

# HOW TO ACTIVATE AND APPLY RESTORE VETERINARY GEL



**STEP 1**  
**OPEN POUCH,  
REMOVE SYRINGE**



**STEP 2**  
**HYDRATE GEL**  
Remove cap. Fill syringe to 5 mL mark with saline or water.



**STEP 3**  
**RECAP & SHAKE VIGOROUSLY**  
Recap the syringe securely and shake vigorously (~5 sec). Allow gel to set before application (~1 min).



**STEP 4**  
**APPLY TO WOUND**  
Liberally apply gel directly to the wound and spread to desired thickness. For large area wounds, additional gel syringes may be required.



**STEP 5**  
**COVER WOUND**  
Covering will extend the lifetime of Restore. Use an occlusive dressing for best results. In areas where it may not be possible to cover the wound we recommend frequent gel reapplication.

# RESTORE BY NOXSANO® Veterinary Wound Gel

**Restore Gel by Noxsano** helps veterinarians speed or restart wound healing after injury, surgery, or disease, to rapidly return patients to full health. Rapid healing reduces risk of infection, number of dressing changes, and clinic workload. This decreases stress on the animal and owner while lowering treatment cost.

**Indications:** Restore is recommended for infection control and the treatment of all wounds in small and large animals, including e.g., lacerations, surgical incisions, wounds treated by secondary intent, bites, and minor scrapes and cuts. Can be used with existing wound technology such as skin grafts, negative pressure, hyperbaric oxygen, laser, etc, if desired.

## Frequently Asked Questions

**How often should I reapply the gel?** We recommend reapplication of gel on a daily basis. If the gel remains hydrated, it may remain active for up to seven days.

**When should I stop using the gel?** When the wound is completely healed.

**What overwrap is recommended?** You may use whatever you like. We do recommend an occlusive secondary dressing for best performance as Restore continues delivering nitric oxide until it dries. Occlusion will keep Restore delivering longer until you are ready to inspect the wound. The Restore gel is non-toxic in small amounts, but covering to prevent the animal from licking or rubbing the gel off will speed healing.

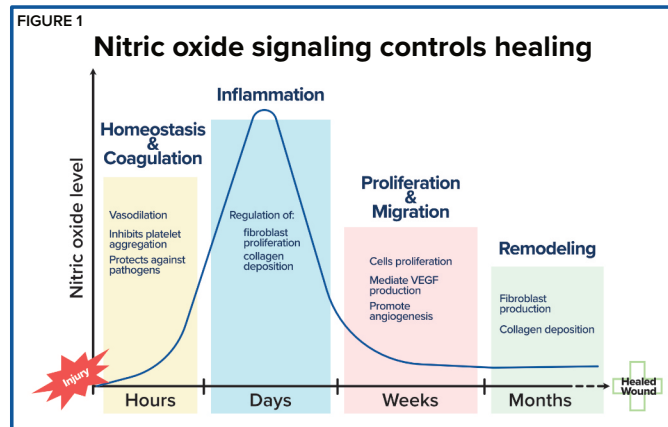
**Will Restore Gel harm the animal if accidentally ingested?** Restore Gel contains food grade and/or non-digestible materials that have been shown not to be harmful to animals. For more details see our website.

For more information or to reorder, go to [www.noxsano.com](http://www.noxsano.com), email us at [contact@noxsano.com](mailto:contact@noxsano.com), or call 513-202-6052.

Patents: [www.noxsano.com/patents](http://www.noxsano.com/patents)

# How Restore by Noxsano Heals Wounds with Nitric Oxide

**Restore by Noxsano** is a nitric oxide delivery system designed to promote healthy and rapid wound closure. Nitric oxide is known to be a critical part of a healthy wound healing cascade<sup>1</sup> - a discovery that resulted in the 1998 Nobel Prize for Physiology and Medicine. The therapeutic value of nitric oxide in wound healing comes from regulating inflammatory response, cell proliferation, collagen formation, antimicrobial action, and angiogenesis (Figure 1).



