BondEase® Topical Skin Adhesive
Instructions For Use

DESCRIPTION
BondEase® Topical Skin Adhesive is a sterile, liquid topical skin closure device composed of a methylidene malonate monomer formulation and the colorant D&C Green #6. It is provided in a single-use applicator, packaged in a foil pouch. The applicator is comprised of a crushable glass ampoule contained within a plastic vial with attached applicator tip and handle. BondEase® is applied to the skin as a viscous liquid which polymerizes to bond approximated wound edges within minutes. In vitro studies have shown that BondEase® acts as a bacterial barrier as long as the adhesive film remains intact. *See* DIRECTIONS FOR USE.

INDICATIONS
BondEase® Topical Skin Adhesive is intended for topical use only, to hold together the skin edges of incisions and lacerations that are under minimal tension and easily approximated. Where significant tension exists on incisions or lacerations, BondEase® Topical Skin Adhesive should be used in conjunction with deep dermal stiches.

CONTRAINDICATIONS
- Do not use on wounds with evidence of microbial, bacterial, or fungal infection, gangrene, or decubitus etiology.
- Do not use on mucosal surfaces or across mucocutaneous junctions (e.g., oral cavity, lips), or on skin which may be regularly exposed to body fluids or with dense natural hair (e.g., scalp).
- Do not apply internally, inject intravascularly, or ingest.
- Do not use on patients with a known hypersensitivity to adhesives.

WARNINGS
- The BondEase® Topical Skin Adhesive product is comprised of a fast setting adhesive capable of adhering to most body tissues and many other materials, such as surgical gloves and stainless steel. Unintentional contact with any body tissue, and any surfaces or equipment that are not disposable or that cannot be easily cleaned with a solvent such as acetone should be avoided.
- Polymerization of BondEase® Topical Skin Adhesive may be accelerated by the presence of water or fluids containing alcohol. BondEase® Topical Skin Adhesive should not be applied to wet wounds.
- BondEase® Topical Skin Adhesive will not adhere to skin pre-coated with petroleum jelly. Therefore, avoid using petroleum jelly on any skin area where BondEase® Topical Skin Adhesive is intended for use.

PN 100-009 revision D, effective 12/21/2015

- BondEase® Topical Skin Adhesive should not be applied to the eye. If contact with the eye occurs, flush the eye copiously with saline or water. If residual adhesive remains, apply an appropriate topical ophthalmic ointment to help loosen the bond and contact an ophthalmologist.
- When closing facial wounds near the eye using BondEase® Topical Skin Adhesive, situate the patient so that any flow of the adhesive is away from the eye. The eye should be closed and protected with gauze. Placement of petroleum jelly near the eye can be effective at preventing inadvertent flow of the adhesive into the eye. Use of liquid adhesives near the eye can inadvertently cause some patients' eyelids to be sealed shut. In some of these cases, general anesthesia and surgical intervention may be needed to open the eyelid.
- BondEase® Topical Skin Adhesive should not be used internally or below the skin because the polymerized material is not absorbed by tissue and may elicit a foreign body reaction.
- Avoid excessive pressure of the applicator tip against wound area or surrounding skin. This can force the wound edges apart and allow adhesive to seep into the wound. BondEase® Topical Skin Adhesive should be applied with a light brushing motion of the applicator tip over the approximated wound edges.
- BondEase® Topical Skin Adhesive should not be used over high skin tension areas such as elbows, knees, and knuckles without joint immobilization or additional support of a device (such as sutures) to relieve tension.
- Wounds treated with BondEase® Topical Skin Adhesive should be monitored for signs of infection. Wounds with signs of infection, such as edema, erythema, warmth, pain, and purulent exudate, should be evaluated and treated according to standard practice for infection.
- BondEase® Topical Skin Adhesive should not be used on wound areas that will be subjected to repeated or prolonged moisture or friction.
- BondEase® Topical Skin Adhesive should only be used after wounds have been thoroughly cleaned, debrided, and are otherwise treated in accordance with standard surgical practices. Local anesthetic may be used when necessary to assure sufficient cleansing and debridement.
- Polymerization of BondEase® Topical Skin Adhesive generates a small amount of heat and should not be applied to sensitive tissues that may be affected by such heat. Application of BondEase® in one thin, continuous layer onto a dry wound and allowing time for polymerization will minimize the warm sensation.
- The adhesive should not be applied to wet wounds or wounds that have excessive moisture. Excess moisture may accelerate polymerization, resulting in the generation of excess heat.
- BondEase® Topical Skin Adhesive is packaged for single patient use. Discard any unused material after each wound closure procedure.
- Do not resterilize BondEase® Topical Skin Adhesive.
- Do not place BondEase® Topical Skin Adhesive in a pack, tray, or kit that will be sterilized prior to use. Exposure of sterilized BondEase® Topical Skin Adhesive to excessive heat (as in autoclaves or ethylene oxide sterilization) or radiation (such as gamma or electron beam) will increase its viscosity and may render the product unusable.

