iovera°

REFERENCE GUIDE

Please see Important Safety Information on inside of back cover.
For more information, visit **www.iovera.com**.

iovera°

Introduction

iovera° is a handheld device that uses cryoneurolysis (application of a thermal neurolytic temperature) to targeted sensory nerves, temporarily destroying the pain-transmitting components of the nerve and immediately reducing pain.

The onset of relief may occur immediately following treatment and can last up to 90 days as the nerve regenerates and sensory function is restored.

Treatment results for chronic OA knee pain

Decreased knee pain

Patients had significantly greater reductions in WOMAC pain score at days 30, 60, and 90.[1]

Less stiffness

Patients treated with the iovera° system experienced less stiffness **30 days** after treatment.[1]

Improved physical function

Patients in the iovera° treatment group had improved physical function at **90 days**.[1]

Prospective knee OA study[1]

This was a multicenter, prospective, sham-controlled, double-blind study at 17 sites across the United States, N=180 (randomized 2:1). The treatment group consisted of 121 subjects treated with iovera°; the control group consisted of 59 subjects treated with a sham tip. iovera° treatment was applied to the infrapatellar branch of the saphenous nerve; patients were followed through to 120 days. The most common side effects were bruising, numbness, redness, tenderness upon palpitation, and swelling. *P*=0.0004 at 30 days post-treatment, *P*=0.0176 at 60 days post-treatment, *P*=0.0061 at 90 days post-treatment, and *P*=0.1610 at 120 days post-treatment.

Treatment results for postsurgical TKA pain

Fewer opioid prescriptions

Patients who received iovera° requested **45%** fewer opioid prescriptions at **12 weeks** after knee replacement surgery.[2]

Reduction in knee pain

Two weeks after surgery, patients treated with iovera° experienced less pain.[2]

Faster discharge

More patients treated with iovera° were discharged within 2 days of surgery.[2]

Retrospective TKA study[2]

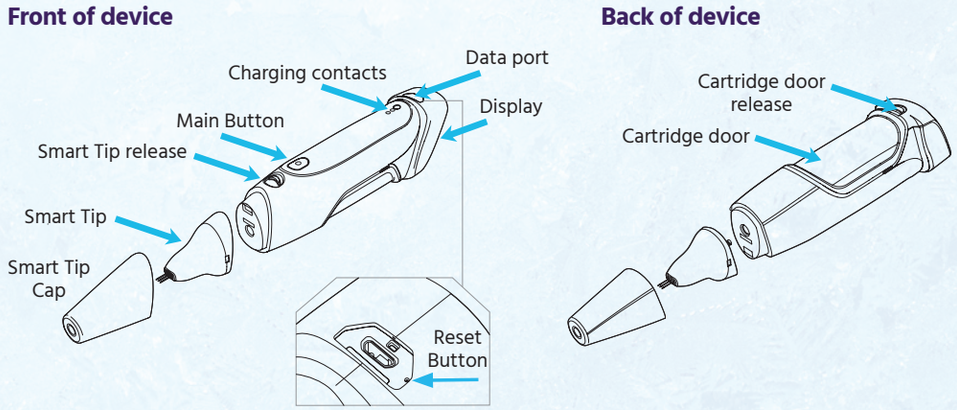
This was a single-site, retrospective review, N=100. The treatment group consisted of the first 50 patients treated after iovera° was introduced; the control group consisted of the last 50 patients treated before iovera° was introduced. iovera° treatment was applied to the infrapatellar branch of the saphenous nerve and anterior femoral cutaneous nerve 5 days prior to TKA. The most common side effect was local bruising at the site of treatment. *P* value was not reported at 2 weeks post-op; *P*=0.0037 at 6 weeks post-op and *P*=0.0011 at 12 weeks post-op.

OA=osteoarthritis; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; TKA=total knee arthroplasty.

