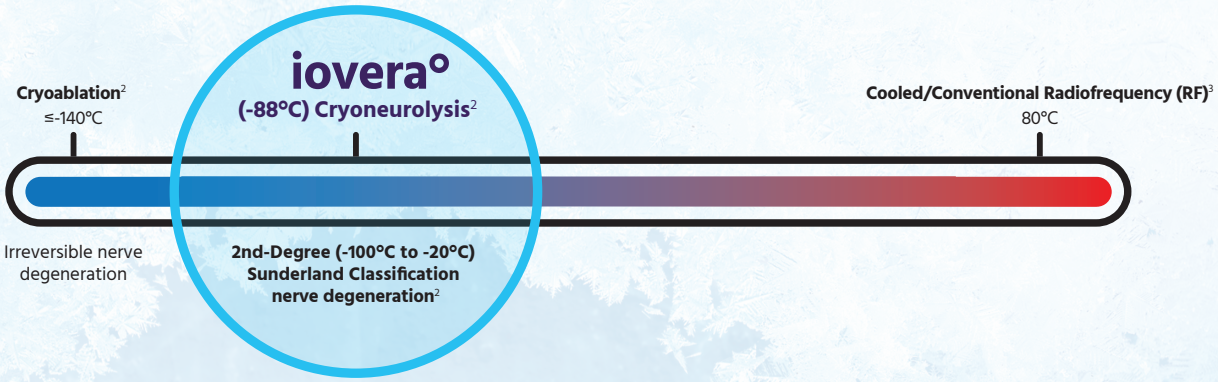
DISCOVER THE ADVANTAGE OF CRYONEUROLYSIS TECHNOLOGY

iovera° is an innovative cryoneurolysis technology that uses freezing cold to destroy the pain-transmitting components of a peripheral nerve—the axon and myelin sheath—to produce an immediate, long-lasting neurolytic block.[1] The structural components of the nerve are not affected by iovera° treatment, and the axon regenerates along its original pathway at a rate of 1 mm to 2 mm per day until nerve signaling is fully restored.[2]

Comparison of thermal neurolytic treatments



	Cryoablation	Cryoneurolysis	Cooled/ Conventional RF[3]
Mechanism of action	Process that uses extreme cold to permanently destroy nerves or abnormal tissues[4]	Treatment that temporarily blocks nerve conduction along peripheral nerve pathways[1]	Heat-based ablation[3]
Clinical application	Tumor destruction[4]	Pain relief[1]	Pain relief[3]
Duration of effect	Permanent[4]	Temporary[1]	Temporary[3]
Temperature	≤-140°C[2]	-88°C[2]	80°C[3]
Safety	Complete destruction of nearby tissues[4]	Risk of local bruising[5]; no effect on nearby tissues[2]	Potential damage to nearby tissues and blood vessels[6]

Please see full Indication and Important Safety Information at the end of this document.
For full safety information, please visit www.ioverapro.com.

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The differences between cryoneurolysis and cryoablation

As a category, cryotherapy ("cold therapy") is the local or general use of low temperatures in medical therapy. The mechanism of action involves the following[7]:

- Positioning a cryoprobe adjacent to the target (nerve or tissue)
- Using cryogens (substance to produce very low temperatures) such as nitrous oxide or liquid nitrogen to flow through a closed cryoprobe system
- Rapid cooling of the cryoprobe takes place due to the Joule-Thomson effect
- Removing heat from the target by conduction via physical contact with the cryoprobe

Nerve ablation is the permanent ablation of the nerve, whereby ablation is defined as removal of a body part or the destruction of its function by surgical procedure, morbid process, or noxious substance.[8]

Note: While the terms "cryoanalgesia" and "cryoneurolysis" are often used interchangeably, there is a subtle difference; cryoneurolysis describes the process taking place during iovera° treatment, while cryoanalgesia refers to the effect experienced by the patient.

	iovera° (cryoneurolysis)	**Cryoablation** (cryosurgery)
Temperature	-88°C[2]	≤-140°C[2]
Target tissue	Deep and superficial peripheral nerves	Tumors[4]
Clinical application	Pain relief	Tumor destruction[4]
Duration of effect	Temporary[1]	Permanent[4]
Safety	• No effect on nearby nerves, tissue, and blood vessels[2] • At the treatment site(s): injury to the skin related to application of cold or heat, hyper- or hypopigmentation[2]	Complete destruction of nearby tissues and blood vessels[4]
Degree of nerve injury (Sunderland Classification)	• 2nd (axonotmesis)[2] • Results in reversible degeneration of the axon (Wallerian degeneration) and myelin sheath. Epineurium, perineurium, and endoneurium are unaffected[2] • Depending on the distance from the axon injury site to the target site, the disruption of signaling can last from weeks to months[2]	• 4th (neurotmesis)[3] • Ablation of the axon, endoneurium, perineurium, and epineurium. The axon may regenerate outside its original pathway and result in neuroma. Reinnervation may be incomplete[3]
Cryogen used	Nitrous oxide[2]	Liquid nitrogen[6]

