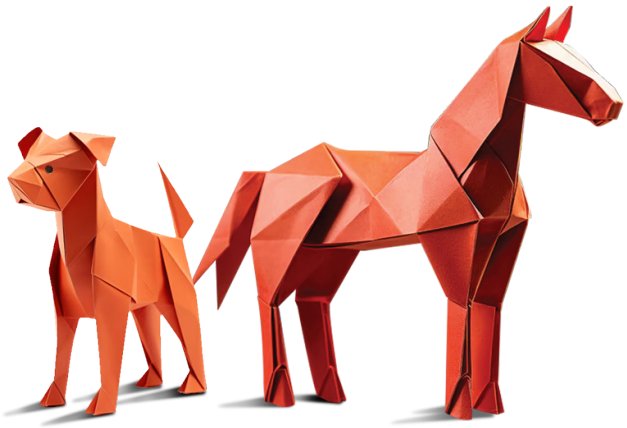
CélulaVet
Veterinary Regenerative Therapy



Vet Information

How to Use:

Mesenchymal Stem Cells for equine and canine can be ordered directly from Celulavet if you are a registered veterinary practice in South Africa. Should you as an owner wish to purchase stem cells, these will be shipped directly to a veterinary practice of your choice. Please note these will need to be used immediately, so preplan your visit to your veterinarian. All orders will be shipped once payment has been received.

- Remove the vial from the shipping container and maintain at 2-8°C until point of care.
- Remove the blue cap from the injection vial containing the cells.
- Aseptically draw the contents from the vial into a syringe. Depending on the volume required for injection, the cells can be further diluted with normal 0.9% sterile saline.
- The entire content of one vial ($6x10^6$) can be used to treat one large joint (eg stifle) or can be divided into two doses ($3x10^6$ each) to be used on two smaller joints (eg both naviculars).
- It is recommended that the cells are injected as soon as possible after receipt. If this is not an option, the cells should be stored at 2-8°C and used within 72hrs from the date of preparation which will be visible on the vial.
- Use sterile technique to prepare the joint for injection.
- **DO NOT ADD ANTIBIOTICS** to the treated joint (antibiotics should not compensate for poor sterility). This will affect the viability and effectiveness of the treatment.
- **UNDER NO CIRCUMSTANCES MUST CORTISONE BE ADDED TO THE STEM CELLS. CORTISONE IS CYTOTOXIC and will interfere with the therapeutic response.**

Drug Interactions:

Special considerations when using MSCs in joints, tendons and ligaments:

- MSCs primarily act by modulating the immune system.
- When planning a treatment, do not use any agents that might inhibit or interfere with the inflammatory response, including antibiotics. These are cytotoxic and Inhibit proliferation and function.
- Allow a 5-day washout period prior to MSC treatment.
- Use sterile technique to prepare the joint for injection.
- In the event of a flare-up, ice joint/ligament/tendon, monitor over 3-5 days.
- When treating soft tissue, PRP is always recommended as an additive as it provides a biological scaffold and releases growth factors.
- When blocking – Marcaine is severely chondrotoxic.

Use Naropin > Procaine > Lignocaine

Treatment can be done within 24hrs after block.

ROMIFIDINE & MEPIVICAINE

The survival and efficacy of MSCs have been shown to not be affected by exposure to romifidine and mepivacaine.
If prolonged, heavy or repeated sedation of a particularly fractious horse is likely to be necessary, sedation with romifidine, or a combination of detomidine and butorphanol should be considered in preference to xylazine.

XYLAZINE

The viability of MSCs exposed to high concentrations of xylazine is significantly reduced.

ANTIBIOTICS

It has been demonstrated that amikacin exerts a rapid dose-dependent toxic effect on normal joint cells, as well as on MSCs.
It is recommended that amikacin doses administered prophylactically intra-articularly be reduced or eliminated pending further in vivo dose titration and toxicity studies.

CORTICOSTEROIDS

Both methylprednisolone and triamcinolone result in the rapid death of significant numbers of MSCs. Cell death occurrs almost immediately (within 20 min) following exposure to methylprednisolone and, in the case of both methylprednisolone and triamcinolone, cell viability is decreased below 50% within 4 hours.

Package Insert

CélulaVET™ MSC
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT
CélulaVET™ MSC suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml dose contains:
Active substance:
4.5-6x10^6 Equine allogeneic adipose-derived mesenchymal stromal cells
Excipients (1ml):
HypoThermosol® FRS preservation medium

3. PHARMACEUTICAL FORM
Suspension for injection.
Equine allogeneic adipose-derived mesenchymal stromal cell suspension: Slightly opaque suspension.