PRECAUTIONS

- BondEase® Topical Skin Adhesive is intended for external dermal application only.
- The safety and effectiveness of BondEase® Topical Skin Adhesive on animal or human bites, puncture wounds, or stab wounds have not been evaluated.
- The safety and effectiveness of BondEase® Topical Skin Adhesive on wounds of patients with peripheral vascular disease, insulin dependent diabetes mellitus, blood clotting disorders, personal or family history of keloid formation or hypertrophy, burst stellate lacerations, or HIV have not been evaluated.
- The safety and effectiveness of BondEase® Topical Skin Adhesive used to treat wounds that have been closed and subsequently been exposed to direct sunlight or tanning lamps for prolonged periods have not been evaluated.
- Prior to application, the wound site should be cleansed thoroughly to remove any topical medications/anesthetics that may interfere with proper bonding and adhesion.
- Do not apply liquid, ointment, or cream medications to the wound after closure with BondEase® Topical Skin Adhesive, as these substances may weaken the polymerized film or interfere with adhesion to the skin surface possibly leading to wound dehiscence.
- The permeability of BondEase® Topical Skin Adhesive to fluids has not been studied.
- BondEase® Topical Skin Adhesive is a viscous liquid prior to polymerization. In order to prevent inadvertent flow of the adhesive to unintended areas, the wound should be placed in a horizontal position. With the wound site as horizontal as possible, BondEase® Topical Skin Adhesive should be applied from above. BondEase® Topical Skin Adhesive should be applied as a thin film to prevent flow of the excess adhesive to unintended areas.
- When preparing the product for use, hold the applicator away from yourself and the patient to prevent inadvertent contact of the adhesive with the user or patient. Using the product handles, crush the ampoule one time only. Repeated attempts to crush the contents of the applicator tube may cause glass shard penetration of the outer tube.
- BondEase® Topical Skin Adhesive should be used immediately after crushing the internal ampoule because the adhesive will polymerize in the applicator, rendering the device unusable.
- If unintended bonding of intact skin with BondEase® Topical Skin Adhesive occurs, removal may be accomplished by using acetone or petroleum jelly. Other agents, such as warm water or saline, may not remove the adhesive but may loosen edges so that the adhesive can be peeled off. Peel the adhesive off gently. Do not pull skin apart.

ADVERSE REACTIONS

Table 1: Device-related adverse reactions encountered during the clinical study (ITT Population)

Clinical Study Outcomes	**BondEase®**	**Control (CWCD)**
	N (%)	**N (%)**
Dehiscence with No Need for Retreatment	2 (1.9%)	0 (0%)
Mild Scar	2 (1.9%)	0 (0%)
Acute Inflammation at 10 days		
Erythema	7 (6.7%)	4 (7.4%)
Edema	1 (1.0%)	0 (0.0%)
Pain	2 (1.9%)	2 (3.7%)
Total AEs	14	6

In the clinical study, both treatments appeared to be well-tolerated. There were no deaths, no treatment-related serious adverse events, device-related complications or infections. There were no events of wound dehiscence requiring supplemental closure. All device-related adverse events were mild and appeared to have no impact on the cosmesis outcome. Signs of inflammation at the wound site were comparable between treatment groups.

