Gain initial control over snakebites quickly.

TIME IS HER TISSUE

WHY RISK IT?

CroFab® delivers strength and speed when you need it most.

With more than **50,000 patients** treated to date, it's proven to quickly address local, systemic, and hematologic effects of US pit viper envenomation safely and effectively.[1-3]

Indication

CroFab® Crotalidae Polyvalent Immune Fab (Ovine) is a sheep-derived antivenin indicated for the management of adult and pediatric patients with North American crotalid envenomation. The term crotalid is used to describe the Crotalinae subfamily (formerly known as Crotalidae) of venomous snakes which includes rattlesnakes, copperheads and cottonmouths/water moccasins.

Important Safety Information

Contraindications

Do not administer CroFab® to patients with a known history of hypersensitivity to any of its components, or to papaya or papain unless the benefits outweigh the risks and appropriate management for anaphylactic reactions is readily available.

Please see additional Important Safety Information throughout and enclosed full Prescribing Information.

CROFab®

crotalidae polyvalent immune fab (ovine)

Strike early. Strike with confidence.

INITIAL CONTROL REQUIRES RESOLVING ALL THREE COMPONENTS OF SNAKE ENVENOMATION[1]

Local

Progression of edema, ecchymosis, and leading edge of local injury has been halted.

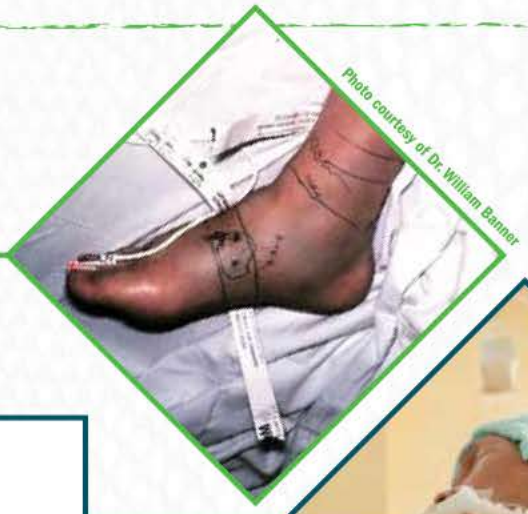

Photo courtesy of Dr. William Banner

Systemic

Patient is normotensive and stable; neurotoxicity resolved or improving; nausea, vomiting, dizziness, or tachycardia resolved.

Hematologic

Coagulation abnormalities, such as thrombocytopenia and spontaneous bleeding, have normalized or are trending toward normal.

When time is tissue®, early and aggressive intervention is critical to gaining initial control.

WHY TREAT SNAKE ENVENOMATION?

Untreated envenomations may lead to irreversible local and systemic damage and can contribute to morbidity and mortality[4,5]

Envenomation is unpredictable. The impact can begin in minutes or be delayed for hours[4,6]

The effects of venom vary widely from patient to patient[6]

98% of venomous snakebites in the United States are from the North American pit viper[5]

WITH CROFAB®, IT DOESN'T MATTER.

CroFab® is the only FDA-approved treatment for all North American pit viper envenomations in adult and pediatric patients.

CroFab® has been proven to*:

- **Halt local effects**, such as edema and ecchymosis, and treat the source of pain[1]
- **Resolve systemic effects**, such as nausea, vomiting, dizziness, or tachycardia[1]
- **Reduce coagulation abnormalities**, such as thrombocytopenia, spontaneous bleeding, and hypofibrinogenemia[1,3]

*Efficacy determined using the snakebite severity score (SSS), a validated objective tool for the clinical evaluation of North American pit viper snakebite in adults. The total score reflects patient evaluation on 6 dimensions: cardiovascular system, local wound, gastrointestinal system, hematologic symptoms, pulmonary system, and central nervous system. The higher the total score, the more severe the snakebite.[7]

Important Safety Information (continued)

Warnings and Precautions

Coagulopathy: In clinical trials, recurrent coagulopathy (the return of a coagulation abnormality after it has been successfully treated with antivenin), characterized by decreased fibrinogen, decreased platelets, and elevated prothrombin time, occurred in approximately half of the patients studied; one patient required re-hospitalization and additional antivenin administration. Recurrent coagulopathy may persist for 1 to 2 weeks or more. Patients who experience coagulopathy due to snakebite should be monitored for recurrent coagulopathy for up to 1 week or longer. During this period, the physician should carefully assess the need for re-treatment with CroFab® and use of any type of anticoagulant or anti-platelet drug.

