

SUMMARY OF: PMA P050044/SUPPLEMENT 021

STRYKER ORTHOBIOLOGICS VITAGEL-RT

DESCRIPTION OF CHANGES/ REASON FOR SUPPLEMENT

Stryker Orthobiologics submitted this 180 day PMA supplement (P050044/S021) in order to seek approval of a modification to the currently approved Vitagel product. The change being made is to replace the bovine thrombin with recombinant human thrombin (rh-thrombin). All other components and product preparation materials will remain unchanged. This new product with rh-thrombin will be named “Vitagel RT.” An additional manufacturing line will also be qualified in order to produce Vitagel RT.

INDICATIONS FOR USE

Vitagel is indicated in surgical procedures (other than neurosurgical and ophthalmic) as an adjunct to hemostasis when control of bleeding by ligation or conventional procedures is ineffective or impractical.

DEVICE DESCRIPTION

Vitagel Surgical Hemostat is composed of a suspension of bovine collagen and bovine thrombin, which, when combined with the patient’s plasma, forms a safe and effective hemostat. Vitagel Surgical Hemostat includes the following components and/or accessories:

- Vitagel Syringe – an aseptically filled, sterile syringe containing a suspension of bovine collagen, bovine thrombin, and calcium chloride
- Transfer Syringe – a sterile empty syringe used following collection of autologous human plasma (using the CellPaker accessory)
- Delivery System – an apparatus designed to combine and mix the contents of the Vitagel Syringe with the patient’s plasma contained in the transfer syringe at the time of administration to the bleeding site. The product’s delivery system is comprised of:
 - A joiner to connect the Vitagel Syringe to the Transfer Syringe
 - A spray head incorporating a mixer element
 - A cannula incorporating a mixer element (provided as an alternate delivery component to the spray head)
 - A syringe clip to permit the depression of the plunger rods of the two syringes simultaneously
 - A syringe support to aid the surgeon in holding the assembled device
- CellPaker Plasma Collection Device – a sterile blood collection accessory containing (b)(4) Trade Secret of a solution comprised of approximately 99% sodium citrate, USP and 1% ethanol. It is used to separate plasma from whole blood via centrifugation.

- Tabletop Centrifuge

MANUFACTURING

Related to the production of this new version of Vitagel, the sponsor will be adding a new aseptic manufacturing line. The following documentation were reviewed and determined to be adequate:

- Design controls
- Design verification testing
- Purchasing controls
- Production & process controls
- Inspection, measuring, and test equipment
- Process validation
- Process failure mode and effects analysis
- Documentation of validation activities

An establishment inspection was conducted by FDA and closed with a No Action Indicated decision. Inspection findings did not indicate any outstanding safety or effectiveness concerns based on the inspection of the manufacturing site and associated processes that are pertinent to the proposed change.

PRECLINICAL/BENCH

BIOCOMPATIBILITY/MATERIALS

The sponsor evaluated the potential for the creation of new risks associated with this change in component to rh-thrombin from bovine thrombin in the Vitagel product. With respect to the biocompatibility of the Vitagel product, the sponsor did not believe that this change presented any new risks that would require the conduct of additional biocompatibility testing. A determination was made that only confirmatory cytotoxicity testing was required to verify the conclusions of the biological safety evaluation. Testing was conducted in accordance to ISO 10993-5. The Vitagel-RT product was assessed to be biocompatible with a reactivity grade = 0 when L-929 cells were exposed to the test article extract. All controls performed as expected.

ANIMAL STUDIES

An animal study conducted in rabbits (rabbit kidney bleeding model) was designed to verify non-inferiority of the Vitagel with rh-thrombin as compared to Vitagel with bovine thrombin. Forty four rabbits were used in this study. Each rabbit received four injuries/insults to the kidneys (two incisions per kidney, each being 2mm deep by 15mm in length). The severity of bleeding was scored by a surgical veterinarian. Gauze was applied with light pressure to the site and removed immediately prior to application of the test or control material. The time from material application to time of hemostasis was recorded to the nearest

second. The surgical veterinarian determined the time of hemostasis as defined by the time at which all bleeding was contained by the applied material. The amount of material used and the number of applications was recorded. Incisions were made and treated in a sequential manner where a new incision was made only after the previous incision had been managed and hemostasis achieved. After hemostasis was achieved on the fourth and final incision, animals were euthanized while still under general anesthesia.

Due to the study design, which did not include an untreated control group, the test cannot prove that either device is effective. However, based on information from the publication cited by the sponsor (Prior, Power and DeLustro, 2000), it suggests that this methodology would lead to hemorrhage in excess of 200 seconds in an untreated control. A major limitation of the study is that the bleeding score cannot be equated to actual clinical severity and the score was subjective and subject to bias. Therefore, the study design does not allow for determination of hemostatic effectiveness of a specific product but does allow for comparative evaluation of hemostatic effectiveness between two products.

Regarding time to hemostasis there was no significant difference between the two groups ($p > 0.05$). The percent of success was comparable and statistically the percent of success was not likely to be in excess of 15% using an appropriately defended confidence interval. The null hypothesis is accepted. Therefore, the test is favorable and supports the finding that the new device is not inferior to the original with the limitations identified above.

STABILITY TESTING

Product stability of Vitagel-RT was evaluated under real-time aging conditions. The following properties were evaluated at $t = 0, 6,$ and 12 months:

- Thrombin activity
- Visual appearance
- pH
- Collagen conformation
- Protein concentration

The available data adequately support a 12 month shelf life for the Vitagel-RT.

CLINICAL DATA

Clinical data were not needed in order to support approval of a change in thrombin source from bovine to recombinant human.

LABELING

The labeling developed for the Vitagel-RT contains identical information as the Vitagel labeling with additional information, including contraindications, warnings, and

precautions, that is specific to the rh-thrombin component. The labeling adequately explains that Vitagel-RT safety and effectiveness is based on the clinical study for Vitagel and the additional animal study to evaluate hemostatic effectiveness. Language related to specific risks associated with bovine thrombin has been removed.

CONCLUSION

The sponsor has conducted an animal study to demonstrate product performance equivalence between the Vitagel (current product) and Vitagel RT (new product). The sponsor has provided 12 month interim data collected from the Vitagel RT stability study to support a 12 month shelf life. The quality systems documentation provided in the original submission and subsequent amendment was reviewed and determined to be adequate. An establishment inspection has been completed and closed with a No Action Indicated decision.

The inclusion of the rh-thrombin in the Vitagel-RT product required a separate BLA supplement approval. This BLA supplement was approved on August 14, 2013.

All labeling issues have been adequately addressed.