The 500 Line to restore mobility and strength

Powered by
SIGMOLECS® Technology

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500™

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For Professional Use Only

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Scan the QR code to watch a webinar in which Dr JO Serrentino discusses the 500 Line

SIGMOLECS® Technology

- Engineered by Dr JO Serrentino for Contrad Swiss Three hydrogel monodoses with peptides, hyaluronic acid and one of the most advanced technologies available for optimum joint and soft tissue wellness.

- Self-penetrating gel imbued with SIGMOLECS® Technology to reach deep tissue, working in situ, by simple topical administration of a sticky patch for maximum effectiveness.

ST500™ AI500™ CR500™

The ST500™ gel revs up connective tissue wellness and is useful for limiting the physiological degeneration of the joints and tissues, to improve their function.

The AI500™ pain reliever aid gel acts like a sentry at the subcellular level of the connective tissue matrix, providing relief in cases of pain and inflammation due to tension in muscles and adjacent tissues.

The CR500™ gel is optimal for attenuating the physiological degeneration of cartilage typical of osteoarthritic processes.

SIGMOLECS® Technology is an advanced chemical profiling through structural assembling of key molecules, mostly proteins and peptides, that form actuated molecules by specifically:

- **IMPROVING**
  their bio-activity in solution and in vivo
- **INCREASING**
  their transmembrane penetration
- **CREATING**
  precise specificity of action within the intracellular signaling pathway

CONTRADWIRE 500™

SIGMOLECS® molecules are configured and assembled to mirror highly specific intracellular peptide factors. This is done by grafting bioactive peptides or amino acid sequences onto a source molecule, usually a natural source protein.

Endogenous signal molecules trigger cellular responses to external stimuli, therefore "programming" the physiological response, similar to computer code within a computer program. Using SIGMOLECS® molecules is like reprogramming the cell's response, like inserting a new code into a computer program, and modulating its function.

A pain management line of products for optimum joint and soft tissue wellness.

The 500 Line of monodoses contains SIGMOLECS® Technology in that it designs scaled molecules that can easily penetrate the skin and enter deep tissue. The shorter the amino acid sequence, the better the penetration, so molecules are fashioned according to sequences that are ‘skin friendly’ and can facilitate permeation through cell membranes.

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AI500™ Monodose Gel

AI500™ is a hydrogel to be applied to intact skin, intended to provide relief in cases of pain due to tension in muscles and adjacent tissues, to improve movement and function.

AI500™ contains SH-Polypeptide 6 which codes for Interleukin 10 (IL-10).

IL-10 is a potent wide-ranging anti-inflammatory cytokine which is particularly important in the resolution of inflammation.[1] IL-10 binding to target cells drives the expression of anti-inflammatory factors.[2] Additionally, IL-10 inhibits the expression and release of numerous pro-inflammatory factors such as GM-CSF, G-CSF, IL-1a, IL-1b, IL-6, IL-8, and TNF-a.[3–6]

In general, AI500™ can be used in conjunction with the other monodose gels to help attenuate pain, especially during the initial stages of healing.

The peptides in ST500™ are SH-Poypeptide 29 which codes for interleukin 3 (IL-3) and SH-Tripeptide 1 which codes for Fibroblast Growth Factor 1 (FGF-1).

IL-3 is a potent growth- and differentiation-promoting cytokine, which also upregulates expression of collagen and chondrocyte-specific genes.[7]
IL-3 has been demonstrated to reduce cartilage destruction and the pathological bone resorption that can result from expression of pro-inflammatory signals and matrix metalloproteinases.[7–9]
Additionally, IL-3 has been linked to expression of nerve growth factor (NGF) and its role in wound healing[10], to the increased migration and wound-healing properties of mesenchymal stromal cells (MSC) through expression of CCRX4[11], as well as the survival of stem and progenitor cell populations[12,13].

FGF-1 is a member of the fibroblast growth factor family which have strong cell survival and growth-stimulating properties. FGF-1 has been shown to increase the growth of new blood vessels[14] and to reduce pulmonary fibrosis[15]. It also has known roles in increased wound healing.[16]

ST500™ Monodose Gel

ST500™ is a hydrogel containing peptides and hyaluronic acid with a soothing action that helps to limit the physiological degeneration of tendons and muscles, thereby aiding joint movement.

CR500™ Monodose Gel

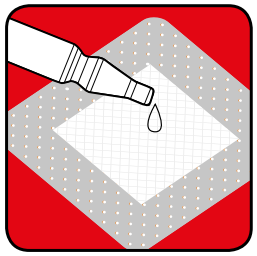
CR500™ is a hydrogel containing peptides and hyaluronic acid with a soothing action that helps prevent and attenuate the physiological degeneration of cartilage in osteoarthritis, thereby protecting against and slowing the progression of joint damage.

