polígono Industrial Ventorro del Cano, Alcorcón, 28925 Madrid, Spain. The site has a manufacturing authorisation issued on 7 June 2021 by the Agencia Española de Medicamentos y Productos Sanitarios

(AEMPS), Spain. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

The master cell bank (MCB) and the active substance are manufactured at the same site.

A GMP declaration for the active substance manufacturing site has been provided by the Qualified Person (QP) at Equicord S.L. (dated 7 June 2021). The declaration is based on an internal on-site audit performed in November 2021, by the QP.

The applicant identifies the sites involved in the quality control of the medicinal product. The quality management system of these sites is partially described, and the corresponding certificates provided. The applicant submitted an audit certificate for an external contractor company which did not have a quality management system implemented, and a commitment for the implementation of a quality management system (ISO 17025) at this site. This is considered acceptable for this specific case.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system is in line with legal requirements.

The quality management system of one external site, involved in quality control will be implemented (post-authorisation commitment).

Part 2 - Quality

Composition

The finished product is presented as a cell suspension of equine umbilical cord mesenchymal stem cells in a dose of $6.0 \times 10^6 – 9.0 \times 10^6$ in 1 ml.

The product contains an excipient (preservative).

Containers

The primary package for the final product is a vial of 2 ml capacity, composed of cyclic polyolefin polymer (resin), which is closed with a sterile bromobutyl rubber stopper (type I) and is sealed with a flip-off aluminium capsule. The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been validated by stability data and it is adequate for the intended use of the product.

The primary packages for the active substance are:

- 250 ml centrifugation tubes
- 1.8 ml cryotubes

They do not comply with the requirements of Ph. Eur. for containers. However, the applicant adequately justified the suitability of these containers for this specific active substance.

Specifically referring to the sterilisation of these containers, the 250 ml tubes and the cryotubes are adequately sterilised.

Development pharmaceutics

The active substance is equine umbilical cord mesenchymal stem cells expanded *in vitro* to passage 4.

The adequacy of the cell type and the dosage was determined through literature review. The efficacy and the safety of the dose chosen are discussed in parts 3 and 4 of the present report.

The single excipient is considered similar to intracellular fluid (in terms of ion concentration). The aim of using this kind of excipient is to improve the cell stability in hypothermic and nutrient-deprived conditions.

The formulation used during clinical studies was the same as that intended for marketing.

Overages and extractable volume: Due to the density of the product, and the shape and size of the vials, it is not possible to extract 100% of the vial content. The strategy of the applicant to solve this issue is to add an overage to the content of the vial. The applicant has calculated the required overage to achieve 1 ml of extractable dose due to the residual volume reported.

Method of manufacture

The manufacturing process consists of the obtaining of equine umbilical cords, isolation and amplification of EUC-MSCs, their resuspension in the excipient, homogenisation of the suspension, and optional freezing.

The method of manufacture is adequately established and described in the dossier. Specifications and in-process controls have been established.

Separate validations of the manufacturing process for the active substance and the final product have been provided. The validation of the final product was done in three separate studies, for three different sizes of batches (15, 20 and 200 vials, respectively). The maximum batch size is 200 vials.

Active substance

The active substance (AS) consists of mesenchymal stem cells derived from equine umbilical cord and expanded *in vitro* up to passage 4.

The AS is not described in Ph. Eur.

The AS can be manufactured by a continuous or by a discontinuous manufacturing process. In the continuous manufacturing process, the EUC-MSCs are expanded *in vitro* up to passage 4 and then directly used to manufacture the finished product. In the discontinuous manufacturing process, frozen active substance, prepared at an earlier time, is thawed, seeded and used to manufacture the final product. The applicant provides a description of the manufacturing process (continuous and discontinuous) and the established in-process controls. Both manufacturing processes render equivalent active substances, as proved by the controls and tests implemented. The obtained final product is released under the same specifications regardless of whether the active substance is manufactured by the continuous or discontinuous process.

The specifications for the AS are the following (quality-controlled):

- **Cell morphology:** The EUC-MSCs are adherent to plastic and have an elongated shape with granular cytoplasm and irregular edges that grow uniformly in a monolayer on the adherent surface. Cell morphology is monitored periodically during the cell amplification and AS recovery by visual inspection under microscope to assess that the defined shape is maintained, and to confirm the expected growth of the adherent cells.

  The manufacturing staff have been trained in the culturing and monitoring of EUC-MSCs, being familiarised with their morphology and confluence evaluation.

- **Mycoplasma control:** Analysed by PCR using a commercial detection kit. The test complies with

Ph. Eur. 2.6.7.

The following mycoplasmas are included as positive controls:

- *M. pneumoniae* (related to respiratory disease in human)
- *M. hyorhinis* (fastidious, a common cell culture contaminant of animal origin, and a mammalian pathogen)
- *M. orale* (opportunistic pathogen in immunocompromised humans)
- *M. synoviae* (avian pathogen)
- *Acholeplasma laidlawii (*typical of burns*)*
- *Ureaplasma urealyticum* and *M. arginini*, related to the human illnesses that can be transmitted to the handled sample, in this case the EUC-MSC culture.

The method was validated.

- **Accumulative population doublings (APD):** The APD number is the number of times a culture has doubled the number of initially seeded cells. The APDs considered as QCs for the AS are calculated at the following points:
  - AS from the continuous manufacturing process: at cell harvesting of the passage 4.
  - AS from the discontinuous manufacturing process: at cell harvesting of the recovered AS.

  Although the MSCs have proliferation capacity, their duplication number is limited. Once the cells leave the proliferative phase (also named the exponential growth phase), they may acquire a senescence state, which leads to a gradual reduction of their potency and significant changes in protein expression, increasing the risk of malignant transformation and compromising the safety of the cells and the finished product. The genetic stability in cell culture has been studied by a cytogenetic assay at early and late APDs. No chromosomal aberrations were observed at these two time points. Number of viable cells and viability: the determination of the total cell number and its viability was performed by the manual dye exclusion method, which is a manual counting with Neubauer chamber (haemocytometer) according to Ph. Eur. 2.7.29. This method has been adequately validated.
- **EUC-MSC phenotype:** the cellular markers CD45, CD79α and MHC II are typical of myeloid and haematopoietic progenitors. A low percentage of these markers are expected in the AS. The markers CD44 and CD90 are conserved in cells with migratory capacity and undifferentiated characteristics. The AS is expected to be positive for them.
- For the **phenotype test**, a sample of EUC-MSCs from the harvested cells at passage 4 is used. These cells are analysed by staining with specific antibodies to determine the expression of the markers indicated above by flow cytometry, using a FACS (fluorescence-activated cell sorting) to acquire and analyse the data, according to Ph. Eur. 2.7.24.
- The presence of **endotoxins** was tested according to Ph. Eur. 2.6.14., method D. The maximum limit specification was determined.
  This determination was performed in one sample from the culture medium supernatant just before the cellular harvest at passage 4 in the continuous manufacturing process. Endotoxins are not determined at AS in the discontinuous manufacturing process since this parameter is directly tested in finished product.

  The validation of the method and suitability test were carried out according to Ph. Eur. to verify that the culture medium, the matrix to analyse, does not interfere with the assay.

- **Potency:** As potency quality control, the applicant implemented the quantification of the constitutive PGE_2 secretion by EUC-MSCs. The quantification of the constitutive PGE_2 secretion by EUC-MSCs was performed in one sample from the culture medium supernatant just before the cellular harvest at passage 4 in both the continuous and discontinuous manufacturing process.

  The method to measure the potency consists of measuring the potency directly on the cellular supernatant of the AS (several aliquots are collected, homogenised and analysed).

  A commercially available ELISA kit (enzyme-linked immunosorbent assay) is used to measure the PGE_2 level. This method is based on the forward sequential competitive binding technique in which PGE_2 present in a sample competes with horseradish peroxidase (HRP)-labelled PGE_2 for a limited number of binding sites on a mouse monoclonal antibody.

  The validation of the method was provided and showed that PGE_2-related compounds are also detected by this method at certain quantities. Due to the complex mechanism of action of this type of products, other prostaglandins (PGs) may also be co-responsible for the mechanism of action of the product. Thus, the proposed potency test is considered adequate. Nevertheless, a more thorough investigation of the cellular supernatant for the presence and identification of other lipid mediator components (e.g. with MS/MS analytics) would have been desirable.

  The method has been adequately validated.

  The sampling strategy is well justified and ensures the representativeness of the batch tested.

  Regarding the threshold value of PGE_2 for specification, the limit has been eventually established. It corresponds to the lowest PGE_2 level in the AS batches used in the clinical trial titled "Confirmatory safety and efficacy clinical trial in the use of xenogeneic mesenchymal stem cells from equine umbilical cord EUC-MSCs in dogs with mild to severe osteoarthritis in field conditions", corrected by the secondary expectation limit obtained in a Shewchart's chart, based on the potency data available from the batches manufactured to that date (55 batches). This limit is considered adequate. In order to ensure a better manufacturing consistency and the possible correlation with the available data on efficacy in target species, an upper limit has also been established.