## Nitric Oxide - Biologic

The enzyme, nitric oxide synthase, converts L-arginine to L-citrulline releasing nitric oxide *in vivo*.<sup>2</sup> Three isoforms of the enzyme have been characterized. Wound healing is principally controlled by endothelial nitric oxide synthase which is primarily expressed in the skin and blood vessels. Endothelial nitric oxide synthase is activated by thrombin when a wound occurs and then orchestrates the cascade of processes necessary for wound closure.

## Nitric Oxide - Natural Antimicrobial

Nitric oxide is utilized in two ways post-coagulation to drive the wound healing process. At low concentrations, nitric oxide acts as a signaling molecule that promotes tissue growth and regulates activity of immune cells. At high concentrations, nitric oxide induces broad spectrum damage to pathogens caused by nitrosative and oxidative reactions.<sup>3</sup> The damage sustained by the pathogens subject to these chemical processes is extensive. Few bacteria are able to escape the antimicrobial effect of nitric oxide. Nitric oxide further controls immune cell signaling and

the biochemical reactions which are used to defend against bacteria, fungi, viruses, and parasites.

Nitric oxide is a biological signal that controls the dispersal of biofilms to the more susceptible planktonic form.<sup>4</sup> Biofilms are notoriously persistent and generally very resistant to antimicrobials and antibiotics while planktonic bacteria are much more sensitive to treatment. Nitric oxide upregulates expression of endogenous collagenase, which autolytically debrides the wound, to further promote the healing process.

## Nitric Oxide - Wound Repair

The role of nitric oxide in wound healing is multifaceted. Its presence and amount delivered are critical in every stage of wound healing. Nitric oxide acts to coordinate proliferation, differentiation, and apoptosis in a number of cell types involved in wound healing. In testing, nitric oxide donors significantly increase fetal bovine serum-induced thymidine incorporation into the DNA of human dermal fibroblasts and enhance fibroblast growth factor or platelet-derived growth factor induced DNA synthesis. Nitric oxide has been shown to stimulate the proliferation of endothelial cells, protect endothelial cells from apoptosis, and mediate vascular endothelial growth factor (VEGF) production. These effects of nitric oxide on endothelial cells guide angiogenesis, the formation of blood vessels. The resulting increased blood flow boosts the transport of proteins into the wound bed facilitating wound healing. Low levels of nitric oxide increase keratinocyte proliferation. Nitric oxide coordinates increased collagen synthesis and deposition in the final phases of wound healing. Treatment with nitric oxide donors has been shown to increase collagen formation from fibroblasts and conversely collagen formation decreases following nitric oxide synthase inhibition.

## Nitric Oxide from Restore

**Restore by Noxsano** solves the challenge of safe, efficient, and effective delivery of nitric oxide at the point of need, the wound bed, to control and drive the healing process. Water activates Restore's patented nitric oxide generating system. Once wetted, simply apply Restore to the wound or incision. Restore will

continue to deliver nitric oxide and promote healing while hydrated. An occlusive dressing can optionally be used to extend lifetime. Depending on secondary dressing, environmental conditions, and the animal's needs, Restore can remain active for up to 1 week. Most veterinarians choose to leave Restore in place for 2 - 4 days.

## Example Case Studies<sup>6</sup>



1. Witte, M. B.; Barbul, A. Role of nitric oxide in wound repair. *Am. J. Surg.* 2002, 183, 406-412
2. Alderton WK, Cooper CE, Knowles RG. Nitric oxide synthases: structure, function and inhibition. *Biochem J.* 2001;357(Pt 3):593-615.
3. Fang, Ferric C. "Perspectives series: host/pathogen interactions. Mechanisms of nitric oxide-related antimicrobial activity." *The Journal of clinical investigation* 99:12 (1997): 2818-2825.
4. Arora, D. P., Hossain, S., Xu, Y. & Boon, E. M. Nitric Oxide Regulation of Bacterial Biofilms. *Biochemistry* 54, 3717-28 (2015)
5. Willey, Alan, and Stevan Samuel. "Electrochemical gasotransmitter generating compositions and methods of using same and dressings and treatment systems incorporating same." U.S. Patent No. 10,342,706. 9 Jul. 2019.
6. For more details and additional examples, see [www.noxsano.com](http://www.noxsano.com).