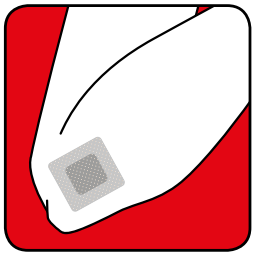
CR500™ contains SH-Polypeptide-85 which codes for FGF-9 (aka Glia-Activating Factor) and SH-Polypeptide-93 which codes for Cellular Communication Network Factor 2 (CCN2).

FGF-9 is important for the homeostasis of articular cartilage through FGFR3 signaling activation[17] and this mechanism plays a role in the correct formation of the joint space and the inhibition of endochondral ossification.[18] The role of FGF9 in joint development and homeostasis is well supported by the literature, especially its role in controlling chondrocyte development and regulating bone growth, both of which contribute largely to the smooth movement of articulations and thus pain-free movement. Disequilibrium within this system will lead to degraded cartilage and the formation of mineralized “bony” deposits within the articulation leading to pain.[19,20]

CCN2 is known for its stimulatory effect on the production of extracellular matrix components, indeed disruption of CCN2 leads to defects in collagen III and IV, laminin, and importantly, hyaluronic acid production.[21–23]. The latter of which is crucial in the viscoelasticity of the synovial fluid that lines and lubricates the joints.[24]

CONTRAD SWISS CR500™





IMPORTANT TIPS:

It is important to cover the gel with an adhesive patch, DO NOT USE IT AS A TOPICAL RUB. Please scan the QR code below to watch a short instructional video on how to use the 500 Line"

Scan the QR code to learn how to correctly apply the 500 Line monodoses in just 1 minute

Use of the 500 line monodoses

The monodoses can be applied in several areas, as needed, on the patient

- Apply the AI500™ to the painful area or above the point of pain.
- Apply the ST500™ on the area in need of repair.
  You can apply an AI500™ patch above the ST500™ and/or CR500™ patch if you need pain relief.
- ST500™ and/or CR500™ are particularly good to apply after a stem cell treatment. This can be done one time post treatment after each stem cell or PRP treatment.
- ST500™ can be used for pre and post regenerative treatments.
  Apply the patch to the affected area 2 x week for 2-4 weeks, then 1 x week for 2-4weeks then 1 x month for 2-4 months.
- AI500™ can be applied to any area in need of pain relief. Multiple patches can be applied at several spots for the patient to remove the next day. For acute cases, the patient can return twice a week for 2-4 weeks for application. It is important to know the source of the pain and position the patch on or along the channel of pain or inflammation.
- For chronic osteoarthritis, an in situ application of two to four patches of CR500™ surrounding the joint in question can be applied 1-2 x week for 1 month, then twice a month for 2-4 months. Several joints can be done at the same time. There is no limit to the amount of monodoses that can be used in one session.

GENERAL TIPS

- **10x5 or 10x6 cm adhesive patches are preferred.**
  Make sure the gel does not contact the adhesive sides.
- **The patch should remain in situ for a minimum of 2.5 hours and optimally for 6-8 hours.**
- **There is no limit, the patients can even remove the patch the next day.**
- **It is important to tell patients not to get the patch wet once in place.**
- **You can wipe the area with alcohol to ensure a clean dry surface.**
  It is important to apply the patch to clean dry skin.