- **Sterility:** Sterility is tested on the AS in both continuous and discontinuous manufacturing processes at passage 3 and in cryopreserved samples, respectively. The results are available before the release of the final product batch. Sterility test is done by Bact-Alert, validated as an alternative method to the Ph. Eur. Sterility test. A suitability test for the method has also been provided. The provided information is considered adequate. Sampling is performed in line with the requirements of new chapter Ph. Eur. 2.6.27.

- **Potential impurities** were discussed. Three kinds of impurities were identified:

  - Cellular impurities: Several types of cells could be present as impurities, such as fibroblasts. Controls have been established by phenotype, microscopy visualisation and fibronectin assay. The specification established in the fibronectin assay ensures the absence of fibroblasts at MCB level.

  - Non-cellular impurities: The non-cellular impurities have been identified and their theoretical quantity established.

  - Adventitious agents: The applicant provides a risk assessment on the adventitious agents potentially present on the active substance (further discussed in the MCB section).

Validation of the active substance manufacturing process: The validation encompassed the manufacturing of six AS batches. Three batches were manufactured using the continuous process. The

other three were manufactured with samples from the AS manufactured by the continuous process, which were frozen and subsequently thawed, in order to mimic the discontinuous manufacturing process. The established quality controls (specifications and IPCs) were analysed, and the results complied with the acceptance criteria.

Control of starting materials

The starting materials are the following:

- Excipient
- Container closure system
- Substances of biological origin: equine umbilical cord (raw material), master cell bank, trypsin, foetal bovine serum, collagenase, antibiotics.

Excipients

The excipient is a physiological intracellular-type solution that closely balances the altered cellular ion concentrations which result from low temperatures and from nutrient-deprived conditions that exist when cells are not kept under normal culture conditions. These properties allow using the excipient as a biopreservation medium that provides the maximum storage and shipment stability for biologicals at 2-10 °C.

It is serum-free and protein-free.

It contains one animal-derived raw material, derived by multi-step isolation and refining processes that include precipitation, evaporation, extensive heating to 60 °C, and crystallisation of milk from USDA-certified sources to produce NF-grade lactose. Based on the processing steps, it could be considered that this component is free of extraneous agents.

Regarding the composition of the excipient, due to confidentiality reasons the exact concentration of each component is undisclosed. The individual components comply with Ph. Eur. or other pharmacopoeias, when applicable. A brief description of the manufacturing method and established controls is included. The certificate of analysis, the certificate of origin and certificate of freedom from BSE have also been provided. The safety of the excipient is based on a bibliography reference (poster communication) and the studies done during the development of DogStem. It can be considered safe.

Packaging materials

There are three different container closure systems: one for the fresh AS, one for the cryopreserved AS and one for the final product.

Container for fresh AS: 250 ml centrifuge tubes made of polypropylene with conical bottom and a plug seal screw cap. They are provided sterile by the supplier. The certificate of analysis of the supplier is provided.

Container for cryopreserved AS: A 1.8 ml polypropylene homopolymer cryovial with internal seal and a cap of the same material. The applicant provided a certificate of analysis of the supplier. The tubes are provided sterile by the supplier.

Containers are manufactured under ISO 13485, sterilised according to ANSI/AAMI/ISO 11137, tested for cytotoxicity according to ISO 10993, tested for biological reactivity according to USP Class VI, and for non-pyrogens according to USP 85. This is considered adequate.

Container for the final product: The container is a vial of 2 ml capacity. It is composed of cyclic olefin polymer. The closure consists of a flip-off aluminium seal and a rubber stopper.

The applicant provided a description of the container closure system of the finished product. The sterilisation method is also described (sterilised by autoclave in Equicord S.L.).

In relation to the vials, the certificate provided by the supplier states the compliance with Ph. Eur. 3.2.2.1 Plastic containers for aqueous solutions for infusion.

The rubber stoppers are also in compliance with Ph. Eur. 3.2.9 Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders.

Starting materials of biological origin

The materials of biological origin are the following:

- Equine umbilical cord (EUC)
- Master cell bank (MCB)
- Trypsin
- Foetal bovine serum
- Collagenase
- Antibiotics

Equine umbilical cord (EUC): The EUC is the tissue from which mesenchymal stem cells (MSCs) are isolated to obtain the starting material, master cell bank (MCB). The EUC is considered a raw material.

The tissue is pink to reddish and surrounded by a thin overlay called amnion.

The umbilical cord is collected from horses (*Equus ferus caballus*) from specific sub-contracted stud farms.

The control of the potential contamination of the umbilical cord is done by the control of the donor, the shipment conditions to Equicord laboratories and the status of the cord at the reception in Equicord S.L.:

- Control of the donor: The equine umbilical cord is collected after foal birth from a mare belonging to a sub-contracted stud farm in Spain. The origin of the umbilical cord is known and controlled under the Local Regulatory Rules on Animal Health, which require the farms to have permanent veterinary staff who monitor the health of the animals, quarantine programmes and an established plan of vaccination and de-worming (annual vaccination against equine influenza, tetanus and rhinopneumonitis; de-worming every 3 months with ivermectin, praziquantel, oxibendazole and pyrantel; control of parasites by coprology assay only in case of infection). The collection of the umbilical cord should be done according to an SOP (standard operating procedure). The controls are:
    - Health status of the foal at birth: the veterinarians responsible for the collection of the tissue fill in a certificate of birth that includes the health status of the foal. The applicant has established inclusion and exclusion criteria for EUC based on this certificate.
    - Quarantine programme: the mares are subjected to a quarantine period before the delivery, which includes a daily veterinary assessment for 15 days before the expected delivery date (clinical signs). The quarantine programme after the delivery includes a daily veterinary assessment for 6 weeks of both the mare and foal. If any clinical sign is observed, a diagnosis protocol is activated. A certificate of quarantine programme is

generated. The cells isolated will not be released until the quarantine programme is completed and the veterinary certificate of the health status of both the mare and the foal is issued.

- Sera and blood sample analysis from the foal.

- Shipment conditions: the EUC collection is standardised. Once collected and cleaned with water, it is introduced into a container with a Stud Washing solution. After 30 minutes, the cord is introduced into a second container containing a shipment solution with PBS 1X and antibiotics. Shipment is done refrigerated (0-15 °C), under Good Distribution Practices (GDP).
- The controls at the reception of the EUC in EquiCord are described in the MCB section.

Process validation: the process to obtain the EUC has been validated together with the process to obtain the MCB. Further details are given in the MCB section.

Master cell bank (MCB): The MCB is a cell reference stock that is prepared, dispensed, characterised and cryopreserved under defined conditions.

This MCB consists of mesenchymal stem cells isolated from equine umbilical cord (EUC-MSCs). The stock has a minimum of 3 cryovials with 6 – 7 x 10^6 viable EUC-MSCs per cryovial in the cryopreservant.

MCB manufacturer is EquiCord, which is responsible of EUC-MSCs isolation, expansion until passage 1 and cryopreservation. This manufacturing process is carried out in non-classified facilities.

Manufacturing process: the master cell bank production consists of three main phases: EUC-MSC isolation, EUC-MSC amplification and MCB cryopreservation. In-process controls have been established.

Specifications were established, controlled by the quality controls: cell morphology, viability, ADP, mycoplasma, phenotyping, sterility test, equine viruses and protozoa, number of cryovials, genetic stability.

Extraneous agents testing of MCB: a risk assessment on extraneous agents has been provided.

The applicant discussed the risk of transmission of the extraneous agents listed in the mentioned guidelines applicable to horses and dogs. When the presence of an agent could not be ruled out, the applicant implemented a quality control.

Process validation: the process validation included the acquisition of an equine umbilical cord and the establishment of the master cell bank. Data from three batches have been provided. The results of the three batches comply with the established specifications.

Trypsin: Two kinds of trypsin solutions are used during the manufacturing process: Trypsin EDTA 2x in non-classified stages (basically the MCB production) and Trypsin EDTA 1x in GMP stages, which includes the active substance manufacturing. Both are prepared from Trypsin EDTA 10x.

The applicant provides, for Trypsin EDTA 10X, a certificate of origin, a certificate of analysis, a BSE/TSE-free certificate, in compliance with the "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathies via human and veterinary medicinal products" (EMEA/410/01), a sterility test certificate according to Ph. Eur. 2.6.1, and a certificate of irradiation (electron beam irradiation, minimum dose 33.5 kGy). The same documentation is provided for Trypsin EDTA 1X.

Trypsin is obtained by acid extraction from porcine pancreas. It is tested for the presence of bacteria and fungi, porcine parvovirus, PCV1/PCV2 and mycoplasma. It is also irradiated and tested for sterility after irradiation.

Foetal bovine serum: The applicant provided a certificate of analysis, batch manufacturing record and an EDQM TSE certificate of suitability (R0-CEPV 2017-132-Rev 01). It is gamma-irradiated at a

minimum dose of 30 kGy.

