KCI
AN ACELITY COMPANY

PREVENA™ 125 THERAPY UNIT WITH PREVENA™ 45ML CANISTER AND ACCESSORIES

INSTRUCTIONS FOR USE

FOR CLINICIANS ONLY

Rx Only

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INSTRUCTIONS FOR USE PREVENA 125™ THERAPY UNIT

KCI customer contact information is located in the back of this guide.

PRODUCT DESCRIPTION

The PREVENA™ 125 Therapy Unit, Canister and associated accessories are components of the PREVENA™ Incision Management System, which can be used with either PREVENA PEEL & PLACE™ Dressings or PREVENA CUSTOMIZABLE™ Dressings.

INDICATION FOR USE AND LIMITATIONS

PREVENA™ 125 and PREVENA PLUS™ 125 Therapy Units manage the environment of closed surgical incisions and remove fluid away from the surgical incision via the application of -125mmHg continuous negative pressure. When used with legally marketed compatible dressings, PREVENA™ 125 and PREVENA PLUS™ 125 Therapy Units are intended to aid in reducing the incidence of seroma; and in patients at high risk for post-operative infections, aid in reducing the incidence of superficial surgical site infection in Class I and Class II wounds.

- The device is not intended to treat surgical site infection or seroma.
- Safety and effectiveness in pediatric population (<22 years old) have not been evaluated.
- Safety and effectiveness in Class III (Contaminated) and Class IV (Dirty/Infected) wounds have not been demonstrated. Furthermore, Class IV surgical wounds are not expected to be closed primarily, and the subject device should only be used on closed surgical incisions.
- The device has not been demonstrated to reduce deep incisional and organ space surgical site infections.
- The device has not been demonstrated to be effective in reducing the incidence of surgical site infection and seroma in all surgical procedures and patient populations; therefore, the device may not be recommended for routine use to reduce the incidence of surgical site infection and seroma.
- Please refer to the 'Summary of Clinical Information' section for the specific surgical procedures and patient populations included in the clinical studies. Surgeons should continue to follow the 'Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection'[2] and the 'American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines'[1] for best practices in preventing surgical site infection.

Clinical studies have been conducted on KCI Negative Pressure Incision Management Systems. Refer to the **Summary of Clinical Information** and the **Bibliography of Published Studies** in the back of this guide.

CAUTION: The PREVENA™ Incision Management System should be applied and removed only by qualified physicians or nurses.

As with any prescription medical device, failure to carefully read and follow all instructions and safety information prior to use may lead to improper product performance and could result in failure of the wound to heal.

The PREVENA™ Therapy System dressings and therapy unit canisters are disposable and are for single use only. Re-use of disposable components may result in wound contamination, infection and/or failure of the wound to heal.

OPTIMUM USE CONDITIONS

For maximum benefit the PREVENA™ Therapy System should be applied immediately post surgery to clean surgically closed wounds. It is to be continuously applied for a minimum of two days up to a maximum of seven days. It can transition home with the patient.

The PREVENA™ Therapy System will not be effective in addressing complications associated with the following:

- ischemia to the incision or incision area
- untreated or inadequately treated infection
- inadequate hemostasis of the incision
- cellulitis of the incision area

The PREVENA™ Therapy System should not be used to treat open or dehisced surgical wounds. The V.A.C.® Therapy System should be considered for treatment of these wounds.

The PREVENA™ Therapy System should be used with caution in the following patients:

- patients with fragile skin surrounding the incision as they may experience skin or tissue damage upon removal of the PREVENA™ Dressing
- patients who are at an increased risk of bleeding from the incision associated with the use of anticoagulants and/or platelet aggregation inhibitors

WARNINGS

The PREVENA™ Therapy System is not intended to manage open or dehisced wounds.

Bleeding: Before applying the PREVENA™ Therapy System to patients who are at risk of bleeding complications due to the operative procedure or concomitant therapies and/or co-morbidities, ensure that hemostasis has been achieved and all tissue planes have been approximated. If active bleeding develops suddenly or in large amounts during therapy, or if frank blood is seen in the tubing or in the canister, the patient should leave the PREVENA™ Dressing in place, turn off the therapy unit and seek immediate emergency medical assistance.

Infected Wounds: As with any wound treatment, clinicians and patients/caregivers should frequently monitor the patient's wound, periwound tissue and exudate for signs of infection or other complications. Some signs of infection are fever, tenderness, redness, swelling, itching, rash, increased warmth in the wound or periwound area, purulent discharge or strong odor. Infection can be serious, and can lead to complications such as pain, discomfort, fever, gangrene, toxic shock, septic shock and/or fatal injury. Some signs or complications of systemic infection are nausea, vomiting, diarrhea, headache, dizziness, fainting, sore throat with swelling of the mucus membranes, disorientation, high fever, refractory and/or orthostatic hypotension or erythroderma (a sunburn-like rash). Silver in the interface layer of the PREVENA™ Dressing is not intended to treat infection, but to reduce bacterial colonization in the fabric. **If infection develops, the PREVENA™ Therapy System should be discontinued until the infection is treated.**

Allergic Response: The PREVENA™ Dressing has an acrylic adhesive coating and a skin interface layer with silver, which may present a risk of an adverse reaction in patients who are allergic or hypersensitive to acrylic adhesives or silver. If a patient has a known allergy or hypersensitivity to these materials, do not use the PREVENA™ Therapy System. If any signs of allergic reaction, irritation or hypersensitivity develop, such as redness, swelling, rash, hives, blisters or significant pruritus, patient should consult a physician immediately. If bronchospasm or more serious signs of allergic reaction appear, the patient should turn off the therapy unit and seek immediate emergency medical assistance.

Defibrillation: Remove the PREVENA™ Dressing if defibrillation is required in the area of dressing placement. Failure to remove the dressing may inhibit transmission of electrical energy and/or patient resuscitation.

Magnetic Resonance Imaging (MRI): All KCI therapy units, including the PREVENA™ 125 Therapy Unit, are MR unsafe. Do not take therapy units into the MR environment. The PREVENA™ Dressings can typically remain on the patient with minimal risk in an MR environment Interruption of PREVENA™ Therapy during MRI may reduce the effectiveness of PREVENA™ Therapy. The PREVENA™ Therapy System Dressings pose no known hazards in an MR environment with the following conditions of use: static magnetic field of 3 Tesla or less, spatial gradient field of 720 Gauss/cm or less and maximum whole-body-averaged specific absorption rate (SAR) of 3W/kg for 15 minutes of scanning.

Diagnostic Imaging: The PREVENA™ Dressing contains metallic silver that may impair visualization with certain imaging modalities.

Hyperbaric Oxygen Therapy (HBO): Do not take therapy units or PREVENA™ Dressings into a hyperbaric oxygen chamber. They are not designed for this environment and **should be considered a fire hazard**. If the PREVENA™ Therapy System is reinitiated after HBO treatment, do not readhere the same dressing; a new dressing must be applied.

Canister Full: If at any time while using the PREVENA™ 125 Therapy Unit the canister becomes full of fluid other than blood, indicated by a therapy unit alert or visual inspection, the patient should turn off the therapy unit and contact the treating physician.

Standard Operation: Do not use accessories or materials not labeled for use with the PREVENA™ 125 Therapy Unit. For a list of acceptable dressings with which the PREVENA™ 125 Therapy Unit may be used, see the **Product Description** section.

PRECAUTION

Standard Precautions: To reduce the risk of transmission of bloodborne pathogens, apply standard precautions for infection control with all patients, per institutional protocol, regardless of their diagnosis or presumed infection status.

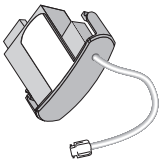
PREVENA™ DRESSING APPLICATION INSTRUCTIONS

NOTE: While the concomitant use of surgical drains is allowable with the PREVENA™ Incision Management System, the system must not be used as an outlet or reservoir for the drain.

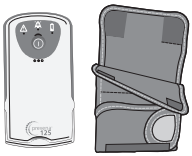
Application instructions for the PREVENA PEEL & PLACE™ and PREVENA CUSTOMIZABLE™ Dressings are provided in the dressing cartons. Refer to those instructions for complete dressing application information.

CAUTION: Do not use the PREVENA™ 125 Therapy Unit with V.A.C.® Dressings or V.A.C.® Therapy System accessories.

