

# **Product Name: RC1002 (ClotIt®)**

## **Protégé Biomedical Hemostasis Technology**

### *Summary of In-vivo Safety and Efficacy*

## **Introduction**

### **Hemostasis Products in General and Clinical Attributes**

There are a variety of hemostatic products available today. Product range from shellfish-derived compositions made up of chitosan such as Hemcon (TriStar Wellness Solutions inc), plant-based products such as Arista™ MPH (CR Bard/Medafors) and Surgicel® (Ethicon), mineral based hemostats such as QuikClot (ZMedica), Fibrin sealants such as Tisseel (Baxter), or styptic powder such as Kwik Stop with Benzocaine which freezes the nerve ends close to the area where applied with ferric subsulfate to control the bleeding; Benzocaine is a topical anesthetic to ease pain and discomfort.

### **Need for Hemostasis Products**

Uncontrolled bleeding is a problem for military, surgical, emergency and dental applications, as well as for animals and the general consumer. Inadequate surgical hemostasis may lead to the need for blood transfusions or cause other serious patient complications. Products within these market segments each have their own set of challenges. Uncontrolled hemorrhage is the leading cause of preventable combat-related deaths. Current products on the market do not work better than pressure alone. Fibrin sealants are commonly used to stop bleeding in surgery. However, they are extremely expensive. Applying pressure alone is remarkably time consuming. Bleeding problems for animals is also large and includes vets, pet owners, and farmers. The only product available for pet owners to purchase to stop bleeding on minor cuts such as nail trimming is styptic powder. Styptic Powder works to temporarily constrict the blood vessels, slowing the blood flow. When surveyed, vets and store employees commented that styptic powder is not effective, and trying to apply pressure or using an absorbent material such as flour or corn starch works equally as well. The most common way of stopping bleeding for dental surgery is to have the patient bite down on gauze until the bleeding stops, which adds significant time to oral surgery – 30-45 minutes after a tooth extraction. In addition, patients are not supposed to talk for a minimum of 2-3 hours after this procedure, and patients are told that bleeding for up to 3 days after extraction is normal.<sup>1</sup> General consumers would also benefit from hemostasis products to help heal shaving cuts, paper cuts, nose bleeds, and scrapes, cuts and abrasions, particularly useful in children who are fearful of blood.



1. <http://www.identalhub.com/dental-bleeding-after-tooth-extraction-877.aspx>

## ClotIt® Technology Overview

Protégé Biomedical's new hemostat, ClotIt®, features a patent-pending, unique compound of all-natural minerals, that acts via a four-pronged pathway to enable rapid hemostasis; factor activation, vasoconstriction, flocculation, and absorption. Upon contact with blood, ClotIt facilitates and accelerates the body's natural coagulation cascade, while simultaneously slowing blood flow, by constricting local vessels and capillaries. Two key components in the ClotIt technology include aluminum sulfate and mullite. The aluminum sulfate in ClotIt causes the formation of multiple loose clumps of cells (flocculation) which brings the cellular components of clotting close together. This clumping in combination with the activation of clotting by the second component, mullite, dramatically accelerates the formation of a clot, and thus decreases the time required to stop bleeding. ClotIt's fine granules rapidly absorb plasma at the wound site, leaving behind platelets and blood cells, to aid in forming a solid clot. This novel multi-action process results in complete clotting in seconds.

ClotIt has been found to have similar clotting ability to another mineral based product, QuikClot, but without the exothermic (heat generating) reaction found in QuikClot's original formula. Protégé Biomedical's product uses a mineral with similar absorptive qualities as QuikClot's Kaolin-based hemostat, but also combines it with a vasoconstrictor to aid in the rapid clotting of smaller wounds.

## In vivo Safety and Efficacy Studies

### Study Designs and Endpoints

Three in vivo studies have been conducted to evaluate the clinical safety and efficacy of ClotIt in comparison to a surgical 'no treatment' control and to a commercially available hemostatic agent. These preliminary, non-GLP studies were conducted in a rabbit model, which is well established for the evaluation of hemostatic agents for hemostasis and subsequent wound healing. A combination of acute as well as 1 and 4 week survival endpoints were assessed across these studies, to enable insights into the initial hemostasis and wound healing progression related to the use of ClotIt or its comparators. An associated goal for these initial evaluations was the determination of the optimal study protocol that could be applied to definitive, GLP studies demonstrating the clinical safety and efficacy of ClotIt.

The safety endpoints for these initial in vivo studies were the absence of local toxicity effects related to the application of ClotIt and the lack of compromise of normal wound healing progression, assessed acutely as well as at 1 week and 4 week endpoints. The efficacy endpoints for these studies were ClotIt's ability to establish hemostasis and its comparative success versus a control and a competitive product, at both acute and longer term (1 week and 4 week) time points. For the longer evaluation time points, the potential for ClotIt to accelerate wound healing in comparison to control and a competitive product was also assessed.

For 2 of the 3 studies, multiple 1 cm dorsal incisions were created by a veterinarian, with each incision being treated with ClotIt or the competitive product, or being left untreated as a control site, in a predetermined pattern, per protocol. The time to acute hemostasis for each test site was observed and recorded by a veterinarian. Subsequent to the acute observations related to the hemostasis at each test site on a test animal, progression to wound healing was recorded at regular intervals for each animal by a veterinarian until the study termination time point. The first study had a 1 week endpoint and the second study had a 4 week endpoint.