Collagenase: Collagenase is used for enzyme digestion of the EUC during the MCB manufacture.

It is manufactured by fermentation using animal origin (bovine and porcine) components in the fermentation broth. The fermentation broth is sterilised at 121 °C and 22 PSI (151.7 kPa) for a minimum of 30 minutes, prior to use and inoculation for the production of collagenase.

It is packaged as a lyophilised powder. For its use, collagenase is diluted in sterile medium (DMEM), and the obtained solution is filtered using a 0.2 µm strainer in order to remove any kind of microorganism present in the product.

Antibiotics: Antibiotics are used during the manufacturing process. The certificates of origin and certificates of analysis are provided.

Control measures to prevent the transmission of TSE

The applicant presented a risk assessment on transmission of bovine spongiform encephalopathy (BSE) from EquiCord S.L. during the MCB and active substance manufacturing process:

1. According to the Certificate of Analysis and Origin, the foetal bovine serum used by the applicant for cell culture is manufactured in Brazil, country included in the list of the 25 countries where the risk of transmission of BSE is negligible, according to the World Organisation for Animal Health (WOAH/ex-OIE).

2. The manufacturer of the following reagents declares that they contain no materials of animal origin or are free from TSE according to the list in the "Note for guidance of minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMEA/410/01 Rev.3-July 2011):
    - Trypsin EDTA 1X
    - Trypsin EDTA 10X
    - Collagenase
    - DMEM
    - DPBS
    - Penicillin / streptomycin
    - In addition, the reagents manufacturer certifies that the entire product line is free from BSE and TSE.
3. Lastly, equine umbilical cord (and subsequently the isolated EUC-MSCs) is a tissue free from BSE/TSE.

For all these reasons, EquiCord considers that the risk of BSE/TSE transmission can be qualified as "absent" for the target species (dog) or for the human.

Control tests during production

Not applicable.

Control tests on the finished product

The finished product (FP), DogStem, is a cloudy colourless cellular suspension with physiological pH, which consists of 7.5 x 10^6 ±20% mesenchymal stem cells derived from equine umbilical cord (EUC-MSCs), with viability higher than 85%, in 1 ml of excipient (the vial contains an overage of 5%, which ensures an administration dose of 7.5 x 10^6 ± 20% cells in 1 ml of excipient to the patient). The cell suspension is packaged in 2 ml cyclic polyolefin (COP, resin) vials, which are sealed with rubber stopper and flip-off aluminium seal.

The maximum batch size is 200 vials.

Appearance of the finished product:

Cloudy homogeneous cellular suspension.

Identification and assay of active substance(s):

The applicant did not establish identification and assay tests of the active substance in the final product, as these parameters are tested in previous stages of the manufacturing process. The following controls were established at FP level:

- Cell quantification. The cell concentration was established as 7.5 x 10^6 ± 20% cells/ml. The method was validated for accuracy, precision and linearity.
- Viability. The specification was established at ≥85%. This value is supported by the recommendation of Food and Drug Administration (FDA) Guideline on "Content and Review of Chemistry, Manufacturing and Control (CMC) information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)" and by different publications detailing the quality controls established for validations of advanced therapy medicinal products manufactured under Good Practices. The method has been validated.

The quantification is performed by the manual dye exclusion method, which is a manual counting with Neubauer chamber (haemocytometer) according to Ph. Eur. 2.7.29.

Identification and assay of excipient components:

The applicant did not establish identification and assay test of the excipient in the final product, as there are no preservatives or antioxidants in the formulation.

Safety tests:

- Endotoxin, according to Ph. Eur. 2.6.14.
- Gram test.
- Sterility, according to Ph. Eur. 2.6.27 by the technique Bact-Alert. Bact-Alert is an alternative method to Ph. Eur. 2.6.1. for sterility testing, which is widely used in cell therapy and accepted by Food and Drug Administration (EMA/CVMP/ADVENT/751229/2016-Rev.1). The results with this method are obtained faster, in 8 days, and 98% of the contaminations can be detected within 72 hours (EMA/CVMP/ADVENT/751229/2016).

  This method has been validated according to Ph. Eur. 5.1.6. In addition, a suitability test has been provided for the final product (in the presence of the excipient).
- The presence of viruses is not tested. The applicant justifies that they are tested in previous stages of the manufacturing process (at MCB level; starting materials of animal origin are provided free of viruses, as certified by suppliers).

- The presence of mycoplasma in the final product is not tested. It is controlled at the active substance level.

The batch release is carried out in two stages:

1. Early/initial certification, which includes an assessment of the batch processing record, results from environmental monitoring, all deviations and the available analytical results reviewed by the Qualified Person (including final results of the Gram test).
2. Final certification, which involves an assessment of the final analytical tests. Due to the short shelf life of DogStem, final results from the sterility test may not be available before administration of this stem cell-based product.

The applicant provided a risk assessment on the possibility of the administration of a contaminated medicinal product. It was estimated to be low (2%). The applicant has also implemented a risk minimisation plan, describing the actions to be followed in case contaminated final product is released. Among other measures, an immediate contact with the veterinarians is planned. As the injection of non-sterile product into a sterile environment (joint) may produce septic arthritis, the applicant recommends an antibiotic treatment based on cefuroxime or amoxicillin/clavulanate, given intravenously initially and then continued with oral medication for a minimum of four to six weeks, or two weeks after resolution of clinical signs. In most cases, a response should be seen within five to seven days (antibiotic of choice in case of contamination in canine musculoskeletal injuries). Additionally, the contaminated batch is to be withdrawn.

Impurities of finished product:

- Cellular impurities are not tested in the final product, as they are tested in the active substance. Only dead cells are assessed in the final product using the viability test previously described.
- Non-cellular impurities are also the same as in the active substance. The applicant considers that the concentration of impurities is in trace amounts, barely detectable by analytical methods. According to the Guideline on *"Test procedures and acceptance criteria for new biotechnological/biological veterinary medicinal products"*, they should not be included in the specifications, as they do not affect the quality of the product.

Stability

The stability studies have been conducted on master cell bank, active substance (cryopreserved) and final product.

The master cell bank is proposed to be stored at -196 °C (liquid nitrogen) for a maximum of 36 months. Based on the stability data, the proposed shelf life of 36 months is acceptable.

The active substance is proposed to be stored at -196 °C for a maximum of 24 months. However, the stability data provided so far are not sufficient to support this period. The available data support the storage of the active substance at -196 ºC for 3 months.

The final product is stored in refrigerated conditions (1-8 °C). Data to support the proposed shelf life of 21 days have been provided.

Other information

During the manufacturing process, including equine umbilical cord collection, master cell bank, active substance and finished product manufacture, a number of reagents, working media and solutions are used. The applicant listed them in this section.

Overall conclusions on quality

DogStem is a cloudy cell suspension for intra-articular injection, which contains the active substance mesenchymal stem cells derived from equine umbilical cord (EUC-MSCs) after *in vitro* expansion up to passage 4.

The active substance is resuspended in the excipient, which acts as diluent and cell preservative.

The manufacturing process includes stages of obtaining the equine umbilical cord, the isolation, amplification and cryopreservation of the mesenchymal stem cells to obtain the master cell bank, the active substance production and the finished product manufacturing. The different stages of the manufacturing process are adequately described. In-process controls and specifications are established in order to ensure consistent manufacturing.

Regarding the overall microbiological control, the strategy proposed by the applicant is considered adequate. The batch release is based on a sterility test as IPC, and on a gram-negative testing at the final product stage.

Process validations were done separately for the active substance and the final product. Three separate validations of the final product have been done for different batch sizes (15, 20 and 200 vials) and the provided information is considered adequate.

The maximum batch size is 200 vials.

The starting/raw materials involved in the production of the active substance are of biological and non-biological origin. They are described and the certificates of analysis have been provided.

The characterisation of the active substance and its impurities is presented.

The TSE risk has been assessed and is considered negligible.

The information on the excipients is adequate.

Regarding the primary packaging for the active substance, the proposed vials are considered adequate and sterilised according to the requirements of Ph. Eur. 5.1.1. The primary packaging for the final product fulfils Ph. Eur. requirements and is considered valid.

Stability studies were performed on the master cell bank, the active substance and the finished product. Master cell bank has been demonstrated to be stable for at least 36 months at -196 °C. The active substance is proposed to be stored at -196 °C for a maximum of 24 months. However, the stability data provided so far are not sufficient to support this stability period. The available data support the storage of the active substance at -196 ºC for 3 months.

The stability of final product has been conducted based on the guidelines on "Human Cell-Based Medicinal Products" (EMEA/CHMP/410869/2006) and on "Stability testing of biotechnological/biological products" (ICH Q5C). The objective of the study was to demonstrate that the final product meets the specifications 21 days post packaging under refrigerated conditions (2-8 °C). The proposed storage conditions are considered adequate.

Overall, the quality of the product is considered satisfactory.

Recommendations

The applicant has provided a commitment for the implementation of an adequate quality management system in one of the external sites, which is considered acceptable in this specific case.