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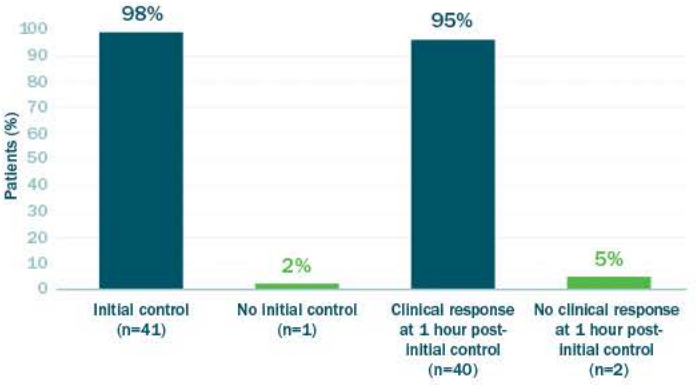
STRENGTH AND SPEED WHEN YOU NEED IT MOST

CroFab® is proven to control envenomation in pediatric and adult patients

Gaining initial control

In 2 open-label trials with 42 patients with mild or moderate envenomation[1,2]*:

- **98% of patients** administered CroFab® gained initial control
- **95% of patients** showed a clinical response† 1 hour after initial control



*These studies excluded envenomation by copperhead snakes.
†Clinical response = pretreatment signs and symptoms of envenomation were arrested or improved.

In a placebo-controlled trial of 74 patients with copperhead envenomation published in 2017‡,

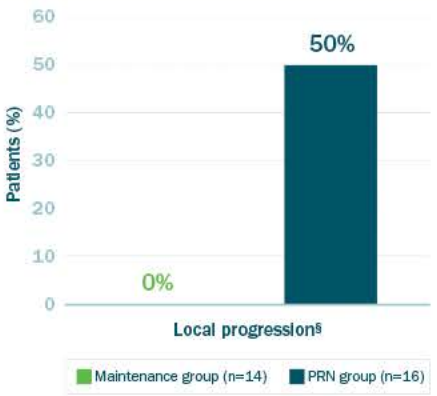
CroFab® administration resulted in improved limb function vs. placebo on Day 14 post envenomation.[7]

‡Trial data was drawn specifically from patients suffering from copperhead snake envenomation, which can result in mild-to-moderate symptoms.

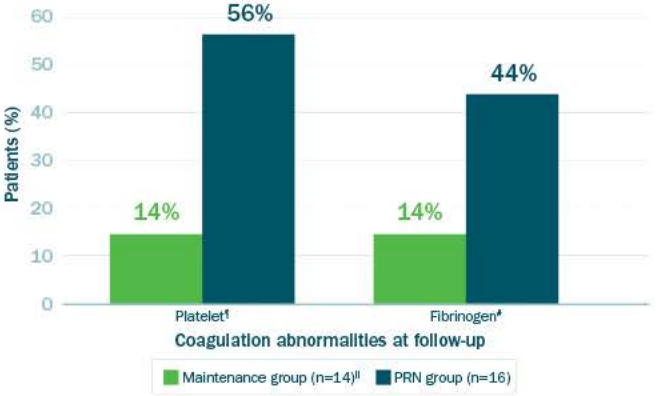
Continuing control

Scheduled maintenance dosing after initial control lowers incidence of coagulation abnormalities due to residual venom.

No local progression with scheduled maintenance dosing[3]



Fewer coagulation abnormalities with scheduled maintenance dosing[1]



§P=0.002
‖Follow-up data not available for 1 patient.
¶P=0.04
#Not statistically significant vs. placebo.

