# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

HorStem suspension for injection for horses

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml dose contains:

**Active substance:**
Equine umbilical cord mesenchymal stem cells (EUC-MSCs) $15x10^6$

Excipients:
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection.

Cloudy colourless suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Target species

Horses.

### 4.2 Indications for use, specifying the target species

Reduction of lameness associated with mild to moderate degenerative joint disease (osteoarthritis) in horses.

### 4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

### 4.4 Special warnings for each target species

The veterinary medicinal product was demonstrated to be efficacious in horses affected by osteoarthritis in the metacarpo-phalangeal joint, distal interphalangeal joint, and tarsometatarsal/ distal intertarsal joint. No efficacy data are available regarding the treatment of other joints.

No efficacy data are available regarding the treatment in more than one arthritic joint at the same time.

The onset of efficacy may be gradual. Efficacy data demonstrated an effect from 35 days after treatment.

### 4.5 Special precautions for use

Special precautions for use in animals

Correct placement of the needle is crucial to avoid accidental injection into blood vessels and an associated risk of thrombosis.

The safety of the veterinary medicinal product has only been investigated in horses at least two years old.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Care should be taken to avoid accidental self-injection.

Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

## 4.6 Adverse reactions (frequency and seriousness)

Very common:
Acute synovitis with an acute onset of severe lameness, joint effusion and pain on palpation was reported 24 hours after administration of the veterinary medicinal product. Substantial improvement was shown in the next 48 hours and complete remission in the following two weeks. In case of severe inflammation, administration of symptomatic treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) could be necessary.

Common:
Moderate joint effusion with no associated lameness has been observed 24 hours after HorStem administration. Complete remission was observed over the following two weeks without any symptomatic treatment.
An increase in mild lameness was observed 24 hours after HorStem administration. Complete remission was observed within 3 days, without any symptomatic treatment.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

## 4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

## 4.8 Interaction with other medicinal products and other forms of interaction

Do not administer simultaneously with any other intraarticular veterinary medicinal product.

## 4.9 Amounts to be administered and administration route

Route of administration:
Intraarticular use.

Dosage:

A single intraarticular injection of 1 ml ($15x10^6$ equine umbilical cord mesenchymal stem cells) into the affected joint.

Method of administration:

The veterinary product must be administered intraarticularly, only by a veterinary surgeon, taking special precautions to ensure the sterility of the injection process. The product must be handled and injected following sterile techniques and in a clean environment.

Swirl gently before use in order to ensure the contents are well mixed.

Use a 20G needle.

Intraarticular placement should be confirmed by the appearance of synovial fluid in the hub of the needle.

### 4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Intraarticular administration of a 2x dose ($30x10^6$/2ml) of HorStem to 4 years old and older healthy horses led to lameness in 5/6 animals and to signs of inflammation in all animals. In 5/6 horses, the adverse reactions were mild and resolved spontaneously within 28 days. One horse required symptomatic treatment (NSAID) and its lameness resolved by day 14.

A second administration of the product at the recommended dose to healthy young horses in the same joint, 28 days after the first administration at the recommended dose, led to an increase in frequency and severity of inflammation related to the treated joint (8/8 horses) and to an increase in the severity of the lameness observed (3/8 horses; up to grade 4/5 according to the American Association of Equine Practitioners lameness scale (AAEP)) compared to the first treatment. In one case, symptomatic treatment (NSAID) was required. Adverse reactions in the other horses resolved spontaneously within a maximum of 21 days; lameness lasted for up to three days.

### 4.11 Withdrawal period(s)

Zero days.

## 5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Not yet assigned
ATCvet code: Not yet assigned

### 5.1 Pharmacodynamic properties

Mesenchymal stem cells have immunomodulatory and anti-inflammatory properties that may be attributed to their paracrine activity, -e.g. prostaglandin (PGE2) secretion, and can possess tissue regenerative properties. These pharmacodynamic properties may be also relevant for equine umbilical cord derived MSCs (EUC-MSCs) but have not been demonstrated in proprietary studies conducted with the product.

The potential of EUC-MSCs to secrete PGE2 with and without stimulation by synovial fluid has been demonstrated in studies *in vitro*.

### 5.2 Pharmacokinetic particulars

To what extent EUC-MSCs from this product persist after intraarticular administration to horses is not known as no proprietary biodistribution studies have been conducted with HorStem.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Adenosine
Dextran-40
Lactobionic acid
HEPES N-(2-hydroxyethyl) piperazine-N´-(2-ethanesulfonic acid)
Sodium hydroxide
L- Glutathione
Potassium chloride
Potassium bicarbonate
Potassium phosphate
Dextrose
Sucrose
Mannitol
Calcium chloride
Magnesium chloride
Potassium hydroxide
Sodium hydroxide
Trolox (6-hydroxyl-2,5,7,8- tetramethylchroman-2-carboxylic acid)
Water for injections

### 6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with any other veterinary medicinal products.

### 6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 21 days.

Shelf life after first opening the immediate packaging: Use immediately.