Part 3 – Safety

DogStem is a veterinary medicinal product comprised of mesenchymal stem cells derived from equine umbilical cord (EUC-MSCs) at a concentration of 7.5 x 10^6 (±20%) in 1 ml of excipient.

The excipient is a serum-/protein-free hypothermic (2 – 8 °C) preservation medium that enables improved and extended preservation of cells.

Safety documentation

Pharmacodynamics

See Part 4.

Pharmacokinetics

Conventional absorption-distribution-metabolism-excretion (ADME) studies with DogStem are not available; however, since they are not considered to be appropriate to determine the fate of administered stem cells in the body, this is acceptable.

Published peer review literature on *in vivo* distribution/disposition and migration/persistence of human mesenchymal stem cells in laboratory animal models (xenogeneic use) was provided, and the applicant used extrapolations from these data to derive conclusions on "pharmacokinetics" of the product DogStem in the target species.

Four publications were cited that reported the fate of human mesenchymal stem cells (hMSCs) administered to laboratory animal models. After intra-articular administration of hMSCs to immunodeficient mice, cells engrafted over the long term in joints and were observed up to 6 months according to one study or 4 months according to the other. Both studies could detect cells to a lesser extent in other organs. Forty-eight hours after intra-articular (knee) inoculation to immunocompetent rabbits, human cells were not detected in any organ apart from knee. One day after intra-articular administration of hMSCs to immunocompetent mice, cells were detected in the treated joints of all mice, only in 3 out of 10 mice at day 10 and disappeared after 30 days. Cells were detected in the tibialis anterior muscle in one mouse at day 1 exclusively.

The submitted publications showed that after intravenous administration of adipose and bone marrow-derived hMSCs, the cells were distributed mainly in the lungs and cleared after 30 days in immunocompetent animals, whereas in immunodeficient mice the cells could be detected for up to 6 months.

Results obtained in these studies were inconclusive. The main finding was that biodistribution and engraftment over time of human mesenchymal stem cells in laboratory animals varied between the routes of administration (intra-articular vs. intravenous) and the immune status of the laboratory animal.

Toxicological studies

Single dose toxicity

No specific studies were conducted to investigate the acute toxicity of DogStem in laboratory animals.

However, the applicant submitted several bibliographic references addressing the single dose toxicity of intravenous (i.v.) or intramuscular (i.m.) administration of xenogeneic mesenchymal cells into laboratory animals at different doses (up to 250 x 10^6 cells/kg b.w.) and observation periods (14 days to 13 weeks).

These studies included the i.v. infusion of human adipose-derived MSCs (hADMSC) in immunodeficient (SCID) mice, the i.v. and i.m. infusion of human bone marrow-derived MSCs (hBMMSC) in rats and rabbits and the i.v. infusion hADMSC in SCID mice. Overall, results indicate a relatively low acute toxicity of MSCs in laboratory animals after single administration. However, it is to be noted that after intravenous injection of a relatively high cell number (130 x 10^6 or 2.5 x 10^8 cells/kg b.w.) a few animals died due to thrombosis or pulmonary embolism.

Repeat dose toxicity

No repeated dose toxicity studies were conducted with DogStem in laboratory animals.

However, the applicant submitted published literature to describe toxic effects of human mesenchymal stem cells after repeated administration to laboratory animals. In one study, 15 x 10^6 hBMMSCs/kg b.w. were administered via i.v. and i.m. route to rats during 14 days and in another study the effects were studied after 4 i.v. applications two weeks apart of human umbilical cord mesenchymal stem cells (hUCMSCs) to cynomolgus monkeys at different doses (2 x 10^6 and 1 x 10^7 cells/kg b.w.). No treatment-related toxicity was seen in any animal upon clinical observation, blood biochemistry or histopathology analyses.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

Study of the effect on reproduction

No conventional reproductive dose toxicity studies with DogStem in laboratory animals were conducted.

No bibliographic references regarding the reproductive toxicity of MSCs in relation to the effect on impairment of male or female reproductive function were submitted.

Study of developmental toxicity

No studies on developmental toxicity of the product are available.

The applicant submitted a published paper, showing that the intravenous administration of three doses (12 x 10^6, 60 x 10^6 and 120 x 10^6 cells/kg b.w.) of xenogeneic stem cells (hBMMSCs) to rats during days 5, 12 and 18 of pregnancy did not cause maternal mortality or pathological findings on foetuses after the caesarean section performed on day 20.

However, it should be noted that another study showed that human cells were detected in testes of immunodeficient mice months after intra-articular administration. Therefore, it cannot be excluded that xenogeneic cells may reach the reproductive organs. However, no cell migration has been observed in immunocompetent mice. Furthermore, the submitted paper showed no adverse effects when the hMSCs were administered during pregnancy; however, it remains to be established whether exposure to MSCs may impair reproductive function or produce effects in offspring in the long term (e.g. during lactation).

Genotoxicity

No genotoxicity tests with EUC-MSCs according to the standard test battery were conducted. It is not expected that the active substance EUC-MSCs would interact directly with DNA or other chromosomal material, therefore conventional genotoxicity tests were not deemed necessary. In fact, it is more

appropriate to investigate genetic alterations of the stem cells during the culturing process. For this purpose, studies to investigate genetic stability of EUC-MSCs were conducted (see Part 2 Quality).

Carcinogenicity

No data were provided on the tumorigenic potential of EUC-MSCs or the final product DogStem.

Chromosome instability and cellular senescence have been identified as a major concern for the risk of malignant transformation of transplanted MSCs. The occurrence of recurrent cell abnormalities appears to be mainly related to the manufacturing process. The controls carried out during the manufacturing process for the production of the EUC-MSCs in DogStem to avoid the risk of tumour formation are discussed in Part 2 Quality.

In addition, the applicant submitted bibliographic references reporting tumorigenesis studies with xenogeneic MSCs in immunodeficient mice. In one study, no evidence was found of tumour formation during an observation period of 26 weeks after the single subcutaneous administration to nude mice of human adipose tissue-derived mesenchymal stem cells (hAdMSCs). The results of another study indicated that no tumour formation was observed two months after single administration of human umbilical cord-derived mesenchymal stem cells (hUCMSCs) into NOD and NOD/SCID mice. The third cited study found no tumour formation during an observation period of 26 weeks after the single administration via s.c. and i.m. of human bone marrow-derived mesenchymal stromal cells (hBMMSCs) to SCID mice.

These studies showed no *in vivo* tumour formation after an observation period of maximum 6 months after the administration of the xenogeneic MSCs to immunodeficient mice.

Studies of other effects

Immunotoxicity:

Based on the provided literature, it is recognised that MSCs interact with the immune system, provoking an immunomodulatory and anti-inflammatory effect responsible, at least in part, for the mechanism of action of this kind of treatments. More details on this matter can be found in Part 4 Pharmacodynamics.

The xenogeneic use of EUC-MSCs has been also discussed. Literature review has been provided. Results of the target animal safety (TAS) study are briefly mentioned.

Both the literature and the results of the TAS study showed that a humoral immune reaction is expected after treatment with xenogeneic stem cells (literature) and also with DogStem (TAS study).

In the TAS study, after a single administration, 50% of the treated dogs generated mild antibody titres against EUC-MSCs. Following a second administration, 28 days after the first administration, 75% of the dogs generated antibodies against EUC-MSCs. The TAS study showed no acute immune response after repeated administration of EUC-MSCs to healthy dogs. Consequently, the applicant stated that the generation of antibodies was not shown to be causing clinical symptoms in treated dogs. In addition, cytotoxicity of EUC-MSCs after single and repeated administration in healthy young dogs was evaluated in the TAS study. No cytotoxic effects were found after single or repeated EUC-MSC intra-articular administration in dogs.

The immune response to this xenogeneic medicinal product has not been specifically studied in other studies. Therefore, the available information on this matter is considered limited. The applicant has discussed the impact of the presence of antibodies on the safety and efficacy of DogStem. Although no safety concerns were identified, its impact on the efficacy of the product could not be addressed. However, as the product is for single use, no further studies are considered needed.

With regard to the possibility that the treatment can have undesirable reactions in the recipient animal, such as increased infections or exacerbated immunosuppression, the applicant referred to a retrospective systematic review in more than 1,000 human patients who received MSC treatments, and there was no evidence of immune alterations or increased susceptibility to infection due to the MSC treatment. There was a significant association between MSCs and transient fever. This publication can only be considered as supportive. The applicant addressed this issue, taking into account the available data for DogStem, and no adverse events were identified.

Persistence and immune rejection of transplanted MSCs:

The time of clearance of the MSCs in mice, as one of the cited papers shows, is shorter in immunocompetent animals. There the complete clearance of the MSCs applied occurs in the first month; on the other hand, in case of immunodeficient mice, there was a longer clearance time, and in some animals MSCs were detected in the joint space for up to 6 months after the application.

Potential interactions of MSCs and other medicinal products

The applicant did not provide proprietary studies on interactions and thus recommends not to combine DogStem with any other intra-articular drug.