Potential Adverse Events

Clinical use of topical skin adhesives has suggested that the following adverse events may occur:

- wound dehiscence
- infection
- acute inflammation including erythema, edema, pain, warmth and drainage
- bonding to unintended tissues such as the eye
- thermal discomfort during polymerization
- allergic reaction
- foreign body reaction
- chronic non-healing of a wound

CLINICAL STUDY

A prospective, randomized, controlled, open-label study was conducted to evaluate the ability of BondEase® Topical Skin Adhesive to close approximated skin edges of traumatic lacerations and surgical incisions in comparison to Conventional Wound Closure Devices (CWCD) including sutures, staples, or adhesive strips, with or without

sutures placed below the skin surface according to investigator judgment. The study was designed to demonstrate that BondEase is non-inferior to conventional wound closure devices (CWCD) in terms of 100% wound edge apposition of surgical incisions and traumatic lacerations.

The study population included patients at least one year of age, in good general health. Patients were excluded if presenting with: significant multiple trauma, peripheral vascular disease, insulin dependent diabetes mellitus, blood clotting disorder, keloid formation or hypertrophy history (patient or family), allergy to the adhesive, burst or stellate lacerations, animal or human bite, HIV, decubitus ulcer, heavily contaminated wounds and evidence of active infection or gangrene. Wound length and width were measured in millimeters; wound depth was not measured according to the study protocol. Types of wounds included traumatic lacerations and surgical incisions with and without deep dermal sutures. The study sample size was calculated based on the assumption of 95% wound apposition rate with BondEase compared to 96% wound apposition rate with CWCD. Based on this assumption, a total of 144 subjects would provide 80% statistical power to demonstrate equivalence with a clinically acceptable 10% margin and a one-sided Type I error rate of 0.05. Table 2 summarizes the subject accountability and Table 3 summarizes the demographic characteristics and baseline wound types. The following factors had no impact on the performance of BondEase® Topical Skin Adhesive in terms of 100% wound edge apposition at day 10: wound type, gender, age, or race, the need for deep dermal sutures, and the location of the wound.

Efficacy assessments included percent wound apposition as determined by the investigator and cosmetic outcome of the wound using a validated scale [Hollander JE, et al, 1995] as determined by a blinded clinician. The effectiveness outcomes measured were: (1) the proportion of subjects in whom 100% wound edge apposition was achieved at 10 days (± 3 days) post-procedure; (2) the incidence of $\geq$50% wound apposition at 10 days (± 3 days) post-procedure; (3) the incidence of wounds with an optimal cosmetic outcome (score of 6) at 28 days (± 5 days) and (4) the mean and median cosmesis scores at 28 days (± 5 days). The efficacy results are presented in Tables 4, 5 and 6.

Table 2: Subject Accountability

	BondEase	CWCD	Total
Randomized*	108	54	162
Randomized and treatment applied	105 (97.2%)	54 (100%)	159 (98.1%)
Completed the study	100 (92.6%)	51 (94.4%)	151 (93.2%)
Early discontinuation**	8 (7.4%)	3 (5.6%)	11 (6.8%)
Intent-to-treat population (ITT)	105 (97.2%)	54 (100%)	159 (98.1%)
Per protocol population (PP)	100 (92.6%)	53 (98.1%)	153 (94.4%)

*20 BondEase and 10 CWCD subjects were enrolled in Part 1 of the clinical study. 88 BondEase and 44 CWCD subjects were enrolled in Part 2 of the clinical study.

**Reasons for early discontinuation included subjects that (1) were randomized but not treated, (2) voluntarily withdrew, (3) were non-compliant, (4) lost to follow-up, (5) had some other medical reason.

Table 3: Demographic Characteristics and Baseline Wound Types by Treatment Group (ITT Population)

