Frequently Asked Questions

for Distributors (Canada)

March 2019

Biocomposites

FAQs

What is STIMULAN® indicated for?

STIMULAN is the perfect partner for your infection management strategy. It can be used at an infected site for bone regeneration. It is indicated for use in musculoskeletal defects created by surgery, a cyst, a tumor, osteomyelitis or traumatic injury. STIMULAN is not intended to provide structural support during the healing process.

What is STIMULAN contraindicated for?

Contraindications for STIMULAN can be found in the IFU. These include contraindications for filling defects which are intrinsic to the stability of the bony structure, renal compromised patients, hypercalcaemia, severe vascular or neurological disease, uncontrolled diabetes, pregnancy, severe degenerative bone disease and uncooperative patients who can't or won't follow post operative instructions including individuals who abuse alcohol or drugs.

What supporting data do you have for STIMULAN?

Biocomposites has a range of data including pre-clinical laboratory testing, *in-vivo* animal model data, and clinical data. Biocomposites also has numerous case studies that show how STIMULAN transforms outcomes in infected non-unions, osteomyelitis, periprosthetic joint infection and soft tissue infections.

Who is using STIMULAN and in which hospitals?

STIMULAN is already used in over 30,000 cases a year. Biocomposites is happy to introduce physicians to an appropriate surgeon if they would like to have a peer-to-peer conversation.

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How long does STIMULAN take to absorb in bone and soft tissue?

STIMULAN is absorbed in approximately 30-60 days when used in accordance with the device labeling. Contributing factors include the vascularity of the surgical site, quantity used and patient health.

Does STIMULAN damage articulating surfaces on joint prosthesis?

This is an area of ongoing research but biomechanical testing (Pin on Plate) indicates that STIMULAN does not significantly scratch implant grade cobalt chrome and does not lead to increased wear of high density polyethylene components, when compared to a control with no STIMULAN present.

Will STIMULAN cause heterotopic ossification if implanted in soft tissue?

STIMULAN is an osteoconductive material and is not osteoinductive or osteogenic in nature. Biocomposites has published a range of clinical data indicating a minimal risk of heterotopic ossification if implanted in soft tissue.

Will STIMULAN grow bone in osteomyelitic or infected non-union cases?

We do have clinical evidence that STIMULAN is remodelled into bone when placed at an infected site following thorough debridement and removal of necrotic tissue. Biocomposites would be happy to provide you with the case studies that demonstrate this for the indication you are interested in.

Can STIMULAN be applied to a wet field?

It is recommended that STIMULAN paste be applied where surrounding bone is healthy and vascular but not actively bleeding at the time of insertion. When implanted as a paste, do not irrigate the site following implantation.

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What is DRy26™?

Each and every synthesis of STIMULAN undergoes a 26 step process that starts with pharmaceutical grade precursors and takes over 6 weeks to reach maturity. We have named this our DRy26 methodology.

What is the compressive strength of STIMULAN?

STIMULAN Kit/Rapid Cure have been shown to have a ‘wet’ compressive strength (as set at implantation time) of 21 MPa. This helps maintain bead integrity immediately following bead placement. The compressive strength reduces rapidly as STIMULAN is absorbed.

What is the powder weight of STIMULAN Rapid Cure per cc of paste volume?

The powder weight of STIMULAN Rapid Cure per cc of paste volume is:

STIMULAN PRODUCT	PASTE VOLUME	BEAD VOLUME	POWDER WEIGHT
Rapid Cure	5cc	12cc	9.5g
	10cc	25cc	19.0g
	20cc	50cc	38.0g

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What volume and size of beads can be prepared using the STIMULAN Rapid Cure bead mat?

The STIMULAN Rapid Cure bead mat can be used to prepare 3mm, 4.8mm or 6mm hemispherical beads. A 10cc pack of STIMULAN Rapid Cure will yield 25cc of bead volume.

How many beads can made from the different sections of the STIMULAN mat using a 10cc pack?

3.0mm beads	4.8mm beads	6mm beads
560	150	95

What volume and size of bullets can be prepared using the STIMULAN bullet mat?

The STIMULAN bullet mat can be used to prepare 7mm and 9mm bullets. Each bullet is 20mm in length. A 20cc pack will yield 50cc of bullet volume.