(1) Garcia, J. M.; Stillings, S. A.; Leclerc, J. L.; Phillips, H.; Edwards, N. J.; Robicsek, S. A.; Hoh, B. L.; Blackburn, S.; Doré, S. Role of Interleukin-10 in Acute Brain Injuries. Front. Neurol. 2017, 8. https://doi.org/10.3389/fneur.2017.00244.
(2) El Kasmi, K. C.; Smith, A. M.; Williams, L.; Neale, G.; Panopoulos, A. D.; Panopolous, A.; Watowich, S. S.; Häcker, H.; Foxwell, B. M. J.; Murray, P. J. Cutting Edge: A Transcriptional Repressor and Corepressor Induced by the STAT3-Regulated Anti-Inflammatory Signaling Pathway. J. Immunol. 2007, 179 (11), 7215–7219. https://doi.org/10.4049/jimmunol.179.11.7215.
(3) de Waal Malefyt, R.; Abrams, J.; Bennett, B.; Figdor, C. G.; de Vries, J. E. Interleukin 10(IL-10) Inhibits Cytokine Synthesis by Human Monocytes: An Autoregulatory Role of IL-10 Produced by Monocytes. J. Exp. Med. 1991, 174 (5), 1209–1220. https://doi.org/10.1084/jem.174.5.1209.
(4) Willems, F.; Marchant, A.; Delville, J. P.; Gérard, C.; Delvaux, A.; Velu, T.; de Boer, M.; Goldman, M. Interleukin-10 Inhibits B7 and Intercellular Adhesion Molecule-1 Expression on Human Monocytes. Eur. J. Immunol. 1994, 24 (4), 1007–1009. https://doi.org/10.1002/eji.1830240435.
(5) Hashimoto, S. I.; Komuro, I.; Yamada, M.; Akagawa, K. S. IL-10 Inhibits Granulocyte-Macrophage Colony-Stimulating Factor-Dependent Human Monocyte Survival at the Early Stage of the Culture and Inhibits the Generation of Macrophages. J. Immunol. 2001, 167 (7), 3619–3625. https://doi.org/10.4049/jimmunol.167.7.3619.
(6) Wang, P.; Wu, P.; Siegel, M. I.; Egan, R. W.; Billah, M. M. Interleukin (IL)-10 Inhibits Nuclear Factor B (NFB) Activation in Human Monocytes IL-10 AND IL-4 SUPPRESS CYTOKINE SYNTHESIS BY DIFFERENT MECHANISMS. J. Biol. Chem. 1995, 270 (16), 9558–9563. https://doi.org/10.1074/jbc.270.16.9558.
(7) Kour, S.; Garimella, M. G.; Shiroor, D. A.; Mhaske, S. T.; Joshi, S. R.; Singh, K.; Pal, S.; Mittal, M.; Krishnan, H. B.; Chattopadhyay, N.; Ulemale, A. H.; Wani, M. R. IL-3 Decreases Cartilage Degeneration by Downregulating Matrix Metalloproteinases and Reduces Joint Destruction in Osteoarthritic Mice. J. Immunol. 2016, 196 (12), 5024–5035. https://doi.org/10.4049/jimmunol.1500907.
(8) Yogesha, S. D.; Khapli, S. M.; Srivastava, R. K.; Mangashetti, L. S.; Pote, S. T.; Mishra, G. C.; Wani, M. R. IL-3 Inhibits TNF-⍺-Induced Bone Resorption and Prevents Inflammatory Arthritis. The Journal of Immunology 2009, 182 (1), 361–370. https://doi.org/10.4049/jimmunol.182.1.361.
(9) Srivastava, R. K.; Tomar, G. B.; Barhanpurkar, A. P.; Gupta, N.; Pote, S. T.; Mishra, G. C.; Wani, M. R. IL-3 Attenuates Collagen-Induced Arthritis by Modulating the Development of Foxp3+ Regulatory T Cells. J. Immunol. 2011, 186 (4), 2262–2272. https://doi.org/10.4049/jimmunol.1002691.
(10) Li, A. K.; Koroly, M. J.; Schattenkerk, M. E.; Malt, R. A.; Young, M. Nerve Growth Factor: Acceleration of the Rate of Wound Healing in Mice. Proc. Natl. Acad. Sci. U.S.A. 1980, 77 (7), 4379–4381. https://doi.org/10.1073/pnas.77.7.4379.
(11) Barhanpurkar-Naik, A.; Mhaske, S. T.; Pote, S. T.; Singh, K.; Wani, M. R. Interleukin-3 Enhances the Migration of Human Mesenchymal Stem Cells by Regulating Expression of CXCR4. Stem Cell Res Ther 2017, 8 (1), 168. https://doi.org/10.1186/s13287-017-0618-y.
(12) Robin, C.; Ottersbach, K.; Durand, C.; Peeters, M.; Vanes, L.; Tybulewicz, V.; Dzierzak, E. An Unexpected Role for IL-3 in the Embryonic Development of Hematopoietic Stem Cells. Developmental Cell 2006, 11 (2), 171–180. https://doi.org/10.1016/j.devcel.2006.07.002.