PREVENA™ 125 THERAPY UNIT COMPONENTS



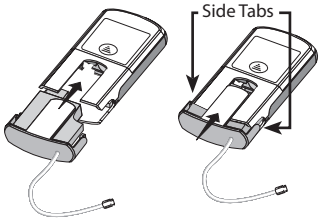
PREVENA™ 45ml Canister - a sterile reservoir for collection of wound fluids



PREVENA™ 125 Therapy Unit - delivers negative pressure to the surgical area. The unit is battery powered. The non-sterile PREVENA™ 125 Therapy Unit Carrying Case is provided to facilitate patient mobility.

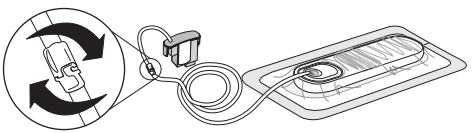
USING THE PREVENA™ DRESSING WITH THE PREVENA™ 125 THERAPY UNIT

CONNECTING THE PREVENA™ DRESSING TO PREVENA™ 125 THERAPY UNITS



1. Remove the PREVENA™ 45ml Canister from the sterile package. Do not use if package has been torn or the sterile seal has been compromised.

2. Insert the canister into the PREVENA™ 125 Therapy Unit and slide inward until canister clicks. Canister is fully inserted when the side tabs are flush with the body of the therapy unit.

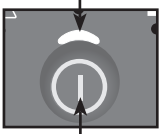


3. Connect the dressing tubing to the canister tubing by twisting the connectors until they lock.

4. Begin therapy.

BEGINNING THERAPY

Green Light



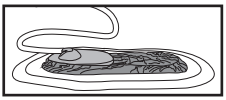
On/Off Button

1. Press and hold the On/Off button for two seconds; an audible beep will confirm that therapy is on. A green light on the front of the unit indicates that therapy is on.

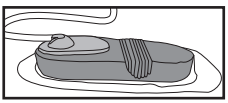
   NOTE: Pressing the On/Off button begins the 192 hour (eight day expected service life) life cycle of the therapy unit. Turning the therapy unit off stops the life cycle counter. Turning the therapy unit on for purposes other than delivering therapy reduces the life cycle of the therapy unit. It is not recommended to press the On/Off button until therapy is ready to begin.

   NOTE: To turn therapy unit off, press and hold the On/Off button for five seconds.

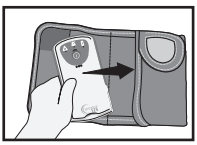
2. With therapy on, assess dressing to ensure integrity of seal.



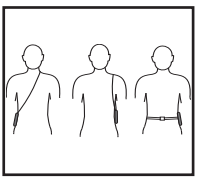
- The dressing should have a wrinkled appearance and the foam bolster should be compressed.



- If the foam bolster is not compressed or the therapy unit alerts, see the **PREVENA™ 125 Therapy Unit Indicators and Alerts** section and the **Correcting a Leak Condition** section.



3. Place the therapy unit into the PREVENA™ 125 Therapy Unit Carrying Case. Make sure the display is visible through the opening in the carrying case when the front flap is lifted.



4. The PREVENA™ 125 Therapy Unit Carrying Case has an integrated belt loop and a separate adjustable strap to allow for versatile positioning.

   CAUTION: Do not wrap carrying case strap or dressing tubing around neck.

DURATION OF PREVENA™ THERAPY

- Therapy should be continuous for a minimum of two days up to a maximum of seven days.
- The PREVENA™ 125 Therapy Unit will automatically time-out after 192 hours (eight days) of cumulative run time.
- Patients should be instructed to contact their treating physician and not to turn therapy off unless:
  - advised by the treating physician
  - bleeding develops suddenly or in large amounts during therapy
  - there are signs of allergic reaction or infection
  - the canister is full of fluid
  - batteries need to be changed
  - system alerts must be addressed
- Patient should be instructed to contact the treating physician if therapy unit turns off and cannot be restarted before therapy is scheduled to end, or if canister becomes full of fluid.
- At end of therapy, patient should return to treating physician for dressing removal.

PREVENA™ 125 THERAPY UNIT INDICATORS AND ALERTS

Caution Indicator

Visual Alerts - Solid LEDs cannot be turned off by the user. Visual alerts will only stop when the alert condition has been corrected.

Audible Alarm (Muted)

Audible Alerts - Repeated beeps (which in some cases will increase in volume) can be temporarily muted (paused) by pressing the On/Off button once. The audible alert will re-occur unless the alert condition has been corrected.

The PREVENA™ 125 Therapy Unit will provide audible and visual alerts as shown below.

Battery Level

If alert conditions cannot be corrected, patient should contact treating physician. For further product support see **Customer Contact Information** section.

Leak Alert

Audible Alert can be muted for eight hours.

One beep, one solid yellow light.
See **Correcting a Leak Condition** section.

When a leak condition is corrected the therapy unit will cancel alert. There may be a delay between when the leak is corrected and when the alert is discontinued.

Canister Full Alert

Audible Alert can be muted for one hour.

Two beeps, one solid yellow light.

Visually inspect canister. If full or near full, turn therapy unit off and call the treating physician immediately.

Low Battery Alerts

Audible Alert can be muted for one hour.

LOW - One slow beep, one solid yellow light. Be prepared to change batteries.

CRITICAL - One beep, repeating rapidly, increasing in volume, one solid yellow light. Change batteries immediately.

Battery replacement will cancel the alert. See **Battery Replacement on the PREVENA™ 125 Therapy Unit** section.

System Error Alert

Audible Alert can be muted for one hour.

One beep, repeating rapidly, increasing in volume, two solid yellow lights. Turn the unit off and then on again.

If alert continues, notify the treating physician.

Device Lifecycle Expired

Three solid yellow lights. If the lifecycle expires while therapy unit is on, a beep will sound for 15 seconds and then automatically shut off.

If the therapy unit is off, has exceeded the run time, and an attempt is made to turn the therapy unit on, the therapy unit will alert for three seconds and automatically shut off. Call the treating physician.

PREVENA™ 125 THERAPY UNIT VISICHECK™ FEATURE

Best

Good

To ensure proper application of the PREVENA™ Dressing, the PREVENA™ 125 Therapy Unit provides the VISICHECK™ Feature.

By double pressing the On/Off button, the unit will display the leak rate of the system for three seconds.

To prevent nuisance leak alarms, the leak rate status should be "Best" (one light illuminated) or "Good" (two lights illuminated).

Marginal

If the VISICHECK™ Feature indicates a "Marginal" (three lights illuminated) leak rate condition, refer to the following **Correcting a Leak Condition** section for methods of reducing the leak rate of the system. The system leak rate is calculated every seven seconds. If a corrective action is taken to reduce a leak rate, use the VISICHECK™ Feature afterward to verify the leak rate condition was corrected.

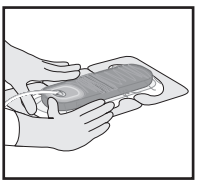
When the therapy unit detects a leak:

- A visual and audible leak alert will activate. See the **PREVENA™ 125 Therapy Unit Indicators and Alerts** section.
- Therapy unit will turn on more frequently.

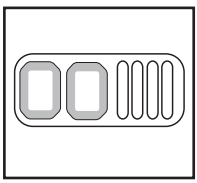
CORRECTING A LEAK CONDITION

(Illustrations in the steps below show PREVENA PEEL & PLACE™ Dressing - 20cm)

See the PREVENA™ Dressings Clinician Guide for additional information.

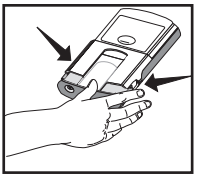


1. With therapy unit on, slowly press firmly around dressing edge to ensure good contact between adhesive and skin.

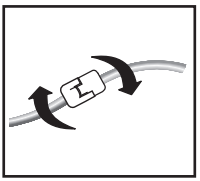


2. If a leak is identified, use PREVENA™ Patch Strips (located in dressing package) to help seal leaks around dressing. If large wrinkles are present, place patch strips so they run in line along the length of the wrinkle and not across the wrinkle.

Check Canister and Tubing Connection



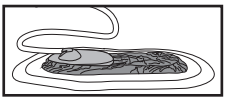
1. Ensure canister is securely locked in the therapy unit. When canister is installed, a distinct click will be heard indicating it has been properly installed. Side tabs on canister should be flush with unit.



2. Check tubing connectors to ensure they are fully engaged and locked.

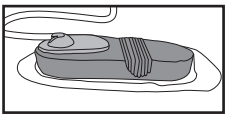
Indications That a Leak Condition Has Been Corrected

- Therapy unit will become quiet, running only intermittently.
- Audible leak alert will stop; visual alert will turn off. There may be a brief delay between when the leak is corrected and the alert is discontinued.
- The PREVENA™ Dressing will be compressed.