How many bullets can be made from the different sections of the STIMULAN bullet mat using a 20cc pack?

7.0mm bullets	9.0mm bullets
32	24

What is the end-to-end length if all bullets in the mat are used?

The end-to-end length refers to the cumulative length if all bullets are used. If all of the 7mm bullets are used, the total end-to-end length of the bullets is 640mm. If all 9mm bullets are used, the total end-to-end length of the bullets is 480mm. The end-to-end length does not correlate to the length of the introducer.

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What are the working and setting times of STIMULAN?

When mixed with the liquid provided STIMULAN has the following setting times:

- STIMULAN Rapid Cure has a 1-2 minute working time and will set ~ 4 minutes after mixing. Following mixing and application onto the bead or bullet mat, allow to set undisturbed for at least 8 minutes prior to release from bead/bullet mat.

- STIMULAN Kit (beads and bullets) have a working time of 1-2 minutes and will set in approximately 8 minutes after mixing. Following mixing and application onto the bead/bullet mat, allow to set undisturbed for at least 15 minutes prior to release from bead/bullet mat.

- STIMULAN Kit (injectable paste) has a 30 second working time prior to injection and begins to set 2-3 minutes after mixing. Following mixing and application, allow paste to set undisturbed for at least 15 minutes prior to closure.

The addition of antibiotics may affect the setting times. Biocomposites currently has a range of clinical data for vancomycin, tobramycin and gentamicin. The IFU and brochure shows the impact on setting times according to how it is mixed.

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Can I mix antibiotics with STIMULAN?

Yes. STIMULAN is approved for mixing with antibiotics when it is placed at an infected site or where there is a risk of infection. The treating physician is responsible for deciding the type and quantity of antibiotic to be used. STIMULAN can be easily mixed with liquid, powder and heat sensitive antibiotics. Biocomposites currently has clinical data for vancomycin, tobramycin and gentamicin and the IFU and brochure shows the impact on setting times according to how it is mixed. If the physician wishes to use an alternative antibiotic Biocomposites may have mixing data from their in-house laboratory tests. If they do, then they can provide guidance on the setting characteristics of the chosen antibiotic upon request.

Can STIMULAN mixed with antibiotics replace I.V. delivery?

STIMULAN is not intended as a replacement therapy for I.V. antibiotics.

Can antibiotic tablets or capsules be mixed with STIMULAN?

The warning information published in the IFU along with any in-house testing has been performed using antibiotic formulations that have been manufactured for I.V. administration use only. Antibiotics in tablet and capsule form may contain excipients that may not dissolve and/or cause adverse effects which may create additional risks if administered locally.

What is the mechanism of release of the antibiotics?

This is an area of ongoing research. However, molecular size, solubility and wound environment all play a role in the release mechanism. It is likely that most antibiotics will be released through a combination of both dissolution and diffusion.

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Can I mix 'X' antibiotic with STIMULAN?

The treating physician is responsible for deciding the type and quantity of antibiotic to be used. Biocomposites currently has clinical data for vancomycin, tobramycin and gentamicin, but they do know from their in-house laboratory tests that STIMULAN can be easily mixed with other liquid, powder and heat sensitive antibiotics. Biocomposites is happy to share the mixing data they hold on file with the physician upon request. For antibiotics for which they don't hold any mixing data on file, they are willing to consider and discuss potential implications.

Note to Sales Representative:

If you share any mixing data with a physician please include the following statement :

These data are provided as a guide to the likely setting characteristics when you mix STIMULAN with X. Please also note:

- The treating physician is responsible for deciding the type and quantity of antibiotic to be used.
- Concurrent use of locally administered antibiotics may affect setting time.
- The mixing of antibiotics with the STIMULAN Kit / STIMULAN Rapid Cure device is considered off-label usage of the medicinal product. To do so is at the professional risk of the surgeon / healthcare professional.
- The ability of STIMULAN Kit / STIMULAN Rapid Cure device to mix and set with antibiotics, alone or in combination, does not imply safety or efficacy in clinical use.
- Antibiotic capsules and tablets contain different excipients to I.V. formulations which may create additional risks if administered locally.

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Is there any evidence of systemic toxicity when antibiotics are mixed with STIMULAN and placed at an infected site?