	BondEase N=105	CWCD N=54	Total N=159
Age (years)			
Mean (SD)	44.4 (23.1)	47.7 (22.3)	45.5 (22.8)
Median	46	47	46
Min-Max	1 – 93	3 – 87	1 - 93
Gender			
Male, n (%)	56 (53.3%)	30 (55.6%)	86 (54.1%)
Female, n (%)	49 (46.7%)	24 (44.4%)	73 (45.9%)
Race			
White or Caucasian, n (%)	83 (79.0%)	46 (85.2%)	129 (81.1%)
Black or African American, n (%)	16 (15.2%)	7 (13.0%)	23 (14.5%)
Asian, n (%)	2 (1.9%)	1 (1.9%)	3 (1.9%)
Other, n (%)	4 (3.8%)	0 (0.0%)	4 (2.5%)
Ethnicity			
Not Hispanic / Latino, n (%)	84 (80.0%)	49 (90.7%)	133 (83.6%)
Hispanic or Latino, n (%)	21 (20.0%)	5 (9.3%)	26 (16.4%)
Wound type			
Injury (Laceration)	27 (25.7%)	13 (24.1%)	40 (25.2%)
Surgical incision	78 (74.3%)	41 (75.9%)	119 (74.8%)

Table 4: 100% Wound Apposition at 10 Days by Treatment Group

	BondEase	CWCD	BondEase-CWCD	95% CI**
Per protocol population*	77.1% (74/96)	80.4% (41/51)	-0.03	-0.13 to 0.11
Intent-to-treat population	73.3% (77/105)	77.8% (42/54)	-0.04	-0.13 to 0.10

*Primary analysis dataset

**The lower bound of the 95% confidence interval of the difference (BondEase-CWCD) is -0.13 which did not reach, but was very close to the pre-specified non-inferiority margin of -0.1.

Table 5: Summary of Secondary Endpoints (ITT Population)

	BondEase*	CWCD*
≥ 50% wound apposition at 10 days, % (n/N)	93.3% (98/105)	96.3% (52/54)
Optimal cosmesis at 28 days (score of 6), % (n/N)	70.5% (74/105)	64.8% (35/54)
Cosmesis at 28 days (all scores), mean / median	5.7 / 6.0	5.6 / 6.0

*There were no significant differences between treatment groups.

Table 6: 100% Wound Apposition at 10 Days by Subgroup (PP Population)

	100% wound apposition		BondEase-CWCD (95% CI)*
	BondEase	CWCD	
Deep dermal sutures used			
Yes, n/N (%)	63/78 (80.8%)	31/39 (79.5%)	0.01 (-0.14 – 0.17)
No, n/N (%)	11/18 (61.1%)	10/12 (83.3%)	-0.22 (-0.53 – 0.09)
Wound type			
Incision, n/N (%)	60/72 (83.3%)	32/40 (80.0%)	0.03 (-0.12 – 0.18)
Injury, n/N (%)	14/24 (58.3%)	9/11 (81.8%)	-0.24 (-0.54 – 0.07)

*There were no significant differences between treatment groups.

While investigators were paid to conduct the study, the value of compensation was not determined by the study outcome. None of the investigators had a proprietary interest or equity in the product.

DIRECTIONS FOR USE

1. The wound site should be completely cleaned before using BondEase® Topical Skin Adhesive. Standard surgical practices for wound preparation should be used before application of the product including cleansing, irrigation, debridement, and achievement of hemostasis. There should be low tension on the wound edges. Additional wound support may be provided by using deep dermal sutures.
2. Dry the wound area using sterile gauze. Moisture may accelerate the polymerization of BondEase® Topical Skin Adhesive and may affect wound closure results.
3. To prevent inadvertent flow of liquid BondEase® Topical Skin Adhesive to unintended areas of the body, the patient's wound area should be maintained in a horizontal position and the adhesive should be applied from above the wound.
4. BondEase® Topical Skin Adhesive should be used immediately after crushing the internal ampoule because the adhesive will polymerize in the applicator, rendering the device unusable.
5. Remove the applicator from the foil pouch.
6. Hold the applicator away from the user and the patient to prevent inadvertent contact of the adhesive with the user or patient.
7. Hold the applicator with the tip facing upwards.
8. Apply pressure to the handle arms, squeezing them towards each other, until the inner glass ampoule is crushed by the handles. Do not attempt to crush the ampoule by placing fingers directly on the plastic tube.
9. Shake the device for 10 seconds, until the contents are a uniform color.
10. Invert and gently squeeze the applicator to express the liquid adhesive.
11. If necessary, approximate the wound edges using either gloved fingers or sterile forceps.
12. Slowly apply the liquid BondEase® Topical Skin Adhesive in one thin, continuous layer to the surface of the approximated wound edges using a gentle brushing motion.
13. The adhesive should cover a target area of approximately 0.5cm on each side of the wound.
14. Manual tissue approximation should be maintained for two minutes, particularly if the wound appears to be under tension. The adhesive may remain "tacky" for up to four minutes.
15. Full apposition strength is expected to be achieved within minutes after the adhesive is applied. Complete polymerization is expected when the BondEase® Topical Skin Adhesive layer is no longer tacky.
16. Do not apply liquid or ointment medications onto wounds closed with BondEase® Topical Skin Adhesive. These substances may weaken the polymerized film, leading to wound edge separation and/or dehiscence.
17. Bandages or dry protective dressings, such as gauze, may be applied only after the BondEase® Topical Skin Adhesive film is completely polymerized and not tacky to the touch. If a dressing or bandage is applied before polymerization is complete, the dressing or bandage can adhere to the film. The film can then be disrupted from the skin when the dressing is removed, possibly causing wound dehiscence.