4. CLINICAL PARTICULARS
4.1 Target species
Horses and dogs

4.2 Indications for use, specifying the target species.
Reduction of mild to moderate recurrent lameness associated with non-septic joint inflammation/degeneration in horses.
Treatment of soft tissue injuries in horses.
Reduction of mild to moderate recurrent lameness associated with non-septic joint inflammation/degeneration in dogs.
Treatment of soft tissue injuries 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 product has been demonstrated to be efficacious in horses showing mild to moderate lameness as a result of joint, tendon, ligament or musculoskeletal injuries/disease. The efficacy of the product was demonstrated in a pivotal field trial after single administration of the product.

4.5 Special precautions for use
Special precautions for use in target animals.
In order to avoid thrombosis in small vessels when administering intraarticular injections, the correct placement of the needle is critical.
Special precautions to be taken by the person administering the veterinary medicinal product to animals.
It is essential that the person administering the product adheres to aseptic techniques and maintain a sterile environment during administration.

4.6 Adverse reactions (frequency and seriousness)
Mild increases in lameness and injection site reactions, such as mild to moderate increases in joint swelling and mild increases in temperature at the injection sites, were common and limited to the first week after use of the product. The use of NSAID should be avoided during these mild reactions as symptoms should subside spontaneously, within 3-4 days, in the absence of secondary complications, such as infections introduced at the time of administration. Maintaining an aseptic field of work is paramount.

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
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 systemic or intra-articular corticosteroids and antibiotics as these products have been shown to elicit an adverse effect, resulting in cell death. Product safe to be used in conjunction with HA, PRP and A2M, as prescribed by registered veterinary practitioners.

4.9 Amounts to be administered and administration route
Route of administration: Intraarticular use, intra-lesional injection, intra-venous injection.

Dosage:
Horses: 4,5 – 6x10^6 million cells per vial

- The contents of the product vial can be diluted with sterile saline for ease of administration.
- Preparation of the suspension for injection: The product is shipped, and should be maintained after receipt, at 2-8oC (degrees Celsius). The veterinary product must be administered by a veterinary surgeon taking special precautions to ensure sterility of the injection process. The product must be manipulated and injected using sterile techniques and in a clean environment. The product needs to be administered within 72 hours of the date of preparation provided by the manufacturer.
- Remove the vial from the shipping container and ensure the contents of the vial are homogenised by gently inverting/stirring the

vial contents in a circular motion. Remove the cap of the vial. To maintain sterility the vial can be cleaned with an alcohol swab if necessary. Using a needle with a diameter greater than or equal to 22G, aspirate the cell suspension into a syringe. The entire dose can be injected into one large joint, or the contents can be diluted by adding 1ml sterile saline to the vile and aspirating 1ml of the suspension into two separate syringes to treat two smaller joints. The product needs to be administered immediately after preparation.

Dogs: 4,5 – $4x10^6$ million cells per vial

- Preparation of the suspension for injection: The product is shipped, and should be maintained after receipt, at 2-8 C. The veterinary product must be administered by a veterinary surgeon taking special precautions to ensure sterility of the injection process. The product must be manipulated and injected using sterile techniques and in a clean environment. The product needs to be administered within 72 hours of the date/time of preparation provided by the manufacturer.
- Remove the vial from the shipping container and ensure the contents of the vial are homogenised by gently inverting/stirring the vial contents in a circular motion. Remove the cap of the vial, to maintain sterility the vial can be cleaned with an alcohol swab if necessary. Using a needle with a diameter greater than or equal to 22G, aspirate the cell suspension into a syringe. The entire dose can be injected into one large joint, or the contents can be diluted by adding 1ml sterile saline to the vile and aspirating 1ml of the suspension into two separate syringes to treat two smaller joints. The product needs to be administered immediately after preparation.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary
No documented cases.

4.11 Withdrawal period(s)
Zero days.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
This product contains equine mesenchymal stromal cells (eMSCs) derived from adipose tissue. The eMSCs counteract catalytic inflammatory processes through modulating the immune response and promotes chondroprotective and anti-inflammatory mechanisms, which promote the production of extracellular matrix components that promote joint health.

5.2 Pharmacokinetic particulars
After injection of the product the stem cells do not migrate or distribute from the treated joint and synovia to tissues surrounding the synovial space.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
HypoThermosol® FRS preservation medium.

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

6.3 Shelf life
Shelf life after reconstitution according to directions: Use immediately, alternatively use within 72hours date/time of preparation provided by the manufacturer if stored and transported chilled (2-8 ℃).

6.4 Special precautions for storage
Store and transport chilled (2-8 ℃). Use within 72hours date/time of preparation provided by the manufacturer.

