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 substances:

Equine umbilical cord mesenchymal stem cells (EUC-MSCs) 15 x 10^6

Excipients:

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

Cloudy colourless suspension.

3. CLINICAL INFORMATION

3.1 Target species

Horses.

3.2 Indications for use for each target species

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

3.3 Contraindications

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

3.4 Special warnings

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.

3.5 Special precautions for use

Special precautions for safe use in the target species:

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

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Horses:

Very common (>1 animal / 10 animals treated):	Synovitis[1]
Common (1 to 10 animals / 100 animals treated):	Joint effusion[2] Lameness[3]

[1] acute, 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.
[2] Moderate, without associated lameness, 24 hours after administration of the veterinary medicinal product. Complete remission was observed over the following two weeks without any symptomatic treatment.

[3] Increase of mild lameness, 24 hours after administration of the veterinary medicinal product. Complete remission was observed within 3 days, without any symptomatic treatment.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

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

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

3.8 Interaction with other medicinal products and other forms of interaction

Do not administer simultaneously with any other intra-articular veterinary medicinal product.

3.9 Administration routes and dosage

Intra-articular use.

Dosage:

A single intra-articular injection of 1 ml into the affected joint.

Method of administration:

The veterinary product must be administered intra-articularly, only by a veterinary surgeon, taking special precautions to ensure the sterility of the injection process. The veterinary medicinal 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.

Intra-articular placement should be confirmed by the appearance of synovial fluid in the hub of the needle.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Intra-articular administration of a 2x dose ($30x10^6$/2 ml) of the veterinary medicinal product to 4-year-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 veterinary medicinal 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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

For administration only by a veterinarian.

3.12 Withdrawal periods

Zero days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QM09AX90

4.2 Pharmacodynamics

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 also be 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*.

4.3 Pharmacokinetics

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

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 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.

5.3 Special precautions for storage

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

5.4 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.

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

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

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

EquiCord S.L.

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/18/226/001

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 19/06/2019

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

ANNEX II

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

None

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.

2. STATEMENT OF ACTIVE SUBSTANCES

Each 1 ml dose contains:
$15x10^6$ Equine umbilical cord mesenchymal stem cells

3. PACKAGE SIZE

1 ml

4. TARGET SPECIES

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intra-articular use.

Swirl gently before use.

To be administered only by a veterinary surgeon.

7. WITHDRAWAL PERIODS

Withdrawal period: Zero days.

8. EXPIRY DATE

Exp. {dd/mm/yyyy}

Once opened use immediately.

9. SPECIAL STORAGE PRECAUTIONS

Store and transport refrigerated.

Do not freeze.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

12. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

EquiCord S.L.

14. MARKETING AUTHORISATION NUMBERS

EU/2/18/226/001

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

HorStem

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

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

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {dd/mm/yyyy}

Once opened use immediately.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

HorStem suspension for injection for horses

2. Composition

Each 1 ml dose contains:

Active substances:

Equine umbilical cord mesenchymal stem cells (EUC-MSCs) 15 x 10^6

Excipients:

Qualitative composition of excipients and other constituents
Adenosine
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L-Glutathione
Sodium hydroxide
Potassium chloride
Potassium bicarbonate
Potassium phosphate
Dextrose
Sucrose
Mannitol
Calcium chloride
Magnesium chloride
Potassium hydroxide
Sodium hydroxide
Trolox (6-hydroxy-2,5,7,8- tetramethylchroman-2-carboxylic acid)
Water for injections

Cloudy colourless suspension.

3. Target species

Horses

4. Indications for use

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. Special warnings

Special warnings:

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 safe use in the target species:

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

Use during pregnancy, lactation or lay:

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Use only according to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:

Do not administer simultaneously with any other intra-articular veterinary medicinal product.

Overdose :

Intra-articular administration of a 2x dose ($30x10^6$/2ml) of the veterinary medicinal product to 4 – year-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 veterinary medicinal 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.

Major incompatibilities:

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

7. Adverse events

Horses:

Very common (> 1 animal / 10 animals treated):
Synovitis[1]
Common (1 to 10 animals / 100 animals treated):
Joint effusion[2] Lameness[3]

[1] Acute, 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.
[2] Moderate, without associated lameness, 24 hours after administration of the veterinary medicinal product. Complete remission was observed over the following two weeks without any symptomatic treatment.
[3] Increase of mild lameness, 24 hours after administration of the veterinary medicinal product. Complete remission was observed within 3 days, without any symptomatic treatment.

Reporting adverse events is important. It allows continuous safety monitoring of a product. 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 contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: {national reporting system}

8. Dosage for each species, routes and method of administration

Intra-articular use.

Dosage

A single intra-articular injection of 1 ml into the affected joint.

Method of administration

The veterinary product must be administered intra-articularly, only by a veterinary surgeon, taking special precautions to ensure the sterility of the injection process. The veterinary medicinal 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

Use a 20G needle.

Intra-articular placement should be confirmed by the appearance of synovial fluid in the hub of the needle.

10. Withdrawal periods

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 carton and the vial label after Exp..

Shelf life after first opening the immediate packaging: Use immediately

12. Special precautions for disposal

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

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

EU/2/18/226/001

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.

15. Date on which the package leaflet was last revised

{MM/YYYY}

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder, manufacturer responsible for batch release and contact details to report suspected adverse reactions:

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