The differences between cryoneurolysis and RF ablation

While the iovera° cryoneurolysis process uses nitrous oxide to rapidly cool the probe, cooled RF controls the probe temperature by circulating water[6]; it may also affect the surrounding tissue during treatment.[3,9]

	iovera° (cryoneurolysis)	**Cooled/Conventional RF** (RF ablation)
Mechanism of action	• Temporarily blocks nerve conduction along peripheral nerve pathways[1] • A drop in temperature, created by nitrous oxide within the closed-end needles, forms ice balls around the targeted nerve[2] • Cold zone degenerates the axon and myelin sheath, blocking nerve signals[2]	• Thermal degradation of nerve structure via ionic heating[3] • Controls probe temperature by circulating water[6]
Procedure	• Less than 20 minutes for AFCN and 2 branches of the ISN[5] • Simple equipment and operation—push of a single button	• Capital equipment and RF generator require setup prior to each procedure[9]
Temperature	**-88°C[3]**	80°C[3]
Target tissue	Deep and superficial peripheral nerves[7]	Deep nerves[9]
Clinical applications	Chronic OA pain or incisional pain (variety of knee pain)[5,10]	Chronic pain[3]
Onset of action	Treatment effect is immediate[2,6]	Delayed effect—patients feel effects 1 to 2 weeks after treatment[3]
Safety	• No risk to surrounding tissue or blood vessels[2] • Minimal-to-no risk of neuritis—cold suppresses inflammatory reactions[2,6] • The most common side effects were bruising, numbness, redness, tenderness upon palpation, and swelling[10]	• Affects surrounding tissue[6] • Patients may experience painful neuritis due to reaction of tissue to heat[6] • Water-cooled technology allows the lesion to grow larger than a conventional RF probe, therefore presenting greater risk to surrounding structures such as blood vessels[6]
Cryogen used	Nitrous oxide[2]	Not applicable

AFCN=anterior femoral cutaneous nerve; ISN=infrapatellar branch of the saphenous nerve; OA=osteoarthritis.

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Indication

The iovera° system is used to destroy tissue during surgical procedures by applying freezing cold. It can also be used to produce lesions in peripheral nervous tissue by the application of cold to the selected site for the blocking of pain. It is also indicated for the relief of pain and symptoms associated with osteoarthritis of the knee for up to 90 days. The iovera° system is not indicated for treatment of central nervous system tissue.

When stimulation compatible components are used, the iovera° system can also facilitate target nerve location by conducting electrical nerve stimulation from a compatible 3rd party nerve stimulator.

Important Safety Information

Contraindications

The iovera° system is contraindicated for use in patients with the following:

- Cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, and open and/or infected wounds at or near the treatment site

Potential Complications

As with any surgical treatment that uses needle-based therapy and local anesthesia, there is a potential for site-specific reactions, including, but not limited to:

- Ecchymosis, edema, erythema, local pain and/or tenderness, and localized dysesthesia

Proper use of the device as described in the User Guide can help reduce or prevent the following complications:

- At the treatment site(s): injury to the skin related to application of cold or heat, hyper- or hypopigmentation, and skin dimpling
- Outside the treatment site(s): loss of motor function

References: 1. Hsu M, Stevenson FF. Wallerian degeneration and recovery of motor nerves after multiple focused cold therapies. *Muscle Nerve.* 2015;51(2)268-275. **2.** Ilfeld BM, Preciado J, Trescot AM. Novel cryoneurolysis device for the treatment of sensory and motor peripheral nerves. *Expert Rev Med Devices.* 2016;13(8):713-723. **3.** Chen AF, Khalouf F, Zora K. Cooled radiofrequency ablation provides extended clinical utility in the management of knee osteoarthritis: 12-month results from a prospective, multi-center, randomized, cross-over trial comparing cooled radiofrequency ablation to a single hyaluronic acid injection. *BMC Musculoskelet Disord.* 2020;21(1):363. **4.** Erinjeri JP, Clark TWI. Cryoablation: Mechanism of action and devices. *J Vasc Interv Radiol.* 2010;21(8 suppl):S187-S191. **5.** Dasa V, Lensing G, Parsons M, Harris J, Volaufova J, Bliss R. Percutaneous freezing of sensory nerves prior to total knee arthroplasty. *Knee.* 2016;23(3):523-528. **6.** Zhou L, Craig J, Parekh N. Current concepts of neurolysis and clinical applications. *J Analgesic.* 2014;2:16-22. **7.** Trescot AM. Cryoanalgesia in interventional pain management. *Pain Physician.* 2003;6(3):345-360. **8.** Stedman's Pocket Medical Dictionary. Wolters Kluwer Health/Lippincott Williams & Wilkins. 2009. **9.** COOLIEF [package insert]. Alpharetta, Georgia: Halyard Health; 2017. **10.** Radnovich R, Scott D, Patel AT. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial. *Osteoarthritis Cartilage.* 2017;25(8):1247-1256.

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