18. Dry protective dressings should be applied for children or other patients who may not be able to follow instructions for proper wound care.
19. Patients should be provided instructions on how to care for the wound after closure with BondEase® Topical Skin Adhesive. *See* PATIENT INSTRUCTIONS. The instructions should be reviewed with each patient or guardian to assure understanding of the proper care for the wound site.
20. Patients should be instructed that the polymerized film of BondEase® Topical Skin Adhesive will slough off naturally (usually in 5–10 days). Until the adhesive falls off, there should be only brief wetting of the treatment site. The site should not be scrubbed, soaked, or exposed to prolonged wetness until after the film has sloughed naturally and the physician has determined that the wound is adequately healed. As directed by their physician, patients may immediately shower or bathe the site gently. Patients should be instructed not to swim during this period.
21. If removal of BondEase® Topical Skin Adhesive is necessary for any reason, carefully apply petroleum jelly or acetone to the film to help loosen the bond. Peel, do not pull, the film off.

PATIENT INSTRUCTIONS

No additional or special care is needed for wounds closed using BondEase® Topical Skin Adhesive. However, it is recommended that the following information be shared with the patient as necessary. A dry protective dressing should be applied for children or other patients who may not be able to follow these instructions for proper wound care.

- Do not pull or pick at the wound or polymerized film of BondEase® Topical Skin Adhesive. Picking at the film can disrupt adhesion to the skin and cause dehiscence of the wound.
- Avoid exposure of the wound site to direct sunlight and do not use tanning beds or lights while the adhesive film is intact.
- Light showering or bathing is permitted. However do not scrub, soak, or expose the wound site to prolonged wetness (including swimming) until after the film has sloughed off naturally (usually in 5-10 days) and your physician has determined that the wound is adequately healed.
- Do not apply liquid or ointment medications onto wounds closed with BondEase® Topical Skin Adhesive. These substances may weaken the polymerized film, leading to wound edge separation and/or dehiscence.
- Report any discomfort or other concerns regarding your wound to your doctor.

HOW SUPPLIED

BondEase® Topical Skin Adhesive is supplied sterile, in a prefilled, single use applicator. The applicator is comprised of a crushable glass ampoule contained within a plastic vial with attached applicator tip and handle. The applicator contains 0.9ml of liquid adhesive and is packaged in a foil pouch to maintain the sterility of the product until opened. Do not use BondEase® Topical Skin Adhesive if the package is damaged.

STORAGE
The recommended storage conditions for BondEase® Topical Skin Adhesive are: below 30°C, 86°F, away from moisture, direct heat, and direct light. Avoid prolonged exposure to elevated temperatures. BondEase® Topical Skin Adhesive should always be stored in its original packaging. Do not use the product after its expiration date.

STERILITY
BondEase® Topical Skin Adhesive is terminally sterilized by gamma irradiation. Do not re-sterilize. Do not use if packaging is opened or damaged. Discard any unused or opened material following completion of medical procedure.

STERILE SINGLE USE ONLY

CAUTION
Federal law restricts this device to sale by or on the order of a physician.

Manufactured by James Alexander Corp., Blairstown, NJ 07825
for OptMed, Inc., New York, NY 10022
212-867-4141

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