Important Safety Information (continued)

Warnings and Precautions (continued)

Hypersensitivity Reactions: Severe hypersensitivity reactions may occur with CroFab®. In case of acute hypersensitivity reactions, including anaphylaxis and anaphylactoid reactions, discontinue infusion and institute appropriate emergency treatment. Patients allergic to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may also have an allergic reaction to CroFab®. Follow-up all patients for signs and symptoms of delayed allergic reactions or serum sickness (e.g., rash, fever, myalgia, arthralgia).

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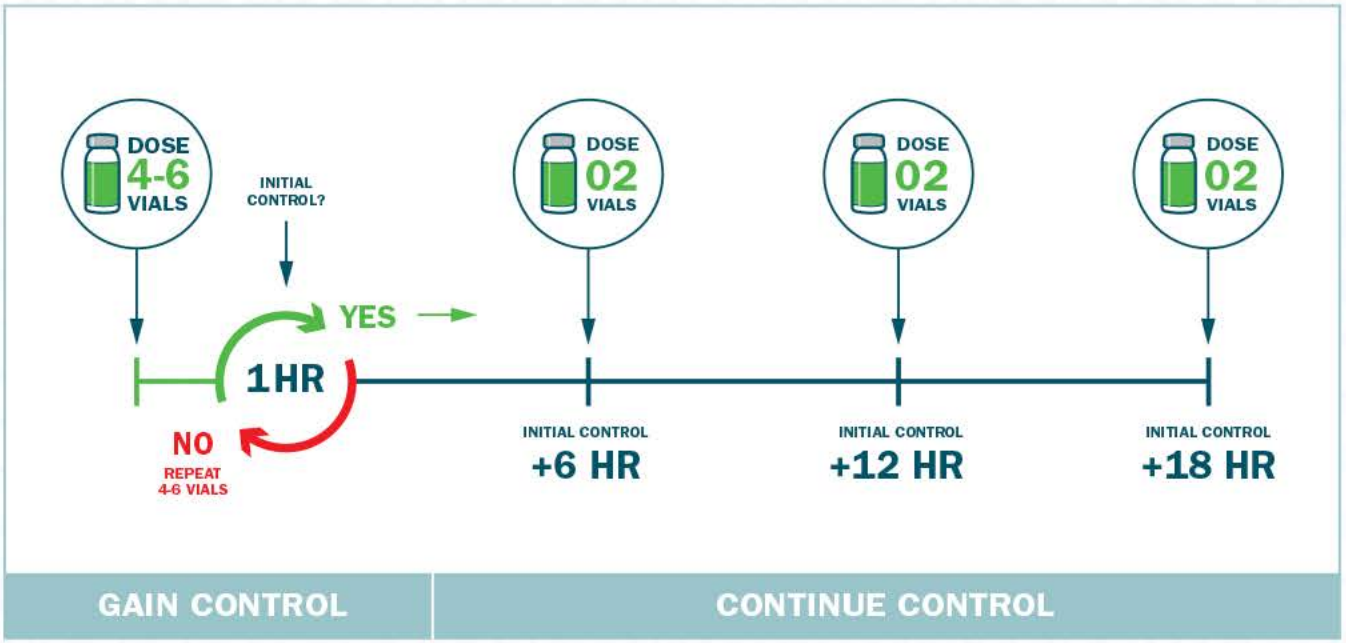
DOSE AND ADMINISTER CROFAB® APPROPRIATELY TO GAIN AND CONTINUE CONTROL OF ENVENOMATION[1,8]

Gaining initial control[1]:

- The starting dose of CroFab® may vary from a minimum of 4 vials to a maximum of 12 vials based on clinical judgment and severity of envenomation*
- If necessary, administer an additional 4 to 6 vials of CroFab® ~1 hour after end of first infusion

*For severe envenomation, a starting dose of 10 to 12 vials may be necessary.