Observations in humans

Several references relevant to safety after intra-articular treatment with MSCs in human patients were submitted. Data on autologous bone marrow-derived intra-articularly administered MSCs to patients with cartilage damage or osteoarthritis were reviewed during a mean follow-up period of 21 months. Low incidences of serious and non-serious adverse effects were reported.

Studies with the final product

No data on the potential local adverse effects of the veterinary medicinal product DogStem were provided (i.e. irritation to skin and eyes, and sensitisation). However, the skin and eye irritating properties of the excipient are addressed in the provided safety data sheet, indicating that none of the components in the proportions used are considered hazardous. In addition, the active substance (stem cells) is assumed not to have irritant properties.

Excipients

The excipient is a cell preservation medium that contains pH buffers, energy substrates, free radical scavengers and osmotic/oncotic stabilisers.

User safety

The applicant presented a user safety risk assessment conducted in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1 including a hazard identification, exposure assessment, risk characterisation and formulation of corresponding warning phrases.

For hazard identification no classical toxicological studies with NOELs and clear dose-effect curves are available either for the product DogStem or for the pharmacological active ingredient EUC-MSCs. Instead, a generalised hazard assessment of MSCs on the basis of scientific literature and the current knowledge of immunological and carcinogenic properties of MSCs has been undertaken. Additionally, it is noted that in the TAS study no abnormal signs were detected at the injection point after product administration, whereas in the exploratory and field pivotal studies the intra-articular administration of EUC-MSCs apparently led to some local adverse reactions like transient pain at the injection site and lameness, which occurred in both study groups (placebo and treated).

The product will be administered by professionals, e.g. the veterinarian. The most relevant route of exposure will be parenteral, by accidental self-injection that may take place during the administration of the VMP. Other routes of exposure may be dermal and ocular by splashes due to accidental release of the product from the syringe. During normal application of the product by professionals, when elementary personal hygiene is maintained, oral exposure (via hand-to-mouth contact) and exposure via hand-to-eye contact is considered negligible. In any case, the probability of occurrence is low for an accidental self-injection, and also for skin and eye exposure.

It is noted that after the intravenous infusion of high doses of stem cells in studies with laboratory animals, several animals died due to pulmonary embolism or thrombosis. The risk of thrombosis after accidental self-injection cannot be completely ignored. However, it has to be borne in mind that thrombosis occurred only after i.v. administration of very high cell counts (after administration of 130×10^6 cells/kg b.w. to rabbits, or 4×10^6 cells/mouse and 2.5×10^8 cells/kg b.w. to immunodeficient mice). In case of accidental self-injection, it is assumed that 10% (0.1 ml) of the injection volume, corresponding to 1.25×10^4 EUC-MSCs per kg b.w. (assuming a body weight of 60 kg), will be injected. This is significantly lower than the cell count that led to thrombosis or embolism. Further, it is unlikely that in case of self-injection the complete injection volume will enter blood vessels.

No skin or eye irritation studies and no sensitisation studies were conducted with DogStem. This is considered acceptable since the active substance (stem cells) is not assumed to have irritating properties and the excipient is not considered to represent a concern.

The major risk in relation to accidental self-injection, which should not be ruled out, consists of immune reactions against the xenogeneic MSCs. However, it should be noted that the clinical studies in the target animal in field conditions (see Part 4) showed in principle local adverse reactions like transient pain at the injection site. Therefore, it could be concluded that there is no serious risk regarding user safety after accidental self-injection of a low volume (0.1 ml) of the VMP. In conclusion, the provided data (literature references) are sufficient to evaluate user safety. The user safety warnings are considered satisfactory to ensure the safety of the user when the product is handled as recommended.

Environmental risk assessment

DogStem is composed of equine umbilical cord mesenchymal stem cells (EUC-MSCs) which are not genetically modified. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Hence, the environmental risk assessment can stop in phase 1 according to Guideline on environmental impact assessment (EIAS) for veterinary medicinal products – Phase I (CVMP/VICH/592/98-FINAL) and no phase II assessment is required. It can therefore be concluded that no risks for the environment are expected when the product is used according to the SPC.

Overall conclusions on the safety documentation

No specific studies were conducted to investigate the acute toxicity of DogStem in laboratory animals. Data from published literature indicate a relatively low acute toxicity of MSCs in laboratory animals after single administration (i.v. or i.m.). However, after i.v. injection of a relatively high cell number (2.5×10^8 cells/kg bw) several animals died due to pulmonary embolism by cellular aggregates or to thrombosis.

No data from repeated dose toxicity studies with DogStem in laboratory animals are available. Data from published literature describe no treatment-related toxicity after repeated administration of mesenchymal stem cells to cynomolgus monkeys and rats. Several monkeys generated antibody response to xenogeneic cells, showing a dose dependence tendency.

No conventional reproductive dose and no developmental toxicity studies with DogStem were conducted in laboratory animals. The submitted bibliographic reference showed no effects on foetuses or maternal toxicity after administration of MSCs during pregnancy. Based on the available references it is not possible to state that MSCs will not reach reproductive organs.

No genotoxicity tests with umbilical cord mesenchymal stem cells according to the standard test battery were conducted. As there are no indications that DogStem or parts of DogStem will directly interact with DNA, conventional genotoxicity tests are not deemed necessary.

No data exist about the tumorigenic potential of umbilical cord mesenchymal stem cells. However, the manufacturing process used for the production of the EUC-MSCs in DogStem is adequately controlled to avoid the risk of tumour formation.

In addition, several references were submitted, addressing specific concern in relation to the treatment with xenogeneic stem cells and their theoretical potential of inducing tumours in experimental animal models. After systemic transplantation of mesenchymal stem cells, there was no evidence of tumour formation in the animal models.

Effect on immunological function was addressed by scientific publications and by the TAS study. Humoral response to the xenogeneic use of stem cells is described in the literature. In the TAS study, humoral response was also observed in treated healthy dogs. As the medicinal product is planned to be administered once, further research on this matter is not considered needed.

The provided information on the possibility that the treatment can have undesirable effects in the recipient animal in the form of an increased infection or exacerbated immunosuppression can only be considered as supportive. The applicant addressed this issue by taking into account the available data for DogStem, concluding that this type of adverse events is not expected.

In relation to the persistence of the cells, literature data indicate complete clearance of the MSCs applied occurs in the first month; on the other hand, in case of immunodeficient animals, there was a longer clearance time, and in some animals MSCs were detected in the joint space for up to 6 months after the application.

Potential interactions of MSCs and other medicinal products have not been studied.

No data on the potential local adverse effects of the veterinary medicinal product DogStem were provided. This is considered acceptable, since it is assumed that neither the excipient nor the active substance (stem cells) are expected to have irritant properties.

A User Risk Assessment (URA) following the relevant CVMP guidance document on user safety (EMA/CVMP/543/03-Rev.1, March 2010) has been presented.

The worst-case scenario for user safety is accidental self-injection. The user safety warnings are considered satisfactory to ensure the safety of the user when the product is handled as recommended.

An appropriate environmental risk assessment was provided. The active substance of the proposed product is a natural substance which will not alter the concentration or distribution of the substance in the environment. The product is not expected to pose a risk for the environment.

Part 4 – Efficacy

Pharmacodynamics

Limited data based on published literature were submitted to describe the pharmacodynamic effects of mesenchymal stem cells. In addition, a proprietary study was provided, investigating the anti-

inflammatory and immunomodulatory capacity of the active substance from this product (*equine umbilical cord mesenchymal stem cells,* EUC-MSCs). The study showed that EUC-MSCs in a pro-inflammatory environment exert an anti-inflammatory, immunomodulatory and chondroprotective effect that is mainly due to their paracrine activity.

Different scientific publications indicated that the secretion of PGE_2 by MSCs is a key factor in their immunoregulatory activity, playing an important role in the mechanism of action. In addition, scientific literature showed that PGE_2 is one of the main local mediators responsible for the paracrine actions of MSCs and may be considered as an adequate marker of its efficacy.

The applicant states that MSCs have been demonstrated to act in a multimodal way on all the inflammatory cytokines and cells involved in the progression of osteoarthritis (OA), and to work in the two key areas involved in the disease: inflammation and release of degradative proteases into the joint environment.

A proprietary in vitro study was provided, investigating the immunomodulatory capacity of EUC-MSCs by inhibition of the proliferation of activated dog peripheral blood mononuclear cells (PBMCs). It was shown that EUC-MSCs were able to inhibit the canine PBMCs proliferation and that the inhibition was mediated by PGE_2 (blocking the PGE_2 restored the proliferation). The study is considered adequate to demonstrate the immunomodulatory capacity of EUC-MSCs in dogs. It is also considered adequate to support the use of PGE_2 as potency assay.

Pharmacokinetics

No proprietary studies were performed to assess the pharmacokinetics of DogStem. Conventional ADME studies are usually not relevant for a cell-based medicinal product. Taking into account the proposed route of administration of the product (from which little biodistribution would be expected to occur), the absence of biodistribution assays in the target species is acceptable for this application for a marketing authorisation for MSCs. This is in line with CVMP guidance "Questions and answers on allogenic mesenchymal stem cell-based products for veterinary use: specific questions on tumorigenicity" (EMA/CVMP/ADVENT/791465/2016).