Dressing compressed - system pressure acceptable.

✓



Dressing not compressed - system pressure not acceptable. Return to the **Correcting a Leak Condition** section to continue pressure correction steps.

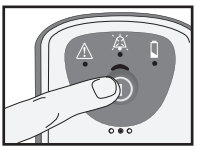
✗

PREVENA™ 125 THERAPY UNIT DISPOSAL

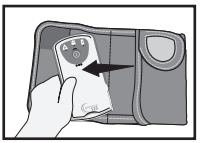
At the end of therapy, the patient should return the PREVENA™ 125 Therapy Unit to the physician for disposal. Dispose of all waste according to local requirements. Improper disposal may run the risk of regulatory non-compliance.

BATTERY REPLACEMENT ON THE PREVENA™ 125 THERAPY UNIT

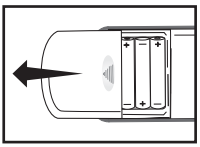
Battery replacement should be done as quickly as possible after a low battery alert to prevent therapy down time.



1. Turn therapy unit off (press and hold On/Off button for five seconds).



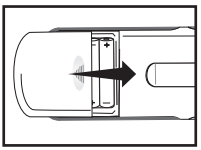
2. Remove therapy unit from carrying case. Turn the therapy unit over to expose the back side of the unit.



3. Locate the battery door and push to slide open. Install three AA batteries (lithium batteries are recommended for optimal performance) into the battery compartment.

NOTE: Always replace with new batteries. Do not mix new batteries with used batteries.

NOTE: The inside of the battery compartment is stenciled with "+" positive and "-" negative to aid in proper battery installation.



4. Close battery door.

5. Return therapy unit to carrying case.

6. Turn therapy unit on to resume therapy (press and hold On/Off button for two seconds).

CANISTER REMOVAL AND REPLACEMENT

1. Turn therapy off.
2. Remove therapy unit from carrying case, if in use.
3. Press tabs on canister to remove used canister from therapy unit.
4. Disconnect canister tubing from dressing tubing.
5. Install new canister (see the PREVENA™ 125 Therapy unit Canister Installation section).
6. Reattach dressing tubing to canister tubing.
7. Turn therapy on.
8. Return therapy unit to carrying case if desired.

NOTE: Dispose of used canister according to institution and local environmental regulations.

INSTRUCTIONS FOR PATIENT

Review the following information with the patient prior to discharge. This information is summarized in the PREVENA™ Therapy System Patient Guide which must be provided to the patient at discharge.

DAILY USE

The PREVENA™ 125 Therapy Unit is portable and small enough that it may be worn beneath clothing during normal patient activities as approved by the treating physician.

CAUTION: Advise patient to NOT SUBMERGE therapy unit or dressing in liquid and to ensure therapy unit is not pulled into a tub or sink where it may become submerged.

CAUTION: The PREVENA™ 125 Therapy Unit is a medical device not a toy. Keep away from children, pets and pests as they can damage the dressing and therapy unit and affect performance. Keep therapy unit free of dust and lint.

SLEEPING

Instruct patient to:

- place the therapy unit in a position where tubing will not become kinked or pinched.
- ensure therapy unit will not be pulled off a table or fall to the floor during sleep.

SHOWERING AND BATHING

Advise patient of the following recommendations:

- Light showering is permissible, bathing is not.
- While showering, the device and dressing should be protected from prolonged direct spray and/or being submerged.
  - The PREVENA™ 125 Therapy Unit may be hung from a soap/shampoo holder or shower head if protected from prolonged direct spray.
  - Dressing may be exposed to common shower soaps and rinsed with indirect shower stream. Do not submerge dressing. Do not remove dressing.
- When towel drying, avoid disturbing or damaging dressing.

STRENUOUS ACTIVITY

Advise patient as to when and at what level physical activities may be resumed. It is recommended that patients avoid strenuous activity while using the therapy system.

CLEANING

Advise patient that the therapy unit and therapy unit carrying case can be wiped with a damp cloth using a mild household soap solution that does not contain bleach.

DEVICE DISPOSAL

At the end of therapy, the patient should return therapy unit to physician for disposal. Dispose of all waste according to local requirements. Improper disposal may run the risk of regulatory non-compliance.

SPECIFICATIONS

Storage Conditions

Temperature Range ..... - 4˚F (-20˚C) to 140˚F (60˚C)
Relative Humidity Range ..... 15% - 95%, non-condensing

Operating Conditions

Temperature Range ..... 41˚F (5˚C) to 104˚F (40˚C)
Atmospheric Pressure Range ..... 1060 hpa (-1253 ft /-381.9 m)
(for Optimum Performance) to 700 hpa (9878 ft / 3010 m)
Expected Service Life ..... 8 days

Equipment not suitable for use in presence of flammable anesthetic mixture with air, oxygen or nitrous oxide.

The PREVENA™ Therapy System is classified as a Type BF applied part under IEC 60601-1.

IP24 - Protection against solid objects greater than 12.5 mm and against liquid water sprays for short periods of time.

All alerts are classified as low priority according to IEC 60601-1-8.

Conforms to IEC 60601-1, IEC 60601-1-6, IEC 62366, IEC 60601-1-8, IEC 60601-1-11.

CUSTOMER CONTACT INFORMATION

For questions regarding this product, supplies, maintenance or additional information about KCI products and services, please contact KCI or a KCI authorized representative, or:

In the US call 1-800-275-4524 or visit www.acelity.com

KCI USA, Inc. 12930 IH10 West, San Antonio, TX 78249

ELECTROMAGNETIC COMPATIBILITY

All electrical equipment may produce interference. If interference is suspected, move equipment away from sensitive devices or contact the manufacturer.

The PREVENA™ 125 Therapy Unit needs special precautions regarding EMC and needs to be installed and put into service according to the EMC information in the following tables.

<table>
<tr><th colspan="3">Guidance and manufacturer's declaration - electromagnetic emissions</th></tr>
<tr><td colspan="3">The PREVENA™ 125 Therapy Unit is intended for use in the electromagnetic environment specified below. The customer or user of the PREVENA™ 125 Therapy Unit should assure that it is used in such an environment.</td></tr>
<tr><td>Emission Test</td><td>Compliance</td><td>Electromagnetic environment</td></tr>
<tr><td>RF emissions
CISPR 11</td><td>Group 1</td><td>The PREVENA™ 125 Therapy Unit uses RF energy only for internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.</td></tr>
<tr><td>RF emissions
CISPR 11</td><td>Class B</td><td>The PREVENA™ 125 Therapy Unit is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.</td></tr>
<tr><td>Harmonic emissions
IEC 61000-3-2</td><td>Not applicable</td><td rowspan="2">Battery operated device</td></tr>
<tr><td>Voltage fluctuations / flicker emissions
IEC 61000-3-3</td><td>Not applicable</td></tr>
<tr><td colspan="3">WARNING: Use of this equipment adjacent to or stacked with other equipment should be avoided because it could result in improper operation. If such use is necessary, this equipment and the other equipment should be observed to verify that they are operating normally.</td></tr>
<tr><td colspan="3">Portable and mobile RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the PREVENA™ 125 Therapy Unit. Otherwise, degradation of the performance of this equipment could result. More precisely, the minimum recommended separation distance should be calculated from the equation applicable to the frequency of the transmitter, as noted in the guidance below.</td></tr>
<tr><td colspan="3">NOTE: This equipment has been tested and found to comply with the limits for medical devices to IEC 60601-1-2: 2014 4th edition. These limits and test levels are intended to provide reasonable safety with regard to electromagnetic disturbances when the device is used in a typical medical installation.</td></tr>
</table>

Guidance and manufacturer's declaration - electromagnetic immunity

The PREVENA™ 125 Therapy Unit is intended for use in the electromagnetic environment specified below. The customer or user of the PREVENA™ 125 Therapy Unit should assure that it is used in such an environment.

Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment Guidance
Electrostatic discharge (ESD) IEC 61000-4-2	± 6 kV contact ± 8 kV air	± 8 kV contact ± 15 kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Electrical fast transient/burst IEC 61000-4-4	± 2 kV for power supply lines ± 1 kV for input/output lines	Not Applicable	Battery operated device
Surge IEC 61000-4-5	± 1 kV line(s) to line(s) ± 2 kV line(s) to earth	Not Applicable	Battery operated device
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	<5 % U_r (>95 % dip in U_r) for 0.5 cycle 40 % U_r (60 % dip in U_r) for 5 cycles 70 % U_r (30 % dip in U_r) for 25 cycles <5 % U_r (>95 % dip in U_r) for 5 cycles	Not Applicable	Battery operated device
Power frequency (50Hz/60Hz) magnetic field IEC 61000-4-8	3 A/m	30 A/m 50Hz or 60Hz	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.