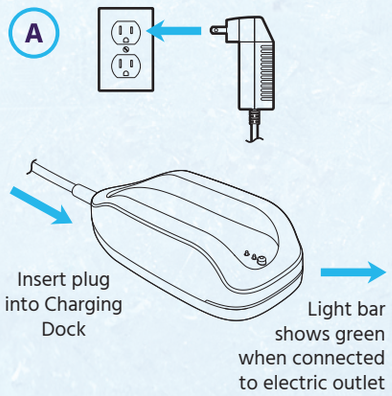
References: 1. Radnovich R, Scott D, Patel AT, et al. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial. *Osteoarthritis Cartilage*. 2017;25(8):1247-1256. **2.** Dasa V, Lensing G, Parsons M, Harris J, Volaufova J, Bliss R. Percutaneous freezing of sensory nerves prior to total knee arthroplasty. *Knee*. 2016;23(3):523-528.

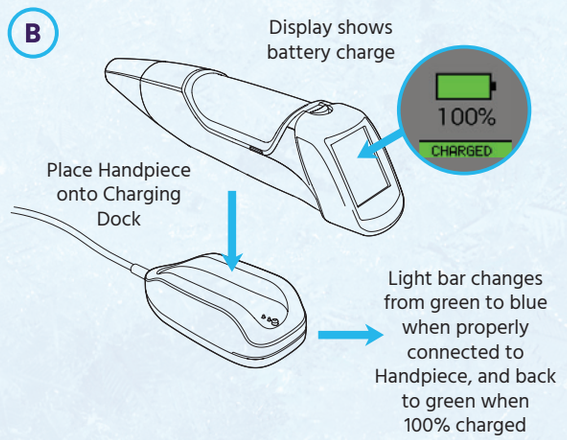
iovera° system setup

I. Device anatomy



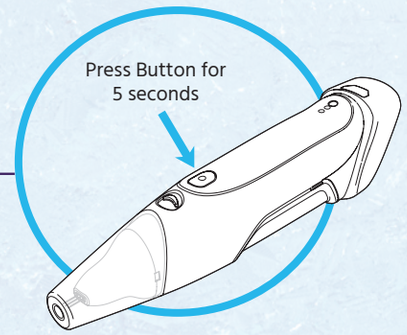
II. Charging device





III. Turning device on/off

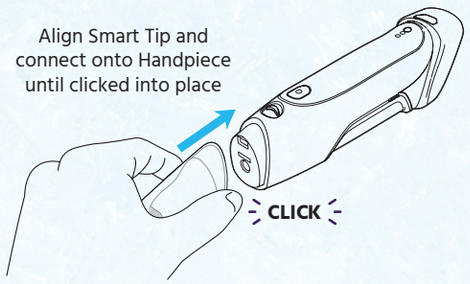
Device will remain powered on when removed from Charging Dock



IV. Attaching and detaching Smart Tip

A Attaching Smart Tip

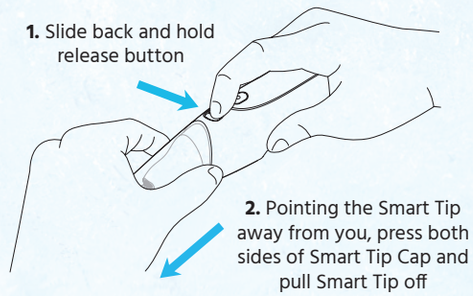
Align Smart Tip and connect onto Handpiece until clicked into place



B Detaching Smart Tip

1. Slide back and hold release button

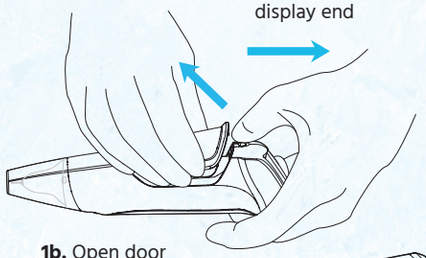
2. Pointing the Smart Tip away from you, press both sides of Smart Tip Cap and pull Smart Tip off



V. Installing Cartridge

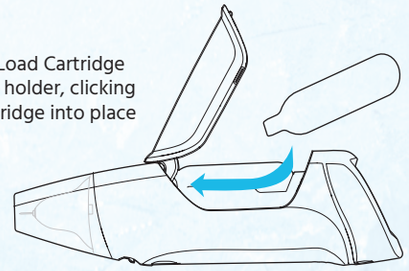
A Insert Cartridge*

1a. Slide and hold Cartridge door release towards the display end

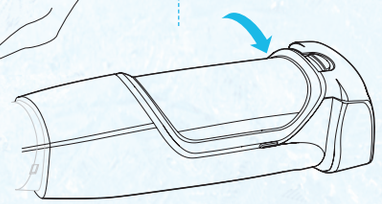


1b. Open door

2. Load Cartridge into holder, clicking Cartridge into place



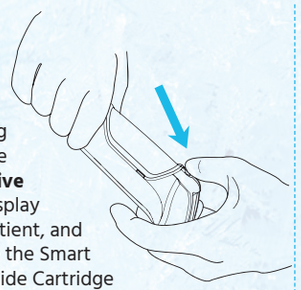
3. Firmly close door until clicked into place



