

HOW TO ACTIVATE AND APPLY RESTORE WOUND PADS



STEP 1

OPEN POUCH

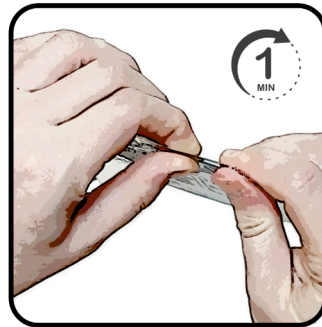
Select appropriate pad size and open pouch by tearing off top.



STEP 2

HYDRATE THE PAD

Measure saline or water and add to the pad in the pouch. Required volumes are marked on the front of each pouch.



STEP 3

ALLOW FLUID TO FULLY ABSORB

Reseal the pouch and lay flat. Wait approximately 1 minute or until fluid is absorbed into the pad.



STEP 4

REMOVE ACTIVATED PAD

Carefully remove pad, knead into shape as necessary. Discard pouch.



STEP 5

APPLY TO WOUND AND COVER

Apply the activated pad directly to the wound. Optionally, an occlusive dressing can be used for extended lifetime.



STEP 6

WRAP TO HOLD SECURELY

Overwrap the pad and covering as necessary to hold in place. Pad can remain in place up to one week. For best results, apply 2 - 3 pads per week.

RESTORE

BY NOXSANO®

5 X 7 cm and 5 x 12 cm wound pads

Restore 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 change the pads? We recommend that Restore pads be changed every 2-4 day. The pad will continue to produce nitric oxide up to 7 days.

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

Can I combine multiple pads over a larger surface area? Yes. Each Restore pad provides localized diffusion of nitric oxide. For larger wounds, multiple pads can be placed in any orientation to deliver nitric oxide to the wound. Each pad is a self-contained nitric oxide generator and will produce nitric oxide independently of other dressings.

What overwrap is recommended? You may use whatever you like. The Restore pad is non-adherent and will require some means of immobilization over the wound. 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.

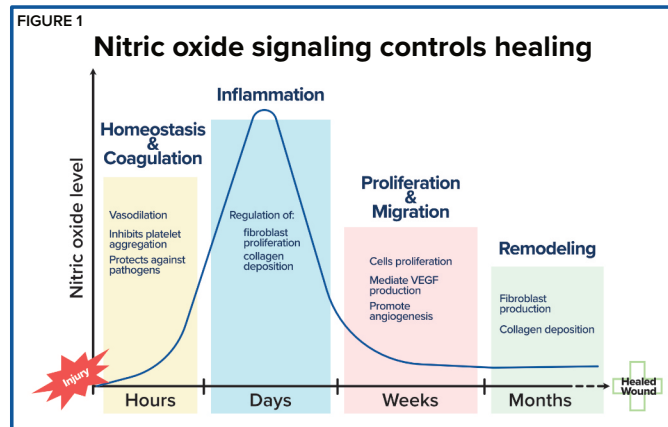
What if I cannot overwrap or adhere Restore to the treatment site? For wounds that are difficult to overwrap or for surface wounds which are left to heal by secondary intent Restore Gel can also deliver accelerated wound closure while reducing risk of infection.

For more information or to reorder, go to www.noxsano.com, email us at contact@noxsano.com, or call 513-202-6052.

Patents: 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 cascade¹ - 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*.² 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.³ 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.⁴ 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

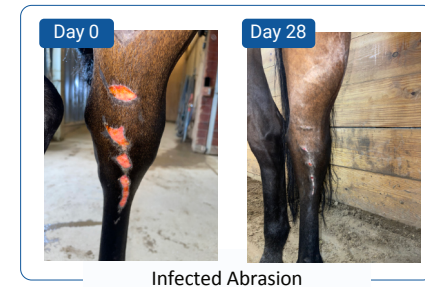
The role of nitric oxide in wound healing is multifaceted. Its presence and amount delivered are critical in every stage of wound healing. Nitric oxide acts to coordinate proliferation, differentiation, and apoptosis in a number of cell types involved in wound healing. In testing, nitric oxide donors 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.

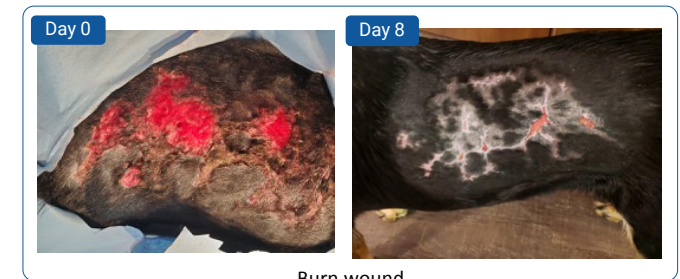
Example Case Studies⁶



Infected Abrasion



Post-surgical Chronic wound



Burn wound

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.