NOTE: U_r is the a.c. mains voltage prior to application of the test level.

Recommended separation distances between portable and mobile RF communications equipment and the PREVENA™ 125 Therapy Unit

The PREVENA™ 125 Therapy Unit is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the PREVENA™ 125 Therapy Unit can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the PREVENA™ 125 Therapy Unit as recommended below, according to the maximum output power of the communications equipment.

Rated maximum output power of transmitter in watts (W)	Separation distance according to frequency of transmitter m		
	150 kHz to 80 MHz $d = 1.2\sqrt{P}$	80 MHz to 800 MHz $d = 0.35\sqrt{P}$	800 MHz to 2.5 GHz $d = 0.7\sqrt{P}$
0.01	.12	.04	.07
0.1	.38	.11	.22
1	1.2	.35	.7
10	3.8	1.1	2.2
100	12	3.5	7

For transmitters rated at a maximum output power not listed above, the recommended separate distance d in metres (m) can be estimated using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

NOTE 1, At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.

NOTE 2, These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from surfaces, objects and people.

Guidance and manufacturer's declaration - electromagnetic immunity

The PREVENA™ 125 Therapy Unit is intended for use in an electromagnetic environment specified below. The customer or user of the PREVENA™ 125 Therapy Unit should assure that it is used in such an environment.

Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment Guidance
Conducted RF IEC 61000-4-6	3 Vrms 150 kHz to 80 MHz	Not Applicable	Portable and mobile RF communications equipment should be used no closer to any part of the PREVENA™ 125 Therapy Unit than the recommended separation distance calculated from the equation application to the frequency of the transmitter.
Radiated RF IEC 61000-4-3	3 V/m 80 MHz to 2.5 GHz	10 V/m 80 MHz to 2.7 GHz 80% AM at 1 kHz	Recommended separation distance $d = 0.35\sqrt{P}$ 80 MHz to 800 MHz $d = 0.7\sqrt{P}$ 800 MHz to 2.5 GHz Where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended separation distance in metres (m) Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey[1], should be less than the compliance level in each frequency range[2]. Interference may occur in the vicinity of equipment marked with the following symbol: 

NOTE 1, At 80 MHz and 800 MHz, the higher frequency range applies.

NOTE 2, These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

[1] Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the PREVENA™ 125 Therapy Unit is used exceeds the applicable RF compliance level above, the PREVENA™ 125 Therapy Unit should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating the PREVENA™ 125 Therapy Unit.

[2] Over the frequency range 150kHz, field strengths should be less than 3 V/m.

SUMMARY OF CLINICAL INFORMATION

A systematic literature review and associated meta-analyses were used to support the safety and effectiveness of the PREVENA™ Incision Management Systems over closed incisions in reducing the incidence of surgical site infections (SSIs) and seromas versus conventional wound dressings. The systematic literature search was performed using PubMed, The Cochrane Library, OVID, EMBASE, ScienceDirect, and alternative resources such as Google searches and QUOSA. Search terms included: ("negative pressure wound therapy" OR "negative pressure" OR "negative pressure therapy" OR "NPWT") AND ("PREVENA™" OR "ciNPT" OR "prophylactic NPWT" OR "preventative NPWT" OR "incision management" OR "incisional management" OR "closed incision negative pressure wound therapy" OR "closed incision negative pressure therapy").

Six (6) independent reviewers performed the study selection. Titles of manuscripts and abstracts that met the search criteria were logged and investigated for duplicates. The abstracts and manuscripts were assessed for inclusion and exclusion criteria (Table 2) by a subset of two (2) independent reviewers. When discordance was identified, the two reviewers deliberated until a consensus was reached.

Table 1. Inclusion and exclusion criteria for the systematic literature review

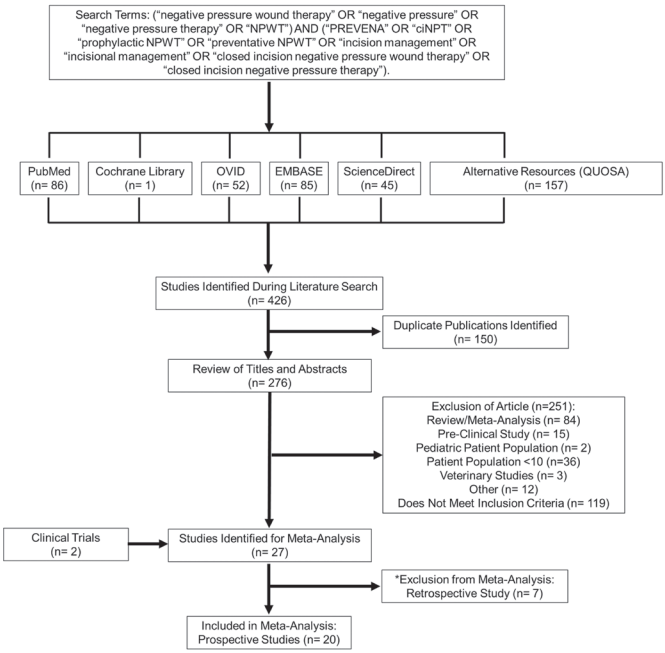
Inclusion Criteria	Exclusion Criteria
• Abstract or manuscript written in English • Published or unpublished study • Studies that compare the use of PREVENA™ Incision Management Systems using -125 mmHg pressure with legally marketed compatible dressing over closed incisions to conventional wound dressings (e.g., occlusive gauze dressing) • Contained an endpoint/outcome of surgical site infection (SSI), dehiscence, seroma, hematoma, or post-operative pain • Studies that followed the subjects/ patients for a minimum of 30 days for the SSI endpoint • Studies that followed the subjects/ patients for a minimum of 10 days for the seroma endpoint	• Meta-analysis studies • Pre-clinical studies (i.e., animal or bench science assessments) • Studies on pediatric patients (age <18 years) • Studies with less than 10 patients • Veterinary studies

For abstracts and manuscripts that met all the inclusion criteria and none of the exclusion criteria, they were examined critically to: i) assess whether containing reference of any other articles that meet the inclusion criteria and ii) extract study characteristics by at least two additional independent reviewers. Registered studies at ClinicalTrials.gov were also reviewed using the same search criteria for completed and terminated studies. The Cochrane Collaboration tool was used for assessing risk of bias.

A total of 426 studies resulted from the initial search. After 150 duplicate publications were removed, a total of 276 unique studies were assessed for inclusion. An additional 251 articles were excluded based on the pre-specified inclusion/exclusion criteria (Table 2), which was comprised of 64 review/meta-analysis, 15 pre-clinical studies, 2 pediatric patient populations, 3 veterinary studies, 12 other (protocol, technical report, subsequent study included in the meta-analysis, and comment), and 119 that did not meet all inclusion criteria. Lastly, seven (7) articles

identified as retrospective studies were removed to minimize bias and ensure only the highest level of evidence for the meta-analyses.

Figure 1. Summary of study selection for the meta-analyses



Ultimately, twenty (20) prospective studies, including two (2) KCI USA, Inc.-sponsored, unpublished clinical studies from ClinicalTrials.gov, were included in the meta-analyses for SSI and seroma characterization. A total of up to 6,403 evaluable patients were included in these meta-analyses with 1,367 in the PREVENA™ Incision Management Systems therapy (treatment) group and 5,036 in the conventional wound dressing (control) group.

The two (2) KCI USA, Inc.-sponsored, unpublished clinical studies from ClinicalTrials.gov can be summarized as follows:

NCT01341444 was a randomized, single center, interventional trial evaluating the safety and effectiveness of PREVENA™ Incision Management Systems on closed surgical incisions in subjects who had undergone open renal transplant surgery. Subjects were randomized 1:1 to receive either the PREVENA™ Therapy (treatment group) or a silver-impregnated occlusive dressing (control group). The purpose of the study was to compare surgical site complications, which include incisional fluid accumulation, dehiscence, and surgical site infections, between the PREVENA™ Therapy (treatment group) and conventional occlusive dressing (control group). The measurement outcome was the incidence of surgical site complications up to 30 days (+/- 2 days) post renal transplant surgery. Due to enrollment difficulties, KCI decided to terminate the study after enrolling 63 of 88 subjects. There were a total 28 subjects in the treatment group with 0 surgical site infections (0%) and 30 subjects in the control group with 2 surgical site infections (6.7%). Adverse events were reported: 25 subjects in the treatment group reported at least 1 adverse event and 24 subjects in the control group reported at least 1 adverse event. In the treatment group, 11 subjects reported at least 1 serious adverse event,

and in the control group, 13 subjects reported at least one serious adverse event. None of the reported adverse events were related to the PREVENA™ Therapy or conventional wound dressings used.