CLICK

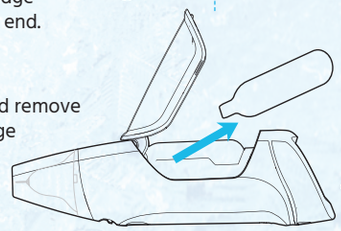
B Remove Cartridge*

1. Replace Smart Tip cap after completing treatment or prior to exchanging a Cartridge. While wearing **protective gloves**, point display away from user, patient, and bystanders. Angle the Smart Tip up at 45° and slide Cartridge door release towards display end.



2. Grip door near display and open to vent N_2O until hissing stops. **Keep hand away from door hinge while Cartridge is venting as exhausting N_2O is very cold**

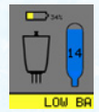
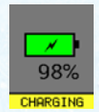
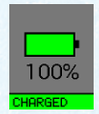
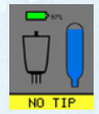
3. Open door fully and remove spent Cartridge



Exercise caution when removing Cartridge as it may be very cold

* IMPORTANT: Ensure that a Smart Tip is always attached to the Handpiece when inserting or removing a Cartridge

VI. LCD display messages

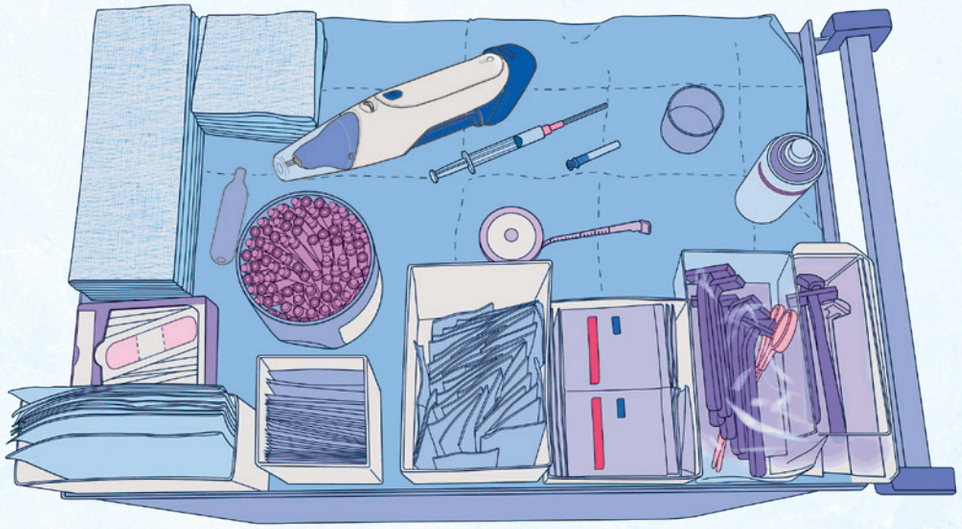
Message	Display*	Notes
LOW BATTERY on yellow field		Note: Yellow battery bar also flashes. Message is displayed when battery charging is recommended.
RECHARGE BATTERY on yellow field		Note: Red battery bar also flashes. Message is displayed when battery is too depleted to allow treatment cycles.
BATTERY CHARGING on yellow field		This display will only appear if Handpiece is receiving power from Charging Dock. Number shows current charge state of battery. Light bar on charger will appear during charging.
BATTERY CHARGED on green field		Light bar on charger will appear green at end of charging.
REPLACE CARTRIDGE on yellow field		Cartridge shows minimum fill level and no cycle count. If Cartridge is removed, empty Cartridge icon flashes on and off.
CARTRIDGE EXPIRED on yellow field		Message is displayed if Cartridge has been left in the Handpiece too long.
TIP ERROR on yellow field		Message is displayed if the tip is detected but is malfunctioning.
NO TIP on yellow field		Tip icon flashes on and off. Cartridge icon will not display a cycle count (as count is tip-dependent). Blue cryogen level in icon will reflect current state.
TIP USE EXCEEDED on yellow field		Message is displayed if no more cycles are allowed from this particular tip.

