Safety and Efficacy Mechanisms of the Claudere Vascular Hemostatic Device (HD)

Claudere Vascular has developed and tested in three human clinical trials a vascular closure system that provides all the safety characteristics of manual compression, but shortens times to hemostasis and times to ambulation. The design of the Claudere Vascular HD system has fully responded to the market's often stated specifications for a safe, easy to use and cost effective closure system.

THE CLAUDERE VASCULAR HEMOSTATIC DEVICE (CLAUDERE VASCULAR HD)

The Claudere Vascular HD system consists of two components:
A standard 12 cc syringe with a 'reactor' chamber in the distal tip containing a porous matrix of inert material coated with a proprietary heparin removing polymer. (Version I of the Claudere Vascular system is designed to work with heparin. The second component is referred to as the 'wall locator' and consists of an 18 gauge wire with a collapsible disc at its distal end. The wall locator prevents anticoagulated blood from exiting the artery while the sealing clot is being deployed.

THE CLOSING PROCEDURE USING THE CLAUDERE VASCULAR HD

At the end of the procedure, approximately eight cc's of blood is drawn from the anticoagulated patient through the side arm of the procedural sheath and into the syringe containing the heparin removing porous matrix. When blood is drawn into the syringe, it passes through the reactor chamber where the polymer selectively and instantaneously binds all available heparin. A patient's heparinized blood entering the system with an elevated activated clotting time (ACT) (ACT greater than 150 seconds) will leave the reactor syringe with a clotting time *below normal baseline* for the patient. The reduction of clotting time below baseline levels is due to the mechanical shear induced by the porous matrix as well as contact with the polymer coated matrix in the reaction chamber of the syringe. Decreasing the baseline will shorten times to hemostasis. This phenomena is attributed to activation of the intrinsic clotting pathway via activation of Factor XII. The clotting time reduction is typically 10% below baseline which reduces the time to clot formation, or hemostasis, to 10% less time than the normal clotting time for that patient.

The heparin-removing polymer is tightly bound to the inert substrate (matrix) in the chamber and therefore does not leach or elute into the passing blood. This has been documented with mass spectroscopy and chromotagraphy studies conducted during the preclinical safety studies. The polymer coating process is carefully controlled to assure that only heparin and not any proteins involved in the clotting process are removed.

MANUAL COMPRESSION STILL COMMONLY USED

Manual compression remains the most frequently employed closure method. While manual compression works it has also proven to be time-consuming, expensive, and very uncomfortable for the patient. Vascular closure devices were intended to shorten the times to hemostasis (cessation of bleeding) and have been adopted in 35%-40% of the procedures

undertaken. Continued safety, cost and ease of use concerns have prevented universal acceptance of vascular closure devices even though they have been available for several years. The Claudere Vascular HD has addressed each of these concerns in its unique design.

Manual compression is used to achieve vascular access hemostasis AFTER the patient's body has metabolized heparin administered during a procedure. In a typical interventional procedure it may take several hours for the ACTs to return to baseline (less than 150 seconds). Metabolic removal of heparin can take from 20 minutes in a patient with healthy liver function to several hours when liver function is compromised. When the ACT reaches baseline, the procedural sheath is removed and an attendant will manually compress the access site using firm two-handed pressure until a clot forms and the patient's own blood seals the tissue tract adjacent to the access site. The compression time can take anywhere from 5 minutes to more than an hour. Sometimes sandbags or clamps are applied to the access site during the compression time. Patients often remain flat on their backs with sandbags on their legs for 6-8 hours. The time from when the patient leaves the catheterization laboratory to the time when the patient can ambulate is often more than six hours and usually requires an overnight stay in the hospital.

When the Claudere Vascular HD system is introduced into the procedure, the wait times for heparin to be metabolized is eliminated and patients are able to ambulate sooner than when manual compression alone is used.

RATIONALE FOR THE CLAUDERE VASCULAR HD PRODUCT DESIGN

With these facts in mind, Claudere Vascular has designed a system that emulates all the safety and efficacy characteristics of manual compression but eliminates the long wait times and patient discomfort. The Claudere Vascular HD sytem is defined as an *adjunct to manual compression* but it operates in a completely different mode than C-clamps or closure patches which are also defined as adjuncts.

As is always the case, use of the Claudere Vascular technique involves some trade-offs. Competing closure systems often claim 3-10 minutes' times to hemostasis but involve metal clips, sutures or other foreign materials left behind which present safety concerns. Using the Claudere Vascular system, times to hemostasis are shortened to 10-15 minutes but without involving the use of any foreign material. *The critical parameter, time to ambulation, is comparable to any competing device.* Times to ambulation usually determine time to discharge which is the metric associated with lowered hospital costs and increased patient satisfaction.

HOW THE CLAUDERE VASCULAR HD FUNCTIONS

Use of Claudere Vascular HD enables the immediate application of the manual compression sealing technique. Even in the case of highly heparinized interventional cardiology patients, a reliable and safe hemostatic seal can be achieved without waiting for circulating heparin levels to drop.

Claudere Vascular HD removes heparin from blood or plasma by simple ion exchange. The heparin-removing polymer is engineered to have specificity for heparin in blood. The basic theory for ion exchange in Claudere Vascular HD is that the positive (cationic) ion exchanges resin in the reactor chamber attracts and holds the negative (anionic) charged heparin. The proprietary polymer is tightly bound to the substrate material and no traces of unbound polymer, measured to parts per million (ppm), can be eluted from the matrix or released into blood. The polymer is known to be biocompatible.