NCT02195310 was a randomized, multi-center, open label, interventional trial evaluating the safety and effectiveness of PREVENA™ Incision Management System (treatment group) on closed sternal midline incisions in patients at high risk for surgical site occurrences to a control group treated with conventional wound dressings, such as gauze with tape, pressure dressing with additional packing and tape, and silver-impregnated dressings. The purpose of the study was to assess the performance of PREVENA™ Incision Management System versus conventional wound dressings on closed median sternal incisions in subjects undergoing cardiac surgery. The primary endpoint was the incidence of surgical site infections (SSI) within 30 days postoperatively per CDC guidelines[21]. Five hundred twenty subjects were expected to be randomized 1:1. An interim data review was conducted on 257 subjects (128 PREVENA™ Subjects, 129 control subjects). The conditional power from this analysis was below 60%. Since the calculated SSI rates from the interim data review were outside the ranges of the sample size assumptions, the study was terminated early due to the lack of evidence to support the objectives and assumptions of the study. A final analysis was conducted on 299 subjects; 145 subjects for the PREVENA™ arm and 154 subjects for the control arm. The incidence rate of SSI in the PREVENA™ arm was 9.0% (13 subjects) and in the SOC arm was 10.4% (16 subjects). There was a 1.5-fold higher rate of SSI in control subjects with a Body Mass Index (BMI) >35 kg/m2. In the treatment group, 6/68 subjects with a BMI >35 kg/m2 had an SSI (8.8%) and 10/75 control subjects with a BMI >35 kg/m2 had an SSI (13.3%). Adverse events were reported. See 'Safety' section below for more detail. There were 286 (83.6%) of subjects that experienced at least one adverse event. In the treatment group, 83.8% subjects experienced an adverse event, while 83.4% of the control group subjects experienced an adverse event. There were 18 subjects that experienced a treatment related adverse event. In the treatment group, 16 (9.2%) subjects experienced a treatment related adverse event, while 2 (1.2%) subjects in the control group experienced a treatment related adverse event. There were 118 serious adverse events. In the treatment group, 36.4% of subjects experienced a serious adverse event, while 32.5% of the control subjects experienced a serious adverse event. There were no device-related serious adverse events in either the treatment or control group.

Surgical Site Infection (SSI)

Sixteen (16) prospective studies were included in the meta-analyses for SSI, which are summarized in Table 3 below. Nine (9) studies are randomized controlled trials, which are considered level I evidence. The remaining seven (7) studies are considered level II evidence, which include five (5) prospective treatment and historical controls studies and two (2) prospective observational studies that alternated patient assignment into either the treatment or control group (i.e., not randomized).

Table 3. Characteristics of studies included in the SSI meta-analyses

Study/Level of Evidence	Study Design	Surgical Procedure	Subjects' Risk Factors	Study Duration	Incisional Dressings Used	No. of Subjects	Treatment Duration Days
Cantero 2016[3] Level II	Prospective & Historical Controlled	Diverting loop ileostomy reversal	NR	30 Days	PREVENA™ System	17	5-7
					Conventional Wound Dressing	43	1-2, then daily
DiMuzio 2017[4] Level I	RCT	Elective vascular surgery†	BMI> 30kg/^{2}, pannus, immuno-suppressant disorder, reoperation, prosthetic graft, HbA_{1c}>8	30 Days	PREVENA™ System	59	NR
					Standard Gauze Dressing	60	NR
Grauhan 2013[6] Level II	Prospective Observational	Median sternotomy†	BMI Mean Treatment: 37kg/m^2, Control: 36kg/m^2, Diabetes; COPD; LVEF	90 Days	PREVENA™ System	75	6-7
					Conventional Wound Dressing	75	1-2
Grauhan 2014[7] Level II	Prospective & Historical Controlled	Median sternotomy	NR	30 Days	PREVENA™ System	237	6-7
					Conventional Sterile Wound Tape Dressing	3508	1-2
Gunatilake 2017[8] Level I	RCT	Cesarean delivery	BMI Mean Treatment: 46.3kg/m^2, Control: 46.8kg/m^2, Diabetes	42+/- 10 Days	PREVENA™ System	39	5-7
					Steri-strips, Sterile Gauze, Tegaderm™	43	1-2

Study/Level of Evidence	Study Design	Surgical Procedure	Subjects' Risk Factors	Study Duration	Incisional Dressings Used	No. of Subjects	Treatment Duration Days
Lavryk 2016[10] Level II	Prospective Observational	Reoperative colorectal surgery†	Diabetes; Hx of smoking	30 Days	PREVENA™ System	55	7 +/- 2
					Standard Gauze Dressing	101	NR
Lee AJ 2016[11] Level I	RCT	CABG with harvesting of GSV†	Diabetes; smoking; COPD; HTN; CHF; LVD; Aortic Stenosis; AF; CVD; Dyslipidemia; CKF; PVD; Hypothyroidism; Arthritis; Gout; Asthma	42 Days	PREVENA™ System	33	Up to 7
					Conventional Dry Dressing	27	NR
Lee K 2017[12] Level I	RCT	Femoral to distal artery bypass; femoral endarterectomy; femoral artery crossover, other†	BMI Mean Treatment : 29kg/m^2; Control: 29kg/m^2; Diabetes; Hx of smoking; COPD; CAD; LVD; HTN; CKD; Anticoagulation; Ischemic tissue loss	30 Days and 90 Days	PREVENA™ System	53	First day of discharge up to 8 days
					Standard Gauze Dressing	49	2
Matatov 2013[13] Level II	Prospective & Historical Controlled	Femoral cutdown for vascular procedures	BMI Mean Treatment: 26kg/m^2; Control 27kg/m^2; Diabetes; Hx of smoking; COPD; CAD; CHF; HTN; Renal insufficiency; Anemia	30 Days	PREVENA™ System	41 (52 wounds)	5-7
					Primapore or Dermabond Adhesive	49 (63 wounds)	3
NCT01341444 Level I	RCT	Renal transplant†	BMI Mean Treatment: 29.0kg/m^2, Control: 28.72kg/m^2; Diabetes; Tobacco use	30 Days	PREVENA™ System	28	5
					Standard Incisional Dressing	30	3

Study/Level of Evidence	Study Design	Surgical Procedure	Subjects' Risk Factors	Study Duration	Incisional Dressings Used	No. of Subjects	Treatment Duration Days
NCT02195310 Level I	RCT	Median sternotomy (elective cardiac surgery)†	BMI Mean Treatment: 35.64kg/m^2; Control: 35.27kg/m^2; Diabetes; Immunosuppressant Disorder; Hx of Smoking; Dialysis; Planned Bilateral Mamery Artery; Chronic Lung Disease; CKD; Previous Chest Wall Radiotherapy; Breast Size D; Age >75 years; LVEF<30%	30 Days	PREVENA™ System	145	4-7
					Traditional Sterile Wound Dressing (included gauze with tape, pressure dressings and silver impregnated dressings)	154	2-3
Newman 2017[14] Level I	RCT	Total hip or knee arthroplasty (elective revision)†	Blood thinners other than aspirin postoperatively, BMI ≥35kg/m^2; PVD; Diabetes mellitus; Current smoker; Hx of Prior Joint Infection; Current use of corticosteroids or immunomodulators; Hx or current cancer/ hematological malignancy; inflammatory arthritis; Renal failure or Dialysis; Malnutrition; Liver disease; Transplant status; HIV Infection	84 Days	PREVENA™ System	80	≥2
					Silver Impregnated Occlusive Dressing	80	7