Message	Display*	Notes
PREPARING FOR CYCLE on yellow field		Message is displayed when system is warming up the cryogen Cartridge prior to allowing a treatment cycle.
READY FOR CYCLE on green field		Number in Cartridge indicates the number of cycles remaining in the Cartridge for the currently attached Tip. Cartridge number flashes for 2 or fewer remaining cycles. Blue cryogen level in Cartridge drops as cryogen is used up.
CYCLE IN PROGRESS on green field		Number in clock indicates number of seconds remaining in current treatment cycle.
CYCLE COMPLETE on green field		This image is displayed for a few seconds, then display reverts to main display (with tip and Cartridge images).
CYCLE STOPPED on yellow field		Message is displayed if user stops a cycle by pressing the Main Button while a cycle is in progress.
TILT UP on yellow field		Message is displayed when angle of Handpiece is not vertical enough for treatment. Message is only displayed during treatment cycle.
SYSTEM FAULT on red field		Message is displayed when a critical failure with system is detected such that treatment cycles are not allowed. See User Guide for next steps.

*Display is representative

Treatment and patient preparation

Supplies



iovera° SYSTEM COMPONENTS:

- iovera° Handpiece
- iovera° Smart Tips
- iovera° Cartridges

ADDITIONAL SUPPLIES:

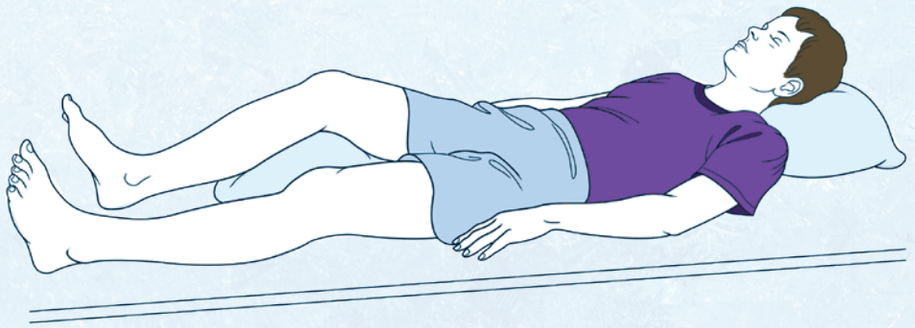
- Measuring tape
- Gloves
- Syringes
- Pillow
- Local anesthetic
- Antiseptic
- Surgical marker/sterile pen
- Alcohol prep pads
- Gauze/bandages
- Razors (optional)
- Ethyl chloride spray (optional)

KEY REMINDERS:

- **Be cognizant of expiration dates on Smart Tips and Cartridges**
- **Do not leave Cartridge in system for more than 3 hours**

Patient preparation

- **Instruct patient to wear loose-fitting clothing (shorts) to treatment**
- **Obtain written consent**
- **Pre-treatment pain and mobility assessment**
  - Ask patient to describe pain
  - Have patient perform activities that reproduce pain
  - Using Numeric Pain Rating Scale, ask patient to rate pain from 0 to 10
  - Palpate joint and mark painful sites
  - Document all findings
- **Set patient expectations**
  - Explain what to expect
  - Sensation type (burning, tingling, pins and needles)
  - Intensity level (mild, moderate, strong)
  - Location and Direction (down/across front of knee, inside of knee)Provide instructions for post-treatment care
- **Post-treatment instructions**
  - Ask patient to describe pain and perform activities that reproduce pain
  - Compare against pre-treatment baseline Numeric Pain Rating Scale
  - Reassess marked palpable pain locations
  - Document all findings