### 6.4 Special precautions for storage

Store and transport refrigerated (2 °C – 8 °C).
Do not freeze.

### 6.5 Nature and composition of immediate packaging

Cyclic olefin vial closed with a bromobutyl rubber stopper and a flip off aluminium cap.

Pack size: Cardboard box with 1 vial containing 1 ml.

### 6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

EquiCord S.L.
103-D Loeches
Polígono. Industrial Ventorro del Cano

Alcorcón
28925 Madrid
Spain
Tel: +34 (0) 914856756
E-mail: horstem@equicord.com

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/2/18/226/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19/06/2019

## 10 DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

## PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. STATEMENT OF THE MRLs**

**D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Administrative office and manufacturing site:
EquiCord S.L.
103-D Loeches
Polígono Industrial Ventorro del Cano
Alcorcón
28925 Madrid
Spain

Name and address of the manufacturer(s) responsible for batch release

Administrative office and manufacturing site:
EquiCord S.L.
103-D Loeches
Polígono Industrial Ventorro del Cano
Alcorcón
28925 Madrid
Spain

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

## C. STATEMENT OF THE MRLs

The active substance, mesenchymal stem cells, is considered as not falling within the scope of the MRL regulation, as it is covered by the entry for stem cells in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009.

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this veterinary medicinal product.

## D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Risk management plan:

The marketing authorisation holder shall perform the required pharmacovigilance activities and interventions as detailed in the agreed risk management plan and any agreed subsequent updates of the risk management plan.

In order to further support the link between PGE2 production and a clinically-relevant therapeutic effect, the marketing authorisation holder shall conduct and submit an updated and validated potency assay (a

product specific *in vitro* model) to the CVMP/EMA for evaluation before batch release and placing the product on the market.

In order to collect further field data, related to both safety and efficacy, from batches that have been released by use of the updated potency assay, the marketing authorisation holder shall conduct and submit the results of a surveillance study. The starting date of the reporting scheme (Day 0) shall be the date of first release of a batch that has been tested with the updated and validated potency assay. The first report shall be submitted 6 months after Day 0, and subsequently at 6-month intervals, until otherwise agreed by the CVMP.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**

**OUTER CARTON**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

HorStem suspension for injection for horses

## 2. STATEMENT OF ACTIVE SUBSTANCES

Each vial contains:
$15x10^6$ /ml Equine umbilical cord mesenchymal stem cells

## 3. PHARMACEUTICAL FORM

Suspension for injection

## 4. PACKAGE SIZE

One 1 ml vial.

## 5. TARGET SPECIES

Horses

## 6. INDICATION(S)

## 7. METHOD AND ROUTE(S) OF ADMINISTRATION

Swirl gently before use.

Read the package leaflet before use.

For intraarticular use. To be administered only by a veterinary surgeon

## 8. WITHDRAWAL PERIOD (S)

Withdrawal period(s): Zero days

## 9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

## 10. EXPIRY DATE

EXP: {day/month/year}

## 11. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.

Do not freeze.

## 12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

## 13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
To be supplied only on veterinary prescription.

## 14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

EquiCord S.L.

103-D Loeches
Polígono Industrial Ventorro del Cano
Alcorcón
28925 Madrid
Spain

## 16. MARKETING AUTHORISATION NUMBER(S)

EU/2/18/226/001

## 17. MANUFACTURER'S BATCH NUMBER

Lot: {number}

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

HorStem suspension for injection for horses

## 2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

$15x10^6$ /ml Equine umbilical cord mesenchymal stem cells

## 3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

1 ml

## 4. ROUTE(S) OF ADMINISTRATION

Intraarticular use

## 5. WITHDRAWAL PERIOD (S)

Withdrawal period(s): zero days

## 6. BATCH NUMBER

Lot: {number}

## 7. EXPIRY DATE

EXP: {day/month/year}

## 8. FOR ANIMAL TREATMENT ONLY

For animal treatment only.