In-vivo data available on systemic levels shows systemic toxicity to be unlikely, with concentrations remaining close to the site of implantation. Clinical data from a 50 patient study by Dr Gerhard Maale shows an undetectable antibiotic level in the majority of patients. For a minority of patients safe transient levels were observed in serum 24 hours post procedure [1].

What concentration levels can be seen when antibiotics are mixed with STIMULAN and placed at an infected site?

An *in-vitro* study conducted by the University of Exeter shows the elution profile of vancomycin and tobramycin mixed with STIMULAN exceeding MIC levels of many common pathogens out to 6 weeks[2]. Data from an *in-vivo* study (Dr Maale) shows antibiotic levels in drains to be well over MIC for the period the drains were left *in-situ* [1]. An *in-vivo* study by K. Kanellakopoulou shows antibiotic levels 300 times greater than MIC for MRSA [3].

Does the addition of antibiotic change the rate of absorption of STIMULAN beads?

Biocomposites has found in their laboratory *in-vitro* trials that adding vancomycin (hydrochloride) to STIMULAN causes the beads to dissolve faster – the more vancomycin added, the faster they dissolve. A potential problem with this is that serum calcium levels can become elevated the faster the beads dissolve resulting in an increased risk of hypercalcaemia. This would be more likely with patients having impaired kidney function.

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Is there an increased risk of hypercalcaemia when using large quantities of STIMULAN?

There have been a small number of reported cases of hypercalcemia in patients where STIMULAN has been used. Vancomycin and aminoglycoside antibiotics are known to be nephrotoxic. Implantation of STIMULAN beads with locally administered vancomycin or aminoglycoside antibiotics may result in elevated serum calcium levels. These levels may be increased further in the absence of adequate kidney function and/or dehydration which may result in an increased risk of hypercalcemia.

In laboratory *in-vitro* trials, Biocomposites has found that large amounts of vancomycin (hydrochloride) with STIMULAN may cause the beads to dissolve faster. This increased rate of dissolution of STIMULAN beads may potentially elevate serum calcium levels which may lead to an increased risk of hypercalcaemia. This would be more likely with patients who are dehydrated or have impaired kidney function.

Uncontrolled diabetes and renal compromised patients.

The kidneys regulate the amount of fluid and various salts in the body, helping to control blood pressure. Kidney disease or nephropathy can happen to anyone but is more common in patients with diabetes and develops very slowly, over many years. It is most common in people who have had the condition for over 20 years. About 1 in 3 people with diabetes may go on to develop nephropathy, although as treatment improves fewer people are affected.

https://www.diabetes.org.uk/kidneys

Can surgeons use STIMULAN when the patient has a known sulfonamide allergy?

The Instructions for Use does not contraindicate STIMULAN for sulfa allergies.

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Do we have any information on the use of antiseptic solutions, such as Betadine (povidone iodine) or chlorhexadine, used as wound irrigants and their interaction with antibiotic loaded STIMULAN beads?

Laboratory testing has shown that chlorhexadine solution chemically reacts with calcium sulfate giving a needle-like precipitate. Also povidone iodine solution (Betadine) has been shown to chemically react with vancomycin hydrochloride giving a black/slimy precipitate. The clinical effects of these are unknown. Placing antibiotic-loaded beads into these solutions should be avoided.

Can wound drainage occur with the use of STIMULAN?

Wound drainage may occur with any implanted material. STIMULAN has a low documented occurrence of wound drainage. It may be attributed to several factors including patient health and surgical methods e.g. 1) large volumes of STIMULAN beads placed in a concentrated area may cause stretching of the tissue envelope during normal range of motion and leakage at the wound site; 2) patients with comorbidities have a much greater probability of draining due to their poor tissue quality, which may not permit a watertight seal. To reduce the risk of drainage ensure complete soft tissue coverage and/or containment is achieved.

Why is there so little drainage associated with STIMULAN?

STIMULAN is a pharmaceutical-grade, synthetic calcium sulfate. The physical and chemical properties are tightly controlled through Biocomposites' patented recrystallization process to ensure optimum purity. Evidence has shown that STIMULAN is associated with reduced drainage rates when compared to non-synthetic calcium sulfates. Naturally occurring mineral sources of calcium sulfate can contain non-absorbing earth impurities, may be of acidic pH and hydrophobic in nature, and are often linked to significant problems with wound healing and drainage.