Four published references were submitted to describe the biodistribution of human-derived mesenchymal stem cells in laboratory animals (xenogeneic use) after intra-articular (IA) application (see part 3). The provided studies did not conclude that MSCs after intra-articular injection will exclusively persist in the joint, as cells were also detected to a certain (lesser) extent in other tissues. No information was provided with regard to the biodistribution, engraftment and potential forming of ectopic tissue of xenogeneic mesenchymal stem cells in the target species.

Data from the literature showed that biodistribution and engraftment over time of human cells in laboratory animals varied depending on the route of administration (intra-articular vs. intravenous) and the immune status of the laboratory animal.

Dose determination/Dose justification

A specific dose determination study under laboratory conditions was not conducted by the applicant. This is in principle acceptable, since the absence of a dose-response pattern in MSCs makes it difficult to design typical dose determination studies. The doses used in the clinical studies were determined based on extrapolation from other animal species, bibliographic reports and direct experience of the applicant in the use of autologous stem cell therapies.

The applicant established a correlation between the doses reported in scientific literature and the size of the joints/amount of synovial fluid in the different species. Based on bibliographic references, rats

received 1 million cells and the physiological synovial fluid volume was determined to be 0.2 ml (Buul *et al.*, 2014). Humans and horses received a similar dose ratio, i.e. 13-15 million cells and synovial volume was determined to be 2-3 ml. In dogs, the synovial fluid volume was calculated to be approximately 0.5-2 ml, and a proportional dose of stem cells for dogs would be around 7-9 million cells per joint. Some doubts may arise from this approach regarding the determination of the synovial fluid volume in the different species and the correlation between volume and number of cells. However, this approach was considered merely as a preliminary step in the dose justification process.

To further justify the proposed dose, the applicant performed a bibliographical search of an adequate number of recent publications on clinical trials in which autologous, allogeneic and xenogeneic MSCs were administered to dogs with osteoarthritis. The bibliography showed that the most commonly used doses ranged between 5 and 10 million cells per joint. Different cell origins and joints were evaluated in the literature reviewed (the elbow and the hip being the main joints mentioned). Regarding the studies conducted with xenogeneic MSCs, one of them used human-derived cells using doses between 2.4 and 9.6 million cells/joint and the other referred to porcine AD-MSCs (dose of 5 million cells/joint), although only 3 dogs were assessed. MSCs seemed to show efficacy and safety in the studies reviewed, some of them using xenogeneic MSCs, with dose ranges similar to that proposed for Dogstem. Thus, based on the bibliographic data, efficacy and safety may be expected after administration of EUC-MSCs to dogs with osteoarthritis at the proposed dose.

Lastly, the applicant stated their wide experience in the use of autologous stem cells in dogs since 2013 using a dose of 7.5 million cells. A retrospective observational analytical study was submitted, showing efficacy and safety profile of autologous MSCs produced by the applicant in the treatment of dogs with osteoarthritis based on a survey performed by the veterinarians covering different issues (score of improvement, length of improvement, need for rescue medication, need for a second administration of the product, satisfaction grade...).

Furthermore, the proposed dose of 7.5 million cells/joint was tested in an exploratory clinical study using different doses of DogStem (NEQC1802, see below) and showed better results than higher and lower doses. The dose of 7.5 million cells/joint was therefore considered by the applicant to be the best dose, and was used in the pivotal clinical study (EQC1902, see below) in which efficacy and safety were demonstrated. Taking into account the data obtained from this scientific literature review, and the data from the dossier, the dose selection is considered to be sufficiently justified.

Target animal tolerance

Information on the target animal tolerance of DogStem in dogs can be drawn from the pivotal target animal safety (TAS) study (NEQC0118A). In addition, tolerance data in dogs were obtained from an exploratory clinical study (NEQC1802) and the pivotal field study (EQC1902) performed by the applicant.

The studies were all GCP compliant, randomised, blinded and placebo-controlled (saline). As this product is considered a novel therapy, related VICH guidelines on target animal safety (VICH GL43 and VICH GL44) are not fully applicable, as outlined in the CVMP Questions and Answers document on 'stem cell-based products for veterinary use: specific question on target animal safety' (EMA/CVMP/ADVENT/791717/2016). The classical approach in the determination of the safety profile of MSCs is also not fully applicable, given the properties of MSCs and there is no clear dose-response relationship for this type of product (based on stem cells).

In addition to these studies, literature references related to the use on autologous, allogeneic and/or xenogeneic stem cells in several species administered by different routes of administration at different doses were provided by the applicant. It can be seen from the literature that MSCs express low immunogenicity and demonstrate immunomodulatory properties *in vitro*, which may safely allow their

transplantation into unrelated immunocompetent recipients without the use of pharmacological immunosuppression. No safety concerns and no evidence of tumour formation were observed in the literature. These references can be considered as supportive.

The pivotal TAS study (NEQC0118A) was a tolerance study in order to assess the systemic, local and immunological tolerance of intra-articular administration of DogStem in 16 healthy dogs under field conditions. Animals included were all homogeneous in age (1-4 years old), weight (between 20 and 40 kg), breeds, training, animal housing and feeding. The duration of this study was 63 days. It was GCP compliant, placebo-controlled, randomised and blinded. DogStem was administered at the intended dose (1 ml, 7.5 x 10^6 EUC MSCs) into a joint representative for osteoarthritis (knee joint). A single and repeated dose of the product were administered. Dogs were injected intra-articularly one dose of DogStem or placebo on day 0 and a second dose on day 28±1 in the right knee. Different parameters were assessed (joint exploration, clinical examination, Glasgow Composite Measure Pain Scale (CMPS) determination, laboratory examination, cellular response, and humoral response). Joint exploration and clinical examination were assessed once before treatment, and on day 0, every day in the first intensive care period of 6±2 days (days 1 to 6±2), 14±2, 21±2, 28±1, every day in the second intensive care period (days 29 to 34±2), day 42±2, 49±2, 56±2 and day 63±2. The Glasgow CMPS score was assessed on every scheduled visit. Laboratory examinations were performed once before product administration (screening visit), and at day 2 (±1), day 28 (±1), day 30 (±1) and day 56 (±2).

Blood samples were taken before product administration (screening visit), and at day 14 (±2), 28 (±1) (pre-treatment), 42 (±2) and day 56 (±2) for co-culture with PBMCs in order to detect the immunological activity of lymphocytes after single and repeated administration of DogStem. Antibody quantification was performed before product administration (screening visit) and at day 28 (pre-treatment), 42 (±2) and 56 (±2).

The local tolerance of DogStem was investigated by clinical evaluation and orthopaedic exploration. The results showed that single or repeated doses of EUC-MSCs applied intra-articularly did not produce any alteration in any of the parameters assessed in the dogs. No abnormal signs were detected in the injection point after a single and repeated product administration in any of the 16 dogs included in the TAS study, except for one dog in the placebo group that showed after the second administration mild lameness and effusion, resolving within 24h. Only the recommended treatment dose was investigated; however, since there is no clear dose-response relationship for this type of cell-based product expected, it is considered acceptable not to include multiples of the recommended treatment dose to assess the local tolerance.

In the field studies, some local adverse reactions were observed (such as pain and lameness), but none of them were considered as serious.

In the exploratory field study (NEQC1802), three different doses of EUC-MSCs were tested - 3, 7.5 and 15 million cells/joint. Only one adverse event was classified as possibly or probably product-related in the highest dose group, consisting of pain and lameness of 2 weeks' evolution (no treatment required).

In the pivotal clinical study (EQC1902), 13 adverse events were considered as possibly or probably product-related by the investigators (7 out of 39 injected dogs (18%) in the DogStem group and 6 out of 40 injected dogs (15%) in the placebo group; no statistically significant differences between the groups). These adverse events were mostly pain and increase of lameness and occurred in both study groups, indicating that they may be due to the intra-articular injection rather than to be product-related. Three of these adverse events in the DogStem group were detected within the first 24 hours after administration and resolved spontaneously within a few days without the need of additional medication, whilst the other four events in the DogStem group were detected within 1-5 days after administration, required additional medication with NSAID and only resolved over several weeks.

It is noted that in the pivotal field study all the dogs were also treated with a single dose of meloxicam at the same time as administration of DogStem. The concomitant use of an NSAID at the time of injection has been appropriately reflected in the SPC. In addition, all dogs were sedated prior to injection in order to ensure a safe application of the product.

The systemic tolerance of DogStem was assessed in the TAS study (NEQC0118A) and the field studies (EQC1902 and NEQC1802). Some findings related to the blood test in the laboratory analysis (such as haemoglobin, mean corpuscular haemoglobin concentration, AST, globulins, platelet count and glucose in the TAS study and mainly an increase of AST and/or ALT in the pivotal field study) were slightly out of range in both placebo and treatment groups, but were not considered pathological.