Treatment guide: Smart Tip 2309
Landmarks for superficial genicular nerves

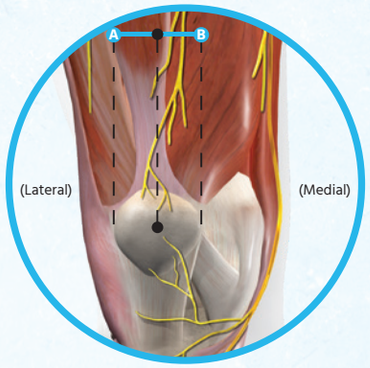
Drawing treatment lines for anatomical landmark technique

AFCN: anterior femoral cutaneous nerve

Anterior superior knee pain

1. Find and mark the center of the patella
2. Measure (in cm) from mid-patella to the inguinal crease; calculate 1/3 of that distance
3. From mid-patella, measure the 1/3 calculation point and mark the thigh
4. Draw vertical dotted lines from the medial and lateral patellar borders to level with the 1/3 mark
5. Draw a horizontal line between the vertical dotted lines

This is your AFCN treatment line.



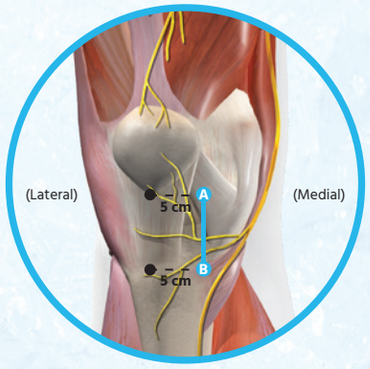
Treatment (right knee pictured)
Treat along the entire line.

ISN: infrapatellar branch of the saphenous nerve

Anterior inferior knee pain

1. Mark the inferior pole of the patella; draw a horizontal dotted line 5 cm medially
2. Mark the inferior point of the tibial tuberosity; draw a horizontal dotted line 5 cm medially
3. Draw a vertical line between these two dotted lines

This is your ISN treatment line.



Treatment (right knee pictured)
Treat along the entire line.

Use of device in treatment

A Attach Smart Tip as shown in system setup (IV A). Insert a new Cartridge as shown in system setup (V)

Wait for system to indicate Ready

B **1.** Removing Smart Tip Cap: Hold Handpiece with Tip pointing away from you, pinch top and bottom of Cap, pull Cap away from your body

2. Insert needles into treatment site

3. Ensure even skin warmer contact with skin

4. Press button to start treatment

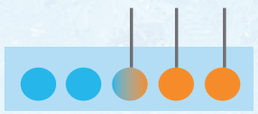
C

Display indicates when cycle is complete

Treatment using Smart Tip 2309

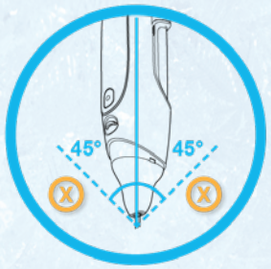
- Treatment area should be flat (knee extended)
- Cleanse skin with antiseptic solution of choice
- Anesthetize the skin
  - Apply anesthetic as superficially as possible into subcutaneous tissue to prevent displacing the target nerve(s) and to prevent a false block
  - Use shallow injections (wheals) along treatment line
  - Massage and press out into the tissue
  - Use only as much as needed for patient comfort
  - If using ethyl chloride spray, follow manufacturer's instructions
- Stabilize skin by stretching above and below the treatment line when inserting and removing Smart Tip
- Insert Smart Tip perpendicular to skin
  - With excess adipose tissue, skin warmer may not reach the skin despite appearing as such. Spread the skin and apply additional downward pressure with the Handpiece
  - For thin patients, it may be necessary to pinch the skin up around insertion point
- Press and release button to begin cycle
- A green checkmark indicates cycle is complete and Smart Tip may be removed from patient
- Overlap next cycles by one insertion site
- Treat along the treatment line until target nerve is blocked
- Verify efficacy by comparing post-treatment to baseline
  - Areas sensitive to palpation at baseline
  - Accomplishment of painful activities

1st insertion site



2nd insertion site
overlaps the 1st insertion site

Treatment considerations



- Treat in an even, straight line
- Treat across the entire treatment line
- Keep Handpiece upright (<45 degree vertical from ground)
  Note: When treating ISN externally rotate patient's leg
- Maintain skin warmer contact with epidermis throughout entire treatment cycle to avoid thermal injury
- Patients may feel altered sensation (paresthesia, tapping, pressure) when treating targeted nerve
- If a cycle is accidently started outside of the skin, press and release button again and the device will reset