6.5 Nature and composition of immediate packaging
Equine mesenchymal stromal cell suspension:
Glass vial with rubber stopper and plastic cap

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
Cellula Staminale (PTY) LTD (2022/775438/07)
SOUTH AFRICA

8. REFERENCES
Barrachina, L., Remacha, A.R., Romero, A., Vitoria, A., Albareda,, J., Prades, M., et al. 2018. Assessment of effectiveness and safety of repeat administration of proinflammatory primed allogeneic mesenchymal stem cells in an equine model of chemically induced

osteoarthritis. BMC Vet Res. 14(241):doi.org/10.1186/s12917-018-1556-3.

Broeckx, S.Y., Suls, M., Beerts, C., Vandenberghe, A., Seys, B., Wuertz-Kozak, K., et al. 2014a. Allogenic mesenchymal stem cells as a treatment for equine degenerative joint disease: a pilot study. Curr Stem Cell Res Ther. 9(6):497-503

Broeckx, S., Zimmerman, M., Crocetti, S., Suls, M., Mariën, T., Ferguson, S.J., et al. 2014b. Regenerative Therapies for Equine Degenerative Joint Disease: A Preliminary Study. PLOS ONE 9(1): e85917. https://doi.org/10.1371/journal.pone.0085917

Broeckx, S.Y., Seys, B., Suls, M., Vandenberghe, A., Mariën, T., Adriaensen, E., et al. 2019a. Equine Allogeneic Chondrogenic Induced Mesenchymal Stem Cells Are an Effective Treatment for Degenerative Joint Disease in Horses. Stem Cells Dev. 28(6):410-422

Broeckx, S.Y., Martens, A.M., Bertone, A.L., Van Brantegem, L., Duchateau, L., Van Hecke, L., et al. 2019b. The use of equine chondrogenic-induced mesenchymal stem cells as a treatment for osteoarthritis: A randomised, double-blinded, placebo-controlled proof-of-concept study. Equine Vet J. 51(6):787–794

Chen, X., Gan, Y., Li, W., Su, J., Zhang, Y., Huang, Y. et al. 2014. The interaction between mesenchymal stem cells and steroids during inflammation.: Cell Death Dis. (2014)5:e1009; doi:10.1038/cddis.2013.537

Da Silva Meirelles, L., Chagastelles, P.C., Nardi, N.B. 2006. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. J. Cell Sci. 119(11):2204–2213.

Edmonds, R. E., Garvican, E. R., Smith, R. K. W., Dudhia J. 2017. Influence of commonly used pharmaceutical agents on equine bone marrow-derived mesenchymal stem cell viability Equine Vet J. 49(3):352-357.

Freitag, J., Bates, D., Boyd, R., Shah, K., Barnard, A., Huguenin, L., et al. 2016. Mesenchymal stem cell therapy in the treatment of osteoarthritis: reparative pathways, safety and efficacy – a review. BMC Musculoskel Dis.17:230.

Fu, Y., Karbaat, L., Wu, L., Leijten, J., Both, S.K., Karperien, M. 2017. Trophic effects of mesenchymal stem cells in tissue regeneration. Tissue Eng Part B Rev. Dec;23(6):515-528. doi: 10.1089/ten.TEB.2016.0365.

Kong, L., Zheng, L.Z., Qin, L., Ho, K.K.W. 2017. Role of mesenchymal stem cells in osteoarthritis treatment. J Orthop Trans. 9:89–103.

Leibacher, J. & Henschler, R. 2016. Biodistribution, migration and homing of systemically applied mesenchymal stem/stromal cells. Stem Cell Res. Ther. 7(7):doi 10.1186/s13287-015-0271-2

Mao, A.S. & Mooney, D.J. 2015. Regenerative medicine: Current therapies and future directions. Proceedings of the National Academy of Sciences 112(47):14452-14459, https://doi.org/10.1073/pnas.1508520112

Otto, W.R. & N.A. Wright. 2011. Mesenchymal stem cells: from experiment to clinic. Fibrogenesis Tissue Repair. 4:20.

Patel, D.M., Shah, J., Srivastava, AS. 2013. Therapeutic potential of mesenchymal stem cells in regenerative medicine. Stem cells international 2013 (2013).

Pezzanite, L., Chow, L., Soontararak, S., Phillips, J., Goodrich, L., Dow, S. 2020. Equine Amikacin induces rapid dose-dependent apoptotic cell death in equine chondrocytes and synovial cells in vitro. Vet J. 2020;52:715–724.

Punzón, E., Salgüero, R., Totusaus, X., Mesa-Sánchez, C., Badiella, L., García-Castillo, M. 2022. Equine umbilical cord mesenchymal stem cells demonstrate safety and efficacy in the treatment of canine osteoarthritis: a randomized placebo-controlled trial. J. Am. Vet. Med. Assoc. 260(15):1947-1955.