Some adverse events such as vomiting and diarrhoea occurred in both groups in the TAS study but they were considered to be associated with the procedure and not treatment-related (e.g. related to stress, confinement and training). No systemic adverse events were observed. Three dogs (1 in the IVP and 2 in the placebo group) had slightly elevated body temperature on days 15, 28+1 and 42, respectively. In all cases the animals were nervous and not presenting any other signs of disease; therefore, this was considered as a casual finding, without being a sign of illness. No signs of illness or abnormal findings were found in any other dog during the trial in the clinical examinations performed.

Given the xenogeneic nature of the MSCs, the applicant also investigated the potential for immunogenicity of these stem cells in the TAS study, in which the repeated use was studied. A humoral immune response in treated dogs was observed (antibodies against EUC-MSCs were detected). It is important to note that this product is intended for single use, and therefore no additional studies are considered needed. This has been appropriately reflected in the SPC. Cellular response was not detected.

Based on current knowledge, after intra-articular administration, the risks are considered to be low for biodistribution of EUC-MSCs from the joint into other tissues, as well as for the formation of ectopic tissue or tumourigenesis.

The applicant conducted a long-term follow-up study in order to collect data on efficacy and safety from all the dogs included in the field study (dogs in the placebo group were administered DogStem at the end of the trial). A survey was sent to the owners of these dogs 12-18 months after the administration of the product to investigate the extent of the effect, the duration of the clinical effect and the occurrence of any adverse effect observed after the completion of the trial. Although this follow-up was not included in the study protocol, this long-term information is considered important in order to confirm the animal health status. The adverse events observed with this product are in line with those observed after the allogeneic use of EUC-MSCs in horses. Information on the frequency of adverse events and the need for concomitant treatment has been appropriately reflected in the SPC.

Clinical studies

Exploratory clinical field study (NEQC1802)

This pilot study was performed in order to obtain preliminary data on the efficacy and safety of different doses of DogStem in dogs with osteoarthritis in order to gain knowledge and experience for the design and conduct of the pivotal study. It also allowed to confirm the efficacy of the xenogeneic MSCs compared to allogeneic MSCs and to confirm the dose pre-selected for the pivotal clinical trial.

The sample size for this study (n=23) was not statistically justified but it is considered to be adequate, taking into account that this was an exploratory study and the known difficulty to enrol client-owned dogs with osteoarthritis into a placebo (saline)-controlled trial. Inclusion criteria allowed dogs older than 1 year, of either sex and any breed and weighing more than 20 kg. The joints included in the trial were tibio-dorsal (n=1), knee (n=2), elbow (n=12) and hip (n=8).

Diagnosis of osteoarthritis in the dogs was based on pain and orthopaedic exploration, force-plate gait analysis (FPGA), radiological exploration and owner's questionnaire. Pain and orthopaedic explorations were performed according to criteria described in scientific literature (although lameness was not assessed within the orthopaedic exploration).

All the dogs were sedated for the administration of the products.

The dogs were allocated in different groups to receive either EUC-MSCs at a high (15 million cells; n=4), medium (7.5 million cells; n=8) or low (3 million cells; n=3) dose, or allogeneic adipose tissue-derived (AD)-MSCs (7.5 million cells; n=4). A placebo group (saline) was also included (n=4).

The primary efficacy variable was the force-plate gait analysis. This is an objective method widely described in the scientific literature and considered as the gold standard to assess the limb function in the context of the efficacy of treatments of canine osteoarthritis. The applicant selected an increase of at least 7% in the peak vertical force (PVF; expressed as percentage of body weight) compared to the baseline value as criterion for efficacy success. The selected primary efficacy endpoint and the criterion for success are acceptable.

The primary efficacy endpoint result confirmed the best efficacy for the medium dose of EUC-MSCs over the other doses and the allogeneic AD-MSCs. The appropriateness of the primary efficacy variable was confirmed with the absence of placebo effect.

However, the results based on the secondary endpoints differed from those obtained using the PVF. Remarkably, a high placebo effect was observed with regard to the parameters 'pain score', 'orthopaedic score' and especially the 'Liverpool Osteoarthritis in Dogs (LOAD) questionnaire' completed by the animal owners.

Vomiting occurred in 4 dogs (groups high dose, medium dose, AD-MSC and placebo) but they were not considered to be product-related.

The results from this exploratory trial should be considered with caution due to the low number of animals included and the absence of statistical analysis. This study may be nevertheless considered supportive to confirm, under field conditions, the efficacy and safety of the proposed intra-articular dose of 7.5 million EUC-MSCs/joint over other doses and positive control (AD-MSCs). It may also show the appropriateness of the selected primary endpoint (PVF) as an objective and reliable measure of the orthopaedic alterations in dogs with osteoarthritis in order to assess the improvement of the treatment.

Pivotal clinical field study (EQC1902)

The pivotal clinical field trial was designed as a GCP-compliant, multicentric, blinded, randomised, parallel and placebo (saline)-controlled trial. It was conducted in two veterinary hospitals in Spain. The objective was to confirm the efficacy and safety of a single intra-articular administration of 7.5 million of EUC-MSCs compared to placebo, for the treatment of pain associated with mild to severe osteoarthritis (OA) in dogs. A total of 78 dogs (ITT population, intent-to-treat) were enrolled in the study and randomly allocated to the EUC-MSCs group or placebo group. The PP population (per protocol, i.e. number of dogs that finished the study) was 72 dogs (DogStem: 35 dogs; placebo: 37 dogs). The dogs presented with OA were diagnosed based on clinical, orthopaedic and radiographic exploration, and confirmed with force plate gait analysis (FPGA) according to criteria described in scientific literature. The study included dogs of different breeds, aged >1 year and weighing ≥15 kg, and with osteoarthritis in the elbow or the hip (only one joint treated per dog). The applicant analysed the mean value and the distribution of the dogs according to these and other factors (OA grade, orthopaedic score, lameness grade, PVF value) in both study groups at baseline, and statistically significant differences were not found. The physical activity of the dogs during the study was restricted, with common instructions for all the owners. Nine different batches of the

test product from 4 different donors were used. The homogeneity of batches in terms of safety and efficacy was demonstrated.

The primary efficacy endpoint was based on the peak vertical force value (PVF, expressed as percentage of body weight) obtained from the FPGA and measured at 4, 8 and 12 weeks after administration of the products.

Treatment success was defined as an improvement of ≥7% in the value of PVF of the affected limb at week 8 compared to baseline. The treatment success rates were 51.4% and 5.4% in the test and placebo group, respectively, with a statistically significant difference between groups. The outcome is considered to be clinically relevant since it was measured with an appropriate and objective method widely described in the literature and consequently obtaining a very low placebo effect. Furthermore, the applicant used a very strict criterion for success (increase of PVF of at least 7%), which is higher than the mean improvement of PVF described in literature when assessing the efficacy of different treatments (mainly NSAIDs) for OA in dogs.

A clear treatment effect with respect to the primary endpoint was shown at week 8 (18/35 dogs were classified as treatment success in the IVP group as compared to 2/37 dogs in the control group). At week 12, some of the dogs being a treatment success (8/17) in week 8 did not fulfil the success criterion anymore, and some other dogs worsened from week 8 to week 12 (although still fulfilling the success criterion). On the other hand, some dogs improved from week 8 to week 12 while some other animals were considered failure at week 8 but were subsequently considered success at week 12.

A number of secondary parameters were included in this study. A significantly higher success rate was observed in the IVP group compared to placebo group at week 12, but not at week 4. An owner's questionnaire (Liverpool Osteoarthritis in Dogs – LOAD) was initially planned but was later substituted with a simpler one (Quality of life – QOL) developed by the applicant due to problems reported by many owners with the previous one (LOAD). The applicant justified the relevance and validity of this questionnaire. The applicant compared the percentage of dogs classified as treatment success based on both the primary objective endpoint and on the secondary subjective parameter (QOL). It was shown that 48.4% of the dogs were considered a treatment success in the test group combining both criteria at week 8 vs. 0% in the placebo group. A high correlation between treatment success obtained with objective vs. subjective parameters was demonstrated by the applicant.

The average improvement of the individual clinical signs associated with osteoarthritis that were included within the orthopaedic exploration (lameness, joint mobility, pain, local heat and effusion) was evaluated separately as a secondary endpoint. "Lameness" was the only clinical sign in which a statistically significant difference was observed between the test and placebo group at all time points. Thus, the applicant was asked to further justify the efficacy of the product for reduction of pain since this effect is claimed within the proposed indications. Considering that the primary efficacy endpoint was PVF, an objective method to assess the lameness (that may be correlated with pain), and the data provided by the QOL scale (clinically relevant improvement in pain, mobility and overall quality of life statistically significantly higher in treated dogs compared to placebo dogs), the claimed indication of pain and lameness has been demonstrated. Mild, moderate and severe OA cases were assessed in the pivotal field study. However, it is questionable whether the number of clinically severe cases of OA included in the study is enough to conclude that the product is effective for reduction of lameness in dogs with severe OA. In the absence of further justification from the applicant of the number of dogs with clinically severe OA, and taking into account the difficulty to classify the severity of OA, the indication was amended as follows: "reduction of pain and lameness associated with osteoarthritis in dogs".