A third study was conducted for the acute assessment of the safety and efficacy of ClotIt in effecting hemostasis in a more significant wound involving the femoral artery. The efficacy endpoint used in this study was the ability of ClotIt to create hemostasis in situations where the patency of the rabbit femoral artery was compromised, due to being nicked or surgically bisected. The safety endpoint was the continued patency and resumption of normal hemodynamics in a nicked femoral artery, after hemostasis was established via the application of ClotIt.

### Results

Results from the first study are presented in Table 1 and representative pictures of hemostasis outcomes are shown in Figure 1. In this initial study, the results indicated that the use of ClotIt appeared to cause much quicker wound healing than did its comparators. In fact, the average time to healing observed for the competitive product, Kwik Stop, did not differ much from the average time required for the untreated control wounds to heal. No safety issues were observed with the use of ClotIt, on a standalone or in regards to its comparators. An additional assessment conducted during this study was the visual assessment of acute hemostasis by ClotIt compared to that obtained by the use of a commercially available fibrin-based hemostatic agent. Representative pictures of this assessment are provided in Figure 2. In this assessment, ClotIt was observed to provide an outcome similar to fibrin in creating acute hemostasis which, given the significantly lower cost of ClotIt, demonstrated an economic advantage for its use over fibrin-based products.

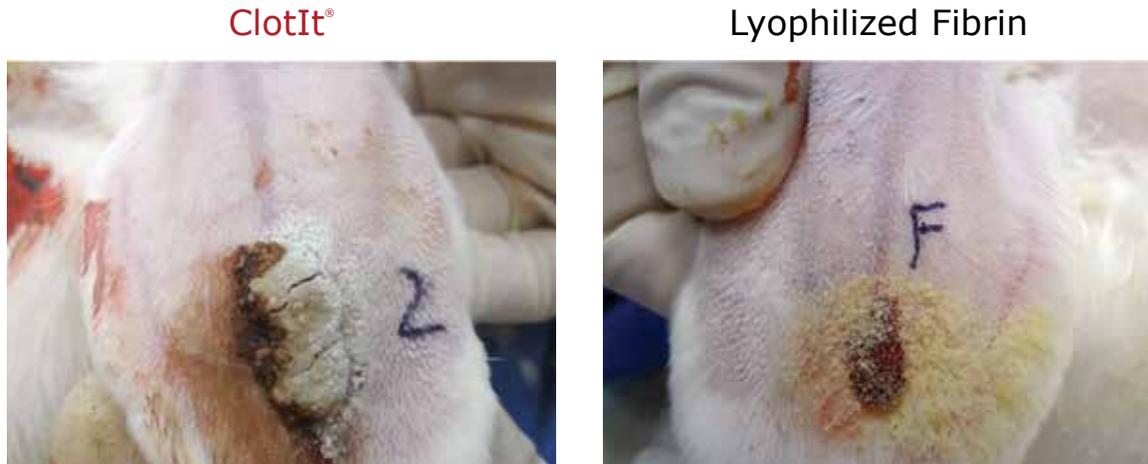
**Table 1:** Effect on Wound Healing

Treatment	Average time to healing (days)
Control (no treatment)	8.00
ClotIt®	2.67
Kwik Stop	9.00

**Figure 1:** Hemostasis Efficacy of ClotIt® and Kwik Stop.



**Figure 2:** Hemostasis Outcomes from Clotit® and Fibrin.



The results from the second study, although impacted by pre-endpoint mortality of some of the test animals in the control and competitor product (Kwik Stop) arms and by post-operative grooming-related compromise of some of the incisions in one of the test animals in the ClotIt® arm, again demonstrated the safety of the ClotIt product.

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The acute hemostasis efficacy of ClotIt® was once again established in this study, and representative pictures of ClotIt compared to control (no treatment) are shown in Figure 3. On the other hand, no clear trends of its impact on wound healing in relation to its comparators could be established in the 4 week study period, given the post-acute animal attrition described previously.

**Figure 3:** Hemostasis Effectiveness for ClotIt® (bottom row in photograph) and Control (no treatment, top row in photograph)



The outcomes from the third in vivo study demonstrated that ClotIt could effectively create hemostasis in a bisected femoral artery. The observations indicated that ClotIt was most effective when applied directly to the wound site and when manual pressure was applied to the site, in conjunction with the application of ClotIt. It was further determined during necropsy that the hemostasis effected by the topical application of ClotIt to a compromised femoral artery did not compromise the patency of its lumen, thus maintaining blood flow through the vessel post-treatment with ClotIt.

## Discussion and Conclusions

The results from this series of preliminary assessments of hemostasis and wound healing in a rabbit model indicate a trend towards equivalent or superior performance of ClotIt compared to currently available competitors like KwikStop and fibrin. The outcomes strongly indicate that ClotIt is safe when used for hemostasis, with no observed acute or late stage local toxicity or wound healing compromise. In fact, while not definitive, this preliminary results indicate the possibility that ClotIt may enable quicker wound healing than competitive hemostatic agents like Kwik Stop. Further, this series of studies enables the robust design of additional in vivo studies which, when conducted per GLP guidelines, should provide definitive evidence of the safety and efficacy of the ClotIt formulation, both on an absolute and when compared to other formulations such as KwikStop and fibrin.

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