# B. PACKAGE LEAFLET

**PACKAGE LEAFLET:**
**HorStem suspension for injection for horses**

## 1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

EquiCord S.L.
103-D Loeches
Polígono Industrial Ventorro del Cano
Alcorcón
28925 Madrid
Spain
Phone: +34 (0) 914856756
E-mail: horstem@equicord.com

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

HorStem suspension for injection for horses

## 3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each vial contains:

Active Substance: $15x10^6$ Equine umbilical cord mesenchymal stem cells

Excipient:
- Adenosine
- Dextran-40
- Lactobionic acid
- HEPES N-(2-hydroxyethyl) piperazine-N´-(2-ethanesulfonic acid)
- Sodium hydroxide
- L- Glutathione
- Potassium chloride
- Potassium bicarbonate
- Potassium phosphate
- Dextrose
- Sucrose
- Mannitol
- Calcium chloride
- Magnesium chloride
- Potassium hydroxide
- Sodium hydroxide
- Trolox (6-hydroxyl-2,5,7,8- tetramethylchroman-2-carboxylic acid)
- Water for injections

Suspension for injection.

Cloudy colourless suspension.

## 4. INDICATION

Reduction of lameness associated with mild to moderate degenerative joint disease (osteoarthritis) in horses.

## 5. CONTRAINDICATIONS

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

## 6. ADVERSE REACTIONS

Very common

Acute synovitis with an acute onset of severe lameness, joint effusion and pain on palpation was reported 24 hours after administration of the veterinary medicinal product. Substantial improvement was shown in the next 48 hours and complete remission in the following two weeks. In case of severe inflammation, administration of symptomatic treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) could be necessary.

Common

Moderate joint effusion with no associated lameness has been observed 24 hours after HorStem administration. Complete remission was observed over the following two weeks without any symptomatic treatment.

An increase in mild lameness was observed 24 hours after HorStem administration. Complete remission was observed within 3 days, without any symptomatic treatment.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

## 7. TARGET SPECIES

Horses.

## 8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Route of administration:
Intraarticular use.

Dosage
A single intraarticular injection of 1 ml ($15x10^6$ equine umbilical cord mesenchymal stem cells) into the affected joint.

Method of administration
The veterinary product must be administered intraarticularly, only by a veterinary surgeon, taking special precautions to ensure the sterility of the injection process. The product must be handled and injected following sterile techniques and in a clean environment.

Swirl gently before use in order to ensure the contents are well mixed.

## 9. ADVICE ON CORRECT ADMINISTRATION

Do not apply simultaneously with other intraarticular veterinary medicinal products.

The product should only be administered by a veterinary surgeon.

Use a 20G needle.

Intraarticular placement should be confirmed by the appearance of synovial fluid in the hub of the needle.

## 10. WITHDRAWAL PERIOD (S)

Zero days.

## 11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Store and transport refrigerated (2 °C – 8 °C).

Do not freeze.

Do not use this veterinary medicinal product after the expiry date which is stated on the vial label.

## 12. SPECIAL WARNINGS

Special warnings for each target species:

The veterinary medicinal product was demonstrated to be efficacious in horses affected by osteoarthritis in the metacarpo-phalangeal joint, distal interphalangeal joint, and tarsometatarsal/ distal intertarsal joint. No efficacy data are available regarding the treatment of other joints.

No efficacy data are available regarding the treatment in more than one arthritic joint at the same time.

The onset of efficacy may be gradual. Efficacy data demonstrated an effect from 35 days after treatment.

Special precautions for use in animals:

Correct placement of the needle is crucial to avoid accidental injection into blood vessels and an associated risk of thrombosis.

The safety of the veterinary medicinal product has only been investigated in horses at least two years old.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Care should be taken to avoid accidental self-injection.

Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interactions

Do not administer simultaneously with any other intraarticular veterinary medicinal product.

Overdose (symptoms, emergency procedures, antidotes):

Intraarticular administration of a 2x dose ($30x10^6$/2ml) of HorStem to 4 years old and older healthy horses led to lameness in 5/6 animals and to signs of inflammation in all animals. In 5/6 horses, the adverse reactions were mild and resolved spontaneously within 28 days. One horse required symptomatic treatment (NSAID) and its lameness resolved by day 14.

A second administration of the product at the recommended dose to healthy young horses in the same joint, 28 days after the first administration at the recommended dose, led to an increase in frequency and severity of inflammation related to the treated joint (8/8 horses) and to an increase in the severity of the lameness observed (3/8 horses; up to grade 4/5 according to the American Association of Equine Practitioners lameness scale (AAEP)) compared to the first treatment. In one case, symptomatic treatment (NSAID) was requiredAdverse reactions in the other horses resolved spontaneously within a maximum of 21 days; lameness lasted for up to three days.

Incompatibilities:

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with any other veterinary medicinal products.

## 13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste.

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

## 14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/

## 15. OTHER INFORMATION

Cyclic olefin vial closed with a bromobutyl rubber stopper and a flip off aluminium cap.
Pack size: Cardboard box with 1 vial containing 1 ml.