Post-treatment

Patient evaluation

- Ask patient to describe pain and perform activities that reproduce pain
- Compare against pre-treatment baseline Numeric Pain Rating Scale
- Reassess marked palpable pain locations
- Document all findings

System care

- With the Smart Tip still attached, remove the Cartridge per the previous instructions
- Replace the Storage Cap
- **Never leave a Cartridge in system for more than 3 hours**
  - If this occurs, the Cartridge will expire

System cleaning

- Use multiple, presaturated 70% isopropyl alcohol wipes
- Keep surface damp for 5 minutes
- Pay close attention to all surface indentations
- Never submerge the Handpiece or Charging Dock

System storage

- Attach the Storage Cap
- Return the Handpiece to the Charging Dock
- Store Handpiece on Charging Dock when not in use
- Never store the system with a Cartridge installed

System maintenance

- There are no user-serviceable parts
- If you suspect a system issue, please contact Product and Technical Support at 1-855-793-9727 or medinfo@pacira.com

Customer service contact

ioveraCS@icsconnect.com

1-800-442-0989

Incident reporting

Any malfunction of the iovera° device or a suspected adverse event should be reported immediately to Pacira BioSciences, Inc.

Device Malfunction:

Notify your Pacira Treatment Solutions Manager or Clinical Education Manager. If unavailable, call 1-855-793-9727 or email medinfo@pacira.com.

Suspected Adverse Event:

Call 1-855-793-9727 or email drugsafety@pacira.com.

You may be asked to provide the following information:

- What issues were encountered?
- How was the product being used?
- What is the Handpiece Serial Number? The Smart Tip Serial Number?
- When is the next scheduled treatment day?
- Is there another Handpiece on site?
- Was there any remedial action taken/necessary?
- What is the contact information for your facility?
- Relevant patient information and date of occurrence

Unpackaging Video with detailed system setup instructions:

iovera° SYSTEM SETUP Gen 2 System Guide

Full User Guide:

Troubleshooting

1. **Handpiece LCD is not on**
   - Press the Main Button for at least 5 seconds to wake up device from standby mode
   - If this does not resolve the issue, place the Handpiece on the Charging Dock and check the battery status to ensure it has sufficient battery charge
   - If the issue is still not resolved, perform a hard reset by opening the data port cover and inserting the end of a paper clip into the pinhole for several seconds to reset the system
   - If the issue continues to persist, contact Pacira Technical Support at 855-793-9727
2. **Cycle won't start/ system indicates no Smart Tip is present**
   - Remove and replace the Smart Tip. Confirm that the system detects that a Smart Tip is present
   - If the issue persists, contact Pacira Technical Support at 855-793-9727
3. **Cycle won't start/ system indicates Smart Tip error**
   - Refer to the "iovera° Smart Tip Errors" section of the System User Guide
   - NOTE: The device must be turned off and back on to clear the error
4. **Handpiece displays a System Fault error with a red background**
   - Refer to the "iovera° System Fault Errors" section of the System User Guide
5. **System indicates a low battery condition with a yellow background**
   - Battery power is low and only a few cycles remain
6. **Handpiece won't charge or wake up while in Charging Dock**
   - Check the dock power and make sure the light bar on the dock is illuminated. Make sure the dock light changes color from green to blue when the Handpiece is placed on the dock. If not, make sure the Handpiece charging contacts are positioned correctly with the pins on the dock
   - If the issue persists, perform a system reset by opening the USB access cover and using a paperclip to press the reset button for at least 1 second. Then place the Handpiece on the dock for 2 to 3 hours
   - If the issue persists, contact Pacira Technical Support at 855-793-9727
7. **Handpiece is leaking cryogen (may hear hissing)**
   - Contact Pacira Technical Support at 855-793-9727 with details
8. **System indicates treatment was canceled**
   - The treatment cycle was canceled (button was pressed or an error was detected). Wait until the system indicates the cycle is complete before attempting to remove the Smart Tip from the patient
9. **Cartridge expired on Charging Dock**
   - Cartridges leak nitrous over time when a Cartridge is left in the Handpiece. If left for over 3 hours, replace the Cartridge

Indication and important safety information

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

For more information, please visit **www.iovera.com.**

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