Study/Level of Evidence	Study Design	Surgical Procedure	Subjects' Risk Factors	Study Duration	Incisional Dressings Used	No. of Subjects	Treatment Duration Days
Redfern 2017[18] Level II	Prospective & Historical Controlled	Total hip or knee arthroplasty (elective primary)	BMI Mean Treatment: 30.5kg/m^2; Control: 30.9kg/m^2; Diabetes; HTN; Hx of Cancer/Tumor; Arthritis; Myocardial Infarction/Heart Disease; Tobacco Use	60 Days	PREVENA™ System	192	6-8
					Traditional Gauze Dressing	400	Standard
Ruhstaller 2017[19] Level I	RCT	Unscheduled cesarean delivery†	Gestational Diabetes; Tobacco Use; HTN	28 Days	PREVENA™ System	67	3
					Telfa bandage with gauze and surgical tape	69	1
Sabat 2016[20] Level I	RCT	Vascular surgery involving groin incision	NR	120 Days	PREVENA™ System	30 wounds	5
					Gauze and Tegaderm™	33 wounds	NR
Swift 2015[21] Level II	Prospective & Historical Controlled	Cesarean section†	BMI ≥ 30kg/m^2; Diabetes; Chronic Hypertension; Preeclampsia; HELLP Syndrome; Rupture of the Membranes > 4 hours; Chorioamnionitis; Anticoagulation; Multiple Gestation	42 Days	PREVENA™ System	110	3
					Standard Sterile Dressing	209	NR

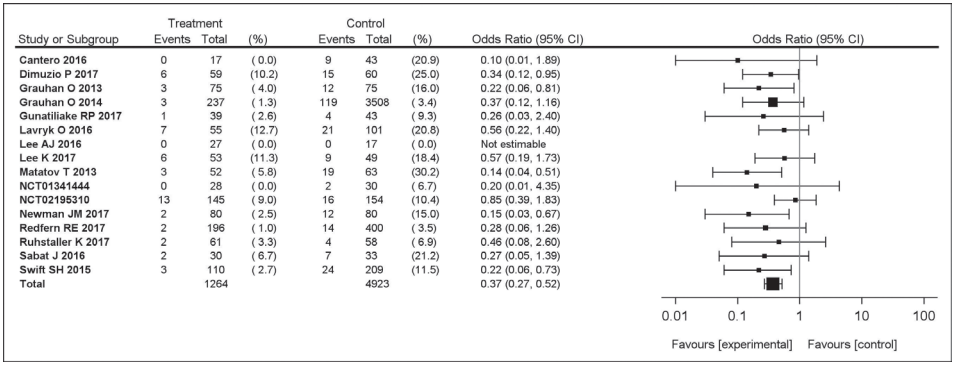
†Population or Procedure identified as high-risk for wound complication
*Oxford Centre of Evidence-Based Medicine
RCT = Randomized Controlled Trial
NR= Not Reported
ciNPWT= closed incision Negative Pressure Wound Therapy
BMI= Body Mass Index
HX= History
COPD= Chronic Obstructive Pulmonary Disorder
GERD= Gastroesophageal Reflux Disease
HTN= Hypertension
AF= Atrial Fibrillation
CVD= Cardiovascular disease
CKF= Chronic kidney failure
PVD= Peripheral vascular disease
LVD= Left ventricle dysfunction
CAD= Coronary artery disease
CKD= Chronic kidney disease
LVEF= Left ventricle ejection fraction
HIV= Human immunodeficiency virus
HELLP = Hemolysis, Elevated Liver enzymes, Low Platelet counts

Together, the sixteen (16) studies contained 1,264 evaluable patients receiving the PREVENA™ Incision Management Systems therapy (treatment group) and 4,923 patients receiving conventional wound dressings (control group). The conventional wound dressings used in each study can be found in Table 3 above and range from occlusive gauze dressings to silver-impregnated dressings. The primary endpoint in the studies was the incidence of surgical site infection in the treatment group compared to the control group for at least four weeks following surgery.

The treatment effect for each study was summarized using odds ratio (OR), which was calculated using the following formula:
OR = AD/BC, where
A = the number of subjects with SSI events for the treatment group
B = the number of subjects without SSI events for the treatment group
C = the number of subjects with SSI events for the control group
D = the number of subjects without SSI events for the control group

An OR of less than 1 suggests a favorable effect by the treatment in reducing SSI, whereas an OR greater than 1 suggests a favorable effect by the conventional wound dressings. The 95% confidence interval (95% CI) for the odds ratio is calculated based on the standard error of Log (OR). The individual study effects for SSI are summarized in Figure 2 below.

Figure 2. Forest plot of meta-analysis studies on surgical site infection (SSI)



Overall, there is an observable trend supporting a favorable effect by the PREVENA™ System in reducing the incidence of SSI. The SSI rates ranged from 0% to 30.2% for the control group in the individual studies, and the SSI rates in the treatment group ranged from 0% to 12.7%. However, the benefit of the PREVENA™ Systems varies considerably across different studies, possibly due to many confounding factors such as different surgical procedures and patient risk factors, which are further explored in subgroup analyses below. Additionally, there are many inherent limitations associated with meta-analyses and biases with each individual study, which are discussed in the 'Limitations of the Clinical Evidence' section below. Because of these confounding factors and limitations of the studies, statistical significance cannot be reliably inferred for the treatment effect based on the combined results from the sixteen (16) studies.

Subgroup analyses were performed to elucidate potential confounding factors contributing to the heterogeneity in the treatment effect. The subgroup analyses conducted were based on: i) Wound classification, ii) Infection depth (i.e., superficial, deep, organ space), iii) Risk factors for surgical site infection.

i. Wound classification

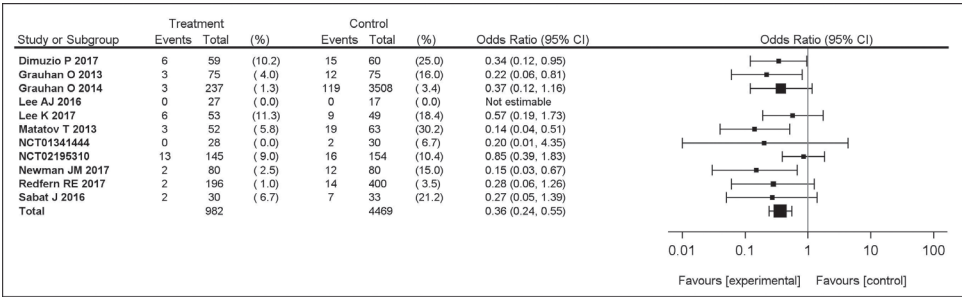
To analyze the effect of the PREVENA™ Incision Management Systems on SSI in wounds of different degrees of contamination, a wound classification designation following the Center for Disease Control and Prevention (CDC) guidelines (Table 4) was assigned to each study based on the surgical procedure performed and CDC wound classification definitions. Each study was reviewed, and a CDC wound classification was assigned by two individuals with appropriate medical and clinical trials background. All the same wound types in each study were treated the same unless the publication (e.g., Newman et. al.[14]) specifically gave guidance that some wounds were more severe in a particular subgroup (e.g., septic revisions). If the publication provided a CDC wound classification, the provided classification was utilized. One study (Lavryk et. al.[10]) was excluded as only patients with wound classifications of II, III and IV were enrolled and could not be separated into the individual wound classification groups.

Table 4. Surgical wound classifications and definitions[21]

Surgical Wound Classification	Definition
Class I/Clean	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.
Class II/Clean-contaminated	An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.
Class III/Contaminated	Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.
Class IV/Dirty-infected	Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

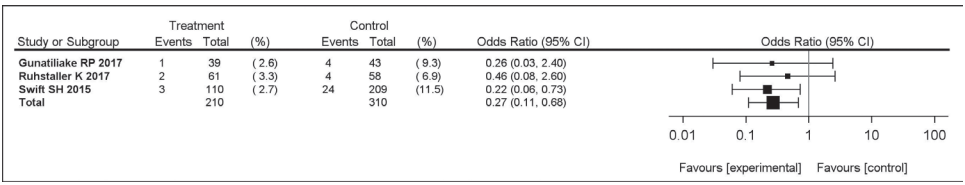
Eleven (11) of the sixteen (16) studies were determined to contain only Class I wounds, and these eleven (11) studies consist of approximately 88% of the total patient population for the overall SSI meta-analysis. The subgroup analysis results of Class I wounds (Figure 3) show a reduction in favor of the PREVENA™ Incision Management Systems therapy and are consistent with the overall reduction in SSI observed in Figure 2.

Figure 3. Forest plot of meta-analysis studies on surgical site infection in Class I wounds



Three (3) of the sixteen (16) studies were included in the subgroup analysis for Class II wounds, and these three (3) studies consist of approximately 8% of the total patient population for the overall SSI meta-analysis. The subgroup analysis results of Class II wounds (Figure 4) show a reduction in favor of the PREVENA™ Incision Management Systems therapy and are consistent with the overall reduction in SSI observed in Figure 2.