(13) Rossmanith, T.; Schröder, B.; Bug, G.; Müller, P.; Klenner, T.; Knaus, R.; Hoelzer, D.; Ottmann, O. G. Interleukin 3 Improves the Ex Vivo Expansion of Primitive Human Cord Blood Progenitor Cells and Maintains the Engraftment Potential of Scid Repopulating Cells. Stem Cells 2009, 19 (4), 313–320. https://doi.org/10.1634/stemcells.19-4-313.
(14) Khanna, O.; Huang, J.-J.; Moya, M. L.; Wu, C.-W.; Cheng, M.-H.; Opara, E. C.; Brey, E. M. FGF-1 Delivery from Multilayer Alginate Microbeads Stimulates a Rapid and Persistent Increase in Vascular Density. Microvasc. Res. 2013, 90, 23–29. https://doi.org/10.1016/j.mvr.2013.08.006.
(15) Shimbori, C.; Bellaye, P.-S.; Xia, J.; Gauldie, J.; Ask, K.; Ramos, C.; Becerril, C.; Pardo, A.; Selman, M.; Kolb, M. Fibroblast Growth Factor-1 Attenuates TGF-⍺1-Induced Lung Fibrosis. J. Pathol. 2016, 240 (2), 197–210. https://doi.org/10.1002/path.4768.
(16) Tan, Y.; Wang, K. Y.; Wang, N.; Li, G.; Liu, D. Ectopic Expression of Human Acidic Fibroblast Growth Factor 1 in the Medicinal Plant, Salvia Miltiorrhiza, Accelerates the Healing of Burn Wounds. BMC Biotechnol. 2014, 14, 74. https://doi.org/10.1186/1472-6750-14-74.
(17) Ornitz, D. M.; Itoh, N. The Fibroblast Growth Factor Signaling Pathway. WIREs Developmental Biology 2015, 4 (3), 215–266. https://doi.org/10.1002/wdev.176.
(18) Garofalo, S.; Kliger-Spatz, M.; Cooke, J. L.; Wolstin, O.; Lunstrum, G. P.; Moshkovitz, S. M.; Horton, W. A.; Yayon, A. Skeletal Dysplasia and Defective Chondrocyte Differentiation by Targeted Overexpression of Fibroblast Growth Factor 9 in Transgenic Mice. J. Bone Miner. Res. 1999, 14 (11), 1909–1915. https://doi.org/10.1359/jbmr.1999.14.11.1909.
(19) Wu, X.; Gu, M.; Huang, L.; Liu, X.; Zhang, H.; Ding, X.; Xu, J.; Cui, B.; Wang, L.; Lu, S.; Chen, X.; Zhang, H.; Huang, W.; Yuan, W.; Yang, J.; Gu, Q.; Fei, J.; Chen, Z.; Yuan, Z.; Wang, Z. Multiple Synostoses Syndrome Is Due to a Missense Mutation in Exon 2 of FGF9 Gene. The American Journal of Human Genetics 2009, 85 (1), 53–63. https://doi.org/10.1016/j.ajhg.2009.06.007.
(20) Zhou, S.; Wang, Z.; Tang, J.; Li, W.; Huang, J.; Xu, W.; Luo, F.; Xu, M.; Wang, J.; Wen, X.; Chen, L.; Chen, H.; Su, N.; Shen, Y.; Du, X.; Xie, Y.; Chen, L. Exogenous Fibroblast Growth Factor 9 Attenuates Cartilage Degradation and Aggravates Osteophyte Formation in Post-Traumatic Osteoarthritis. Osteoarthritis and Cartilage 2016, 24 (12), 2181–2192. https://doi.org/10.1016/j.joca.2016.07.005.
(21) Hall-Glenn, F.; De Young, R. A.; Huang, B.-L.; van Handel, B.; Hofmann, J. J.; Chen, T. T.; Choi, A.; Ong, J. R.; Benya, P. D.; Mikkola, H.; Iruela-Arispe, M. L.; Lyons, K. M. CCN2/Connective Tissue Growth Factor Is Essential for Pericyte Adhesion and Endothelial Basement Membrane Formation during Angiogenesis. PLoS One 2012, 7 (2). https://doi.org/10.1371/journal.pone.0030562.
(22) Yuhua, Z.; Wanhua, R.; Chenggang, S.; Jun, S.; Yanjun, W.; Chunqing, Z. Disruption of Connective Tissue Growth Factor by Short Hairpin RNA Inhibits Collagen Synthesis and Extracellular Matrix Secretion in Hepatic Stellate Cells. Liver Int. 2008, 28 (5), 632–639. https://doi.org/10.1111/j.1478-3231.2008.01730.x.
(23) Tong, Z.; Chen, R.; Alt, D. S.; Kemper, S.; Perbal, B.; Brigstock, D. R. Susceptibility to Liver Fibrosis in Mice Expressing a Connective Tissue Growth Factor Transgene in Hepatocytes. Hepatology 2009, 50 (3), 939–947. https://doi.org/10.1002/hep.23102.
(24) Kawata, M.; Okamoto, A.; Endo, T.; Tsukamoto, Y. - Viscoelasticity of Synovial Fluids and Additive Effect of Hyaluronate. In Hydrocolloids; Nishinari, K., Ed.; Elsevier Science: Amsterdam, 2000; pp 343–348. https://doi.org/10.1016/B978-044450178-3/50104-9.

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