The applicant performed an analysis of co-variables on the dogs that reached therapeutic success according to the primary efficacy endpoint. It was shown that efficacy of the product was not affected by

either gender, age, joint, OA grade (according to the radiological assessment), lameness grade or pain grade.

Batches from different donor horses were used for the DogStem group. The homogeneity of batches in terms of efficacy and safety was demonstrated.

Regarding tolerance, see above (target animal safety).

In addition, a long-term follow-up study (study number: Sur-NEQC2006) was performed in order to collect data on efficacy and safety from all the dogs included in the study (dogs in the placebo group were also administered DogStem after the end of the trial). A survey was sent to the owners of these dogs 12-18 months after the administration of the product to investigate the extent of the effect, the duration of the clinical effect and the occurrence of any adverse effect observed after the completion of the trial. A total of 55 owners out of 75 whose dogs received DogStem responded to the survey. From these, 73% (n=40) reported an improvement of their dog after the treatment. From these 40 animals, 5% (n=2) considered that the effect lasted less than 3 months; 35% (n=14) stated that the effect lasted between 3 and 6 months; 32.5% (n=13) reported an effect lasting 6 to 12 months and 27.5% (n=11) considered that the effect lasted more than 12 months.

As conclusion, this clinical field study was overall well designed and conducted. The primary efficacy endpoint, based on an objective measure, is appropriate, and statistically significant superiority over placebo was demonstrated for the primary parameter PVF. Some of the secondary efficacy parameters seem to support this result.

Overall, the results from the primary and secondary endpoints, together with data from the long-term follow-up study, support the indication. A statistically significant efficacy in the pivotal study was obtained both at 8 weeks (primary endpoint) and 12 weeks (secondary endpoint) after treatment. Furthermore, the data from the long-term follow-up study confirmed an effect of between 12 weeks and more than 12 months for the vast majority of dogs. Taking the overall results from the primary and secondary endpoints together with the data from the long-term follow-up study, the CVMP considered that overall, in dogs responding to treatment, data indicate a duration of effect between 8 weeks and more than 12 months. This has been adequately reflected in the product literature.

Overall conclusion on efficacy

Pharmacodynamics:

Mesenchymal stem cells (MSCs) in a pro-inflammatory environment exert an anti-inflammatory, immunomodulatory and chondroprotective effect that is mainly due to their paracrine activity. Bibliographic data indicated that the secretion of PGE_2 by MSCs is a key factor in their immunoregulatory activity.

A proprietary *in vitro* study by the applicant demonstrated the anti-inflammatory/immunomodulatory activity of equine umbilical cord (EUC) MSCs when they are in contact with activated canine peripheral blood mononuclear cells (PBMCs). The study showed the immunomodulatory capacity of the EUC-MSCs and the relevance of the PGE_2 on this mechanism.

Pharmacokinetics:

No proprietary studies were performed to assess the pharmacokinetics of DogStem in the target species. Data from the literature showed that biodistribution and engraftment over time of human-derived MSCs in laboratory animals (xenogeneic use) varied depending on the route of administration and the immune status of the laboratory animal. Generally, after intra-articular administration the risk of biodistribution, as well as of the ectopic tissue formation or tumourigenesis, is considered to be low.

Dose determination:

A specific dose determination study under laboratory conditions has not been conducted by the applicant. The dose evaluated in the clinical studies was selected mainly based on scientific literature. MSCs seemed to show efficacy and safety in the studies reviewed, some of them using xenogeneic MSCs, with dose ranges similar to that proposed for Dogstem. Thus, based on the bibliographic data, efficacy and safety may be expected after administration of EUC-MSCs to dogs with osteoarthritis at the proposed dose. Based on these data, the applicant selected a dose within the range of 5-10 million cells.

The proposed dose is considered to be justified, taking into account that its safety and efficacy was confirmed by a TAS study, an exploratory clinical study using different dose levels, and the pivotal field trial.

Tolerance:

The tolerance of the product at the recommended dose was evaluated in a TAS study and (exploratory and confirmatory) clinical studies. Some local adverse reactions after intra-articular administration were observed (increase of lameness and pain) which required symptomatic therapy with an NSAID in some individual animals in both study groups (treatment and placebo), but were not considered as serious adverse events. No systemic tolerance concerns were observed. Some findings, related to the results of blood test in the laboratory analysis being slightly out of range, were found in both placebo and treatment groups but were not considered pathological.

The immunogenicity of the medicinal product has been studied. A humoral response was observed in some treated dogs after repeated treatment; however, DogStem is only indicated for single use. No cellular response was detected.

Efficacy:

The efficacy of the product at the proposed intra-articular dose of 7.5 million cells per joint was evaluated in two clinical studies, as well as a follow-up study.

An exploratory study was conducted to compare the efficacy of the proposed dose with a higher (15 million cells) and a lower (3 million cells) dose and with that of a positive control (allogeneic AD-MSCs) in osteoarthritic dogs. Due to the low number of animals (n=23) and the absence of statistical analysis, results are only indicative, but supported the choice of the selected dose and the study design/endpoints used for the pivotal study.

The 3-month pivotal field study (DogStem: 35 dogs; placebo: 37 dogs) was conducted to confirm the efficacy of a single dose of DogStem in the reduction of pain and lameness in dogs with diagnosed osteoarthritis, using the improvement of peak vertical force (PVF) value at week 8 after treatment as primary endpoint, and a number of secondary parameters. A clear treatment effect with respect to the primary endpoint was shown at week 8. The results at week 12 (secondary endpoint) also showed a statistically significant treatment success, although these results were variable. In addition, a long-term follow-up study (survey of animal owners) was conducted, which investigated the long-term (18 months) safety and efficacy of DogStem. The majority of dog owners reported an improvement of their dog after treatment, with the effect lasting between 3 months and more than one year.

In both studies the primary efficacy endpoint (improvement of PVF value) was considered appropriate and showed good results in terms of improvement of PVF (%BW). Taking into account the results from primary and secondary endpoints from both the preliminary, the pivotal field study as well as the follow-up study, it is considered that the efficacy of a single dose of DogStem for reduction of pain and lameness associated with osteoarthritis has been sufficiently demonstrated. Overall, in dogs responding to treatment, data indicate a duration of effect between 8 weeks and more than 12 months.

Part 5 – Benefit-risk assessment

Introduction

DogStem is a suspension for injection for dogs. The active substance, equine umbilical cord mesenchymal stem cells (EUC-MSCs), are a biological, cell-based product, which have immunomodulatory and anti-inflammatory properties attributed to their paracrine activity, e.g. prostaglandin E_2 (PGE_2) secretion. At the time of submission, the applicant applied for the indication "Reduction of pain and lameness associated with mild to severe osteoarthritis in dogs".

DogStem suspension contains approximately 7.5 million equine umbilical cord mesenchymal stem cells in 1 ml and is presented in packs containing 1 vial of 1 ml. It is administered as a single intra-articular injection of 1 ml into the affected joint.

The eligibility to the centralised procedure (optional scope) was agreed upon by the CVMP on 10 December 2020, as DogStem contains a new active substance which was not authorised in the Community on the date of entry into force of the Regulation (EC) No 726/2004.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

Benefit assessment

Direct therapeutic benefit

The benefit of a single dose of DogStem is its efficacy in the reduction of pain and lameness associated with osteoarthritis in dogs, which was investigated in an exploratory clinical study and the pivotal field study, as well as in an 18-month follow-up study, conducted to an acceptable standard. The effect lasted between 8 weeks and more than 12 months.

Additional benefits

The active substance increases the number/choice of treatments available to treat osteoarthritis in dogs.

Risk assessment

Quality:

Information on the composition, development, manufacturing process, controls and stability have been presented.

The overall results from the in-process and finished product testing in place indicate a consistent quality of the product, and these relate to satisfactory and consistent performance in clinical use.

Safety:

Risks for the target animal:

Adverse reactions observed in clinically diseased animals after intra-articular injection of DogStem at the recommended treatment dose mainly comprised orthopaedic reactions in the treated joint (increase of lameness and pain), which required additional symptomatic therapy with an NSAID in some animals.

Risks for the user:

The user safety warnings are considered satisfactory to ensure the safety of the user when the product

is handled as recommended.

Risks for the environment:

The product is not expected to pose a risk for the environment when used as recommended.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, the environment, and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: "Reduction of pain and lameness associated with mild to severe osteoarthritis in dogs." Following evaluation of the data, the CVMP agreed that the indication should be: "Reduction of pain and lameness associated with osteoarthritis in dogs".

Information on development, manufacture and control of the active substance and finished product has been presented and led to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Based on the data presented to date, the overall benefit-risk evaluation for the product is favourable.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for DogStem is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.