Figure 4. Forest plot of meta-analysis studies on surgical site infection in Class II wounds



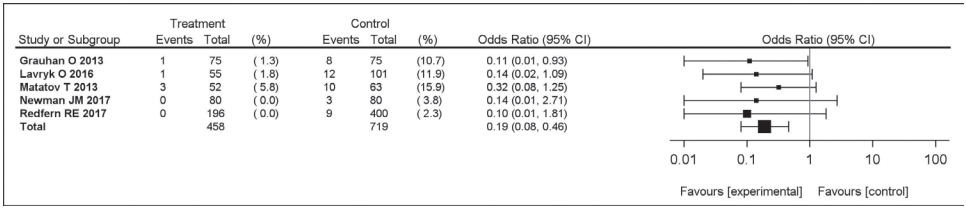
There was only one (1) study identified as having Class III wounds; therefore, a subgroup analysis for Class III wounds was not performed. In this study, no SSI events were reported for the treatment group (0 out of n=17) and nine (9) SSI events were reported for the control group (9 out of n=43). There were no studies containing Class IV wounds that could be isolated for analysis; therefore, a subgroup analysis was not performed for Class IV wounds. It should be noted that the PREVENA™ Systems are intended to be used only on closed incisions. As Class IV wounds are generally not expected to be surgically closed primarily, the PREVENA™ Systems should not be used on Class IV wounds.

ii. Infection depth

Surgical site infection (SSI) can be divided into three (3) subgroups: superficial incisional SSI, deep incisional SSI, and organ space SSI[9]. Superficial incisional SSI is infection that is limited to the skin or subcutaneous tissue of the surgical incision. Deep incisional SSI is infection that has spread to deep soft tissues such as fascial and muscle layers. Organ space SSI is deeper infection that involves any part of the anatomy that was opened or manipulated during the operation[9].

Five (5) of the sixteen (16) studies selected for SSI meta-analyses included information to stratify patient SSI events into superficial, deep, and organ space infections. Subgroup analyses examining the effect of the PREVENA™ Systems on different SSI locations were conducted based on these five (5) studies. Among the three subgroups, the PREVENA™ Systems demonstrated the greatest benefit in reducing superficial incisional SSIs (Figure 5). The reduction in superficial SSI appears to be greater than the SSI reduction in the overall data (Figure 2). There was little to no benefit of the PREVENA™ Systems in reducing deep incisional SSIs and organ space SSIs when compared to the control group.

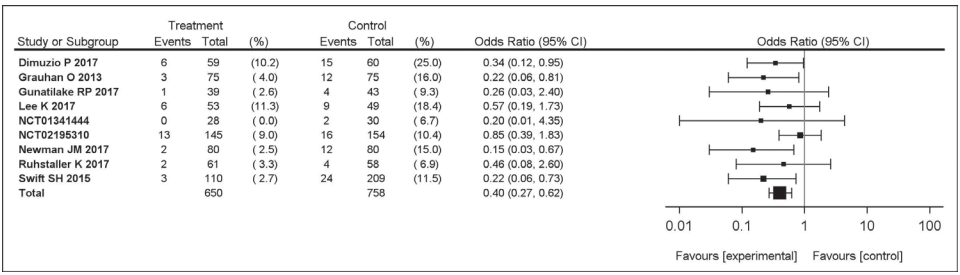
Figure 5. Forest plot of meta-analysis studies on surgical site infection in superficial incisional SSI



iii. Risk factors for surgical site infection

Patients having one or more co-morbidities are generally considered to be at higher risk for surgical site complications. High risk patients were defined in the selected studies as having one or more of the following co-morbidities: obesity (body mass index ≥30 kg/m2); diabetes; history of smoking; immune suppression or receiving drugs that can cause immune suppression, such as steroids, chemotherapeutic medications, and/or antimetabolites; malnutrition with a hydrated serum albumin of less than 3.0 grams/deciliter; neutropenia; preeclampsia; patients who have cardiac, pulmonary, liver or renal disease; history of previous surgery or radiation in the treatment area. Subjects' risk factors for each of the sixteen (16) studies are described in Table 3; however, some of the studies contain all comers with only a portion being high-risk patients. Upon further examination, nine (9) studies were determined to contain only high-risk patients. A subgroup analysis was performed on these nine (9) studies (Figure 6). As expected, the incidence of SSI, in both the treatment and control groups, is higher in high-risk patients (5.5% and 12.9%, respectively) compared to the overall study population (4.2% and 5.8%, respectively). Additionally, there appears to be a greater overall percentage reduction in SSI in high risk patients. Thus, while the reduction in SSI, as measured by odds ratio, in high risk patients does not appear to be significantly different than the reduction observed in the overall data (Figure 2), there is a greater clinical benefit of the PREVENA™ Systems in patients at high risk for surgical site infection based on a greater absolute percentage reduction in the incidence of SSI.

Figure 6. Forest plot of meta-analysis studies on surgical site infection in high risk patients



Together, the subgroup analyses on wound classification, infection depth, and patient risk factors for surgical site infection serve as the basis for granting the following Indications for Use:

When used with legally marketed compatible dressings, PREVENA™ 125 and PREVENA PLUS™ 125 Therapy Units are intended to aid in reducing the incidence of seroma and, in patients at high risk for post-operative infections, aid in reducing the incidence of superficial surgical site infection in Class I and Class II wounds.

Additional subgroup analyses for surgical site infection were performed based on surgical procedure risk factor, combination of surgical procedure and patient risk factors, and incision location. While the results from these subgroup analyses were reviewed, they did not serve as the basis for granting this De Novo request.

Seroma

Seven (7) prospective studies were included in the meta-analysis for seroma, which are summarized in Table 5 below. Five (5) studies are randomized controlled trials, which are level I evidence. The remaining two (2) studies are considered level II evidence, which include one (1) prospective treatment and historical controls study and one (1) prospective observational study that alternated patient assignment into either the treatment or control group (i.e., not randomized).

Table 5. Characteristics of studies included in the Seroma meta-analysis

Study/Level of Evidence	Study Design	Surgical Procedure	Subjects' Risk Factors	Study Duration	Incisional Dressings Used	No. of Subjects	Treatment Duration Days
Ferrando 2017[5] Level II	Prospective Observational	Breast conserving surgery, oncoplastic surgery, tissue sparing, simple mastectomies[†]	BMI Mean Treatment; 27kg/m^2; Control: 29.5kg/m^2; Diabetes; Hx of Smoking; HTN; Use of Corticosteroids; Artery and Liver Disease; Chemotherapy; Radiation; Previous Surgery; Invasive Surgery	1 Year	PREVENA PLUS CUSTOMIZABLE™ Dressing	17 (25 wounds)	7
					Steri-strip skin adhesive closure	20 (22 wounds)	14
Gunatilake 2017[8] Level I	RCT	Cesarean Delivery	BMI Mean Treatment: 46.3kg/m^2; Control: 46.8kg/m^2; Diabetes	42 +/- 10 Days	PREVENA™ System	39	5-7
					Steri-strips, sterile gauze, Tegaderm™	43	1-2
NCT01341444 Level I	RCT	Renal Transplant[†]	BMA Mean Treatment: 29.05kg/m^2; Control: 28.73kg/m^2; Diabetes; Tobacco Use	30 Days	PREVENA™ System	28	5
					Standard Incisional Dressing	30	3
Pachowsky 2012[15] Level I	RCT	Total Hip Arthroplasty	NR	10 Days	PREVENA™ System	9	5 Days
					Standard Wound Dressing	10	NR

Study/Level of Evidence	Study Design	Surgical Procedure	Subjects' Risk Factors	Study Duration	Incisional Dressings Used	No. of Subjects	Treatment Duration Days
Pauser 2016[16] Level I	RCT	Hip Hemiarhtroplasty†	NR	10 Days	PREVENA™ System	11	5
					Standard wound dressing consisting of dry wound coverage	10	NR
Pleger 2017[17] Level I	RCT	Vascular procedures with access in common femoral artery†	BMI Mean Treatment: 26.7kg/m^2; Control: 27.8kg/m^2; Diabetes; Hx of Smoking; COPD; Renal Insufficiency; Malnutrition; Age >50 years; Overweight	30 Days	PREVENA™ System	43 (58 wounds)	5-7
					Conventional Adhesive Plaster	57 (71 wounds)	1
Redfern 2017[18] Level II	Prospective & Historical Controlled	Total hip or knee arthroplasty (elective primary)	BMI Mean Treatment: 30.5kg/m^2; Control: 30.9kg/m ; Diabetes; HTN; Hx of Cancer/Tumor; Arthritis; Myocardial Infarction/Heart Disease; Tobacco Use	60 Days	PREVENA™ System	192	6-8
					Traditional Gauze Dressing	400	Standard