Continuing control[1]:

- Treat adult and pediatric patients with scheduled maintenance dosing after initial control is established
  - Administer an additional 2-vial dose of CroFab® every 6 hours for up to 18 hours (a total of 3 doses)

Important Safety Information (continued)

Adverse Reactions

The most common adverse reactions (incidence ≥ 5% of subjects) reported in the clinical studies were urticaria, rash, nausea, pruritus and back pain. Adverse reactions involving the skin and appendages (primarily rash, urticaria, and pruritus) were reported in 12 of the 42 patients. Two patients had a severe allergic reaction (severe hives and a severe rash and pruritus) following treatment and one patient discontinued CroFab® due to an allergic reaction. Recurrent coagulopathy due to envenomation and requiring additional treatment may occur.

Please see additional Important Safety Information throughout and enclosed full Prescribing Information.

References: 1. CroFab® [prescribing information]. BTG International Inc.; May 2017. **2.** Data on file. Conshohocken, PA; BTG International Inc. 2015. **3.** Dart RC, Seifert SA, Boyer LV, et al. A randomized multicenter trial of crotalinae polyvalent immune Fab (ovine) antivenom for the treatment for crotaline snakebite in the United States. *Arch Intern Med*. 2001;161(16):2030-2036. **4.** Gold BS, Barish RA, Dart RC. North American snake envenomation: diagnosis, treatment, and management. *Emerg Med Clin North Am*. 2004;22(2):423-443. **5.** Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, Banner W. 2016 Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS): 34th Annual Report. *Clin Toxicol*. 2017;55(10):1072-1252. **6.** Dart RC, Hurlbut KM, Garcia R, Boren J. Validation of a severity score for the assessment of crotalid snakebite. *Ann Emerg Med*. 1996;27(3):321-326. **7.** Gerardo CJ, Quackenbush E, Lewis B, et al. The efficacy of crotalidae polyvalent immune Fab (ovine) antivenom versus placebo plus optional rescue therapy on recovery from copperhead snake envenomation: a randomized, double-blind, placebo-controlled clinical trial. *Ann Emerg Med*. 2017;70(2):233-244. **8.** Lavonas EJ, Ruha AM, Banner W, et al. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. *BMC Emerg Med*. 2011;11:2. **9.** Khobrani M, Huckleberry Y, Boesen KJ, et al. Incidence of allergic reactions to Crotalidae polyvalent immune Fab. *Clin Toxicol*. 2019;57(3):164-167. **10.** Kleinschmidt K, Ruha AM, Campleman S, et al. Acute adverse events associated with the administration of Crotalidae polyvalent immune Fab antivenom within the North American Snakebite Registry. *Clin Toxicol*. 2018;56(11):1115-1120.

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WHEN TIME IS TISSUE

WHY RISK IT?

Strength and speed when you need it most

98%

of patients administered CroFab® gained initial control[1,2]

Proven to halt local effects, resolve systemic effects, and reduce coagulation abnormalities[1,3*]

95%

of patients showed a clinical response 1 hour after initial control[1,2]

Established performance backed by over 15 years of clinical experience

- Studied in pediatric and adult patients in all North American pit viper species in all levels of severity[1]
- Post-marketing data reports low rates of hypersensitivity reactions (1.4 to 2.7%) in two studies of 1,340 and 373 patients, respectively[9,10]
- More than 50,000 patients treated to date[2]

Broad species coverage

The only FDA-approved treatment derived exclusively from US snakes and approved to treat all North American pit viper envenomations in adult and pediatric patients.[1]

Produced in a country with livestock free from prion disease[2]

CroFab® is manufactured from serum obtained only from sheep located in Australia in order to protect humans from exposure to unnecessary pathogens.[2]

*Efficacy determined using the snakebite severity score (SSS), a validated objective tool for the clinical evaluation of North American pit viper snakebite in adults. The total score reflects patient evaluation on 6 dimensions: cardiovascular system, local wound, gastrointestinal system, hematologic symptoms, pulmonary system, and central nervous system. The higher the total score, the more severe the snakebite.[7]

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BTG

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