At the end of the procedure, 5-10 cc's of the patient's blood is drawn into the 12cc syringe containing the heparin-removing matrix (reactor) from the side arm of the procedural sheath. The wall locator is deployed in its collapsed position and once it is inside the artery, the disc is expanded and drawn against the inner aspect of

the punctured artery to prevent anticoagulated blood from exiting. The treated blood is deployed into the tissue tract and around the punctured artery.

The fact that blood is in a semi-liquid to liquid state at this time provides an advantage no other closure system can provide. The blood not only fills the tissue tract to form a seal but also flows around the artery and up and down the neurovascular sheath that contains the artery. This facilitates sealing inadvertent needle sticks to the posterior side of the artery. *'Back sticks' are a primary cause of the most common complication of interventional procedures: retroperitoneal bleeding*.

The ability to reduce or eliminate hemorrhage from posterior wall punctures is a significant advantage of Claudere Vascular HD.

The final step is 10-15 minutes of manual compression which allows the clot to mature and a robust seal to form.

The reliability of this clot formation is achieved by three factors which define Claudere Vascular HD:

1. Heparin is removed from circulating blood
2. The intrinsic clotting pathway (Factor XII) has been activated by mechanical shear and by polymer surface contact
3. The extrinsic clotting pathway (Factor VII) becomes operative when blood passes through the tissue tract and tissue clotting proteins are released.

This is the same mechanism that occurs when a finger is cut and the injured person instinctively holds pressure until it stops bleeding. The blood in the capillaries, arteries and veins in contact with the endothelial lining do not clot but the free blood at the cut site clots quickly and forms a seal.

CLAUDERE VASCULAR HD WORKS IN THE PRESENCE OF PLATELET INHIBITORS

Heparin works by inhibiting the fibrinogen to fibrin system which is a step in the coagulation cascade. In the absence of heparin, blood will form a firm clot regardless of the state of platelet aggregation activity. Plasma, or blood with red and white cells and platelets removed, will still clot provided heparin is not present. Platelet aggregation is not a necessary condition for the formation of a stable clot capable of effecting hemostasis.

Platelet aggregation inhibitors such as IIb/IIIa, Plavix or aspirin (not an inclusive list) do not affect the efficacy of Claudere Vascular HD. Several studies were completed at the Mayo Clinic research facility both on the bench and in living organisms that demonstrate that hemostasis is achieved in the presence of platelet inhibitors.

OTHER SAFETY CONCERNS ABOUT THE USE OF DEVICE-MEDIATED CLOSURE THAT ARE ADDRESSED BY CLAUDERE VASCULAR HD

The single most significant adverse event that has been known to occur with device-mediated vascular access closure is the inadvertent occlusion or partial occlusion of the accessed vessel. This can occur in the event of deployment or positioning of hemostatic material into the artery rather than into the adjacent tissue tract. Biologic materials such as collagen and thrombin are potent clot inducing agents so powerful that they will overwhelm the body's defenses against clot generation within the vascular system. Absorbable polymers such as the polyethylene glycol (used in the Access Closure system) or Polyglycolic acid (used in the Cordis ExoSeal) are not affected by any clot-dissolving agent that might be used to treat a normal blood clot-induced ischemic event. If accidentally deployed into the artery, they have the potential to impair blood flow and may have to be removed surgically.

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WHITE PAPER

Closure devices such as the Abbott PerClose and StarClose products use clips and sutures to close puncture wound arteriotomies. When inaccurately deployed, these two can impair blood flow and surgical removal may be necessary.

Claudere Vascular HD has addressed these safety concerns:
Claudere Vascular HD eliminates the incremental risk of an ischemic occlusion caused by the use of a sealing device. It has no intravascular component and except for the wall locator, Claudere Vascular HD never enters the body and does not form, create or provide a hemostatic agent such as collagen, thrombin or sutures. Autologous blood, without the addition of any clot inducing material, is the only hemostatic agent.

In tests conducted in living organisms to support a U.S. clinical trial protocol, it has been established that even in the event of deployment of the treated blood directly into a manually occluded artery, an ischemic event will not occur. Additionally, large amounts of treated blood have been introduced into renal arteries and femoral arteries followed by full body X-ray scans, biochemical testing and necropsy, and no clot formation or fibrin organization was ever observed. Had this same blood been deployed outside the artery a clot would have quickly formed.

In summary, the important safety advantages are the following:

A. Nothing is left behind, no foreign material such as thrombin, collagen, sutures, clips or polymer plugs are used to achieve hemostasis. Because of that:

1. The possibilities of allergic or inflammatory response to a foreign material is eliminated
2. Emergency or chronic re-entry is possible: no clips, sutures or plugs to block re-entry
3. No possibility of intra-arterial occlusion or flow impairment because of the autologous nature of the sealing clot

B. Semi-liquid clotting blood seals inadvertent needle sticks on the back side of the artery (back sticks). Back sticks are the major cause of retroperitoneal bleeding; one of the most lethal complications of interventional procedures.

C. Claudere Vascular HD was designed to be "fail-safe," meaning that if there is a device or operator error, recovery is as simple as reverting to manual compression. No surgical intervention would ever be necessary. All that is lost is a little time.

D. The device is easy to operate that deployment (operator) errors are minimized.

CLAUDERE VASCULAR