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Can STIMULAN cause an adverse soft tissue response?

As part of a recent study by the University of New South Wales Australia, soft tissue inflammatory response to implanted STIMULAN was determined. The study describes a novel small animal model to investigate dead-space management in muscle tissue[4]. Results from histology and serological analysis indicated no significant unusual inflammatory response to the implanted materials.

What should I do if my surgeon experiences an adverse event?

In this case the event should be reported as per the hospital policy and reported to the Compliance Department, Biocomposites Inc.

What should I do if my surgeon requires technical or clinical information or peer-to-peer communication?

Information requested by the surgeon or their medical team should be directed to your Biocomposites representative.

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How does STIMULAN compare to Osteoset® T?

STIMULAN is truly absorbable, causes no third body damage, and is associated with low levels of drainage. Osteoset T may contain non-absorbable materials, may cause third body damage to articulating surfaces and has reported drainage rates ranging from 23-50%.

How does STIMULAN compare to Collatamp® G?

STIMULAN has an optimal absorption rate, a predictable elution profile, and can be easily placed into hard to reach defects. Collatamp G can become a nidus for infection, elutes quickly and cannot be easily placed in hard to reach defects.

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Why should I choose STIMULAN over other lower priced calcium sulfates?

STIMULAN is a truly absorbable calcium sulfate that is uniquely recrystallized for consistent and reliable performance in the presence of infection.

When you need it – STIMULAN delivers every time:

- Controlled Purity – contains no traces of non-absorbable impurities.
- Hydrophilic – can be easily mixed with liquid, powder and heat-sensitive antibiotics
- Predictable elution profile – for gentamicin, vancomycin and tobramycin.
- Physiologic pH level - STIMULAN has a controlled physiologic pH for improved biocompatibility.
- Truly absorbable – fully absorbs within 30-60 days
- Low levels of drainage in clinical use
- No third body damage to articulating surfaces
- Case-by-case flexibility – it can be used in three bead sizes, two bullet sizes, as a paste or for injection

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References

1. Maale, G.E. and J.J. Eager, *Local Elution Profiles of a Synthesized CaSO4 Pellet, Loaded with Vancomycin and Tobramycin, Infected Total Joints.*, in *American Academy of Orthopaedic Surgeons Annual Meeting*. 2012, American Academy of Orthopaedic Surgeons: San Francisco, CA, USA. p. 75.

2. Aiken, S.S., et al., *Local release of antibiotics for surgical site infection management using high-purity calcium sulfate: an in vitro elution study.* Surg Infect (Larchmt), 2015. **16**(1): p. 54-61.

3. Kanellakopoulou, K., et al., *Treatment of experimental osteomyelitis caused by methicillin-resistant Staphylococcus aureus with a synthetic carrier of calcium sulphate (Stimulan) releasing moxifloxacin.* Int J Antimicrob Agents, 2009. **33**(4): p. 354-9.

4. Oliver, R.A., et al., Development of a Novel Model for the Assessment of Dead-Space Management in Soft Tissue. PLoS ONE, 2015. 10(8): p. e0136514.

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For any other questions please contact your Biocomposites representative.

For Indications, contraindications, warnings and precautions see Instructions for Use. The treating physician is responsible for deciding the type and quantity of antibiotic used. Concurrent use of locally administered antibiotics may affect setting time.
The mixing of antibiotics with the STIMULAN Kit/ STIMULAN Rapid Cure device is considered off-label usage of the medicinal product. To do so is at the professional risk of the surgeon / healthcare professional.
This brochure may include the use of STIMULAN or techniques that go beyond the current clearance / approval granted by the relevant regulatory authority. Please contact your local representative for further information.

Patents granted: GB2367552, EP 1204599 B1, US 6780391, EP 2594231 B1, US 8883063, CN ZL201210466117.X, GB2496710, EP 3058899 B1
Patents pending: GB1502655.2, US 15/040075, CN 201610089710.5, US 15/288328, GB1704688.9, EP 18275044.8, US 15/933936, CN 108619579A

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