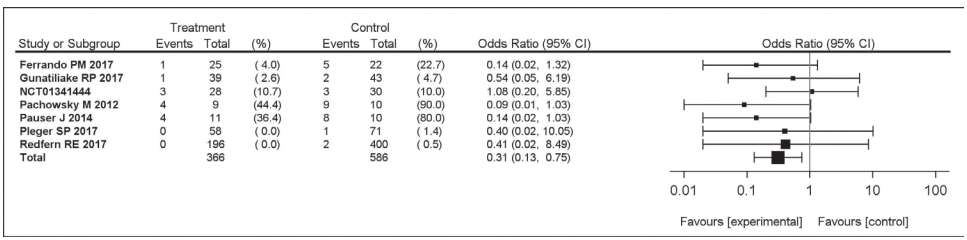
†Population or Procedure identified as high-risk for wound complication
*Oxford Centre of Evidence-Based Medicine
NR= Not Reported
RCT = Randomized Controlled Trial
ciNPWT= closed incision Negative Pressure Wound Therapy
BMI= Body Mass Index
HX= History
COPD= Chronic Obstructive Pulmonary Disorder
GERD= Gastroesophageal Reflux Disease
HTN= Hypertension
AF= Atrial Fibrillation
CVD= Cardiovascular disease
CKF= Chronic kidney failure
PVD= Peripheral vascular disease
LVD= Left ventricle dysfunction
CAD= Coronary artery disease
CKD= Chronic kidney disease
LVEF= Left ventricle ejection fraction
HIV= Human immunodeficiency virus

Together, the seven (7) studies contained 366 evaluable patients receiving PREVENA™ Incision Management Systems therapy (treatment group) and 586 patients receiving conventional wound dressings (control group). The conventional wound dressings used in each study can be found in Table 5 above and mostly consist of gauze and occlusive dressings. The primary endpoint in the studies was the incidence of seroma in the treatment group compared to the control group for at least 10 days following surgery.

The treatment effect for each study was summarized using odds ratio (OR), which was calculated using the following formula:
OR = AD/BC, where
A = the number of subjects with seroma events for the treatment group
B = the number of subjects without seroma events for the treatment group
C = the number of subjects with seroma events for the control group
D = the number of subjects without seroma events for the control group

An OR of less than 1 suggests a favorable effect by the treatment in reducing seroma, whereas an OR greater than 1 suggests a favorable effect by the standard of care in reducing seroma. The 95% confidence interval (95% CI) for the odds ratio is calculated based on the standard error of Log (OR). The individual study effects are summarized in Figure 7 below.

Figure 7. Forest plot of meta-analysis studies for seroma.



Overall, there is an observable trend supporting a favorable effect by the PREVENA™ Systems in reducing the incidence of seroma formation. The seroma rates ranged from 0.5 % to 90 % for the control group in the selected studies, and the seroma rates in the treatment group ranged from 0 % to 44.4 %. However, the benefit of the PREVENA™ Systems in reducing the incidence of seroma formation varies broadly across different studies, possibly due to many confounding factors such as different surgical procedures and patient risk factors. Subgroup analyses for seroma were not conducted as there are only seven (7) studies total and dividing them into subgroups would not result in meaningful analyses. Additionally, there are many inherent limitations associated with meta-analyses and biases with each individual study, which are discussed in the 'Limitations of the Clinical Evidence' section below. Because of these confounding factors and limitations, statistical significance cannot be reliably inferred for the treatment effect on seroma rates based on the combined results from the seven (7) studies.

Safety

Adverse events (AEs) and Serious Adverse Events (SAEs) were reported in three (3) of the twenty (20) studies included in the meta-analyses [Gunatilake (Cesarean section) 2017[8], NCT01341444 (Renal transplant), NCT02195310 (Sternotomy)]. There were no treatment related AEs or SAEs reported in the Cesarean section study (Gunatilake 20178). In the two studies conducted by KCI (NCT01341444 (Renal transplant), NCT02195310 (Sternotomy)), there were no SAEs, and the twenty one (21) reported AEs related or possibly related to the device including pain (5), blisters (4), dehiscence (4), draining/wound secretion (2), erythema (2), skin irritation (2), ecchymosis (1), and hematoma (1), which are known adverse events that may be seen with the use of the device on surgical incisions.

No significant differences were reported in AEs or SAEs between the PREVENA™ Systems (treatment group) and conventional wound dressings (control group). No adverse device events, serious adverse device events, or device failures were reported. These results suggest that the PREVENA™ Systems have a similar safety profile as conventional wound dressing for closed surgical incisions.

Limitations of the Clinical Evidence

There are many inherent limitations to meta-analyses, such as publication bias and selection bias. In addition, surgical site infection (SSI) and seroma are complex post-operative outcomes that have many potential causes. While efforts were made in the study identification and selection process to ameliorate biases by including both published and unpublished studies and only the highest quality studies, not all aspects of each selected meta-analysis study are identical. First, even though only prospective studies were included in the meta-analyses, these studies often had many potential sources of bias. Bias assessment was conducted using the Cochrane guidelines and focused on randomization, allocation concealment, differences in baseline patient and risk characteristics, blinded assessments, loss to follow up, comparing purpose of study to outcomes reported, and when possible, comparing outcomes to those listed on ClinicalTrials.gov, when available. Fourteen (14) of the twenty (20) meta-analysis studies were identified as high-risk for bias (Cantero 2016[3], DiMuzio 2017[4], Ferrando 2017[5], Gunatilake 2017[8], Lavryk 2016[10], Lee AJ 2016[11], Matatov 2013[13], NCT013471444, Newman 2017[14], Pleger 2017[17], Redfern 2017[18], Sabat 2016[20], Swift 2015[22]). One (1) study was assessed as low risk for bias (Lee K 2017[12]). Risk for bias was unclear in the remaining five (5) studies due to the lack of information reported in the studies. Second, the unit of the analysis is not consistent in all studies. Some studies used the wound as the unit of analysis and others used the patient as the unit of analysis. As a result, some of the data used in these analyses were based on wounds and some patients contributed more than one (1) wound to the analyses. Third, the timing of the outcome

assessments was not consistent across each of the different studies. For example, although all the SSI studies evaluated SSI events for at least four weeks post-surgery, the duration of some of the studies was much longer. Similarly, although all the seroma studies evaluated the incidence of seroma for at least ten days after surgery, the duration of some of the studies was much longer. Fourth, the reported SSI rates in the meta-analysis studies varied broadly across different studies. It should be noted that the following SSI rates based on wound classification and types of SSI (Table 6) have recently been reported based on a retrospective review of the 2011 American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database[9]:

Table 6. Surgical Site Infection (SSI) rates based on ACS NSQIP database[9].

30-d postoperative outcomes	Total	Wound Classification			
		Class I	Class II	Class III	Class IV
Surgical Site Infection (SSI)	3.4%	1.8%	4.8%	5.6%	8.5%
Superficial incisional SSI	1.9%	1.2%	2.6%	2.8%	2.7%
Deep incisional SSI	0.6%	0.4%	0.6%	0.8%	1.5%
Organ space SSI	1.1%	0.3%	1.6%	2.2%	4.4%

The SSI rates reported in the studies selected for the meta-analysis, even for the control groups, are generally higher than those reported in the literature. Factors contributing to this discrepancy may be surgeon-, procedure-, or patient-dependent, but nevertheless cannot be pinpointed based on the information provided in the studies. Fifth, five (5) of the seven (7) prospective studies included in the meta-analysis for SSI and one (1) prospective study included in the meta-analysis for seroma compared the PREVENA™ Systems to historical controls. There have been significant evidence-based changes in patient care to define and reduce the risk for post-operative complications, including surgical site infections. Additionally, surgical site infection reduction measures vary among surgeons, hospitals, and countries. Changes in disease definitions, interventions, and treatment effectiveness over time contribute to non-contemporaneous bias. Results of studies using historical controls should be evaluated with caution.

These limitations should be considered when examining the results from these meta-analyses.

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SYMBOLS USED

	Refer to Clinician Guide		Consult Instructions for Use
IP24	Ingress Protection		Type BF applied part
	Sterile using radiation		Lot Number
	Date of Manufacture		Manufacturer
	Do Not Resterilize		Use By
	Fragile		Catalog Number
	Keep Dry		Single Use Only
	Content Information		Temperature Limit
	Do not use if package is damaged or open		MR Unsafe
Rx Only	CAUTION: Federal (US) law restricts this device to sale by or on the order of a physician.		
	This product is designated for separate collection at an appropriate collection point. Do not dispose of as household waste.		

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