

SUMMARY REVIEW MEMO

Date: January 4, 2010

From: (b) (6) (b)(6) Ph.D.
FDA/CDRH/ODE/DSORD/PRSB

Subject: P990009/Supplement 025
Floseal Hemostatic Matrix 5ml/10ml Kit
Baxter Healthcare Corporation

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To: The Record

Reason for Supplement

Baxter, the sponsor, is seeking approval of the following two changes to their Floseal Hemostatic Matrix:

1. Introduction of a second viral inactivation step in the manufacturing process to the human thrombin. The thrombin manufacturing process change will be submitted as a Prior Approval Supplement to (b) (6) (b)(4) (reviewed by CBER).
2. Updated instructions for use to reference the additional viral inactivation step for the thrombin component. Other additional updates include: addition of a new symbol, removal of outdated symbols, revision of labeling format, and streamlining content to remove redundancy.

Review Team

(b) (6) (b)(6) Ph.D. (Biomedical Engineer)

Indications For Use

Floseal Hemostatic Matrix Kit is indicated in surgical procedures (other than in ophthalmic) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

Device Description

The Floseal Hemostatic Matrix Kit consists of a bovine-derived gelatin matrix component, a human thrombin component that is comprised of lyophilized human thrombin and a calcium chloride diluent, plastic applicator tips, and several mixing accessories.

Summary of Pre-Clinical Data

In this submission, the name "Flo seal VH" refers to the version of Flo seal in which human thrombin is subjected to one viral inactivation step (as is currently marketed). The name "Flo seal VH S/D" refers to the version of Flo seal where thrombin is subjected to two viral inactivation steps: vapor heat and solvent detergent (approval being sought in this supplement).

The following two manufacturing changes are being reported:

1. Two batch size configurations for thrombin manufacture to allow for a larger batch size in addition to the current batch size. The larger batch size configuration will be validated for maximum lyophilization loading and longer process filtration time.
2. The manufacturing process for thrombin has been modified to improve the purity (specific activity).

The above manufacturing changes to the thrombin component were reviewed by CBER as a supplement to (b) (4)

The following six biocompatibility tests were conducted on the Flo seal VH S/D.

1. Genotoxicity testing (in accordance to ISO 10993-3)
2. Hemocompatibility testing (in accordance to ISO 10993-4)
3. Cytotoxicity testing (in accordance to ISO 10993-5)
4. Muscle implantation testing (in accordance to ISO 10993-6)
5. Intracutaneous reactivity and delayed dermal contact sensitization testing (in accordance to ISO 10993-10)
6. Acute systemic toxicity (in accordance to ISO 10993-11)

According to the conditions of these tests, Flo seal VH S/D was determined to be biocompatible.

Thromboelastography was conducted on three types of thrombin: human thrombin VH S/D, human thrombin VH, and bovine thrombin-JMI; time to clot formation was evaluated. For each type of thrombin, 3 different lots (4 samples per lot) were evaluated. Each type of thrombin was reconstituted according to label instructions then diluted further into 5 concentrations between 0.625 and 10 IU thrombin/ml. The assay was conducted using citrated human plasma. Results demonstrate similar clotting times for each of the three thrombin variants.

The supplement is being submitted to seek approval for a new version of Flo seal which incorporates human thrombin that has been subjected to an additional solvent detergent process for viral inactivation. In order to demonstrate that there are no adverse effects on product effectiveness from this additional manufacturing step, the sponsor demonstrated that the new version of Flo seal is equivalent in safety and effectiveness to the current version of Flo seal through data collected from an animal study. Clinical study data were not necessary to demonstrate equivalence in safety and effectiveness between the new and current versions of Flo seal.

In the original submission, data collected from a study of time to hemostasis evaluated in a rabbit liver model was submitted in order to demonstrate that there are no adverse effects on product effectiveness from this additional manufacturing step for the thrombin component. The study compared the performance of three versions of Floseal to a control topical hemostat. The three versions of Floseal differed only in the thrombin component: human thrombin VH S/D (500 IU/ml), human thrombin VH (500 IU/ml), or bovine thrombin-JMI (1000 US units/ml). Spongostan gelatin sponge was used as a control topical hemostat.

At least 30 minutes prior to surgery, rabbits were given high doses of heparin and a plasma expander infusion in order to decrease clotting ability. Full penetrating lesions were created on the liver using punches through median laparotomy. The control Spongostan and the three Floseal variants were reconstituted and applied according to labeling instructions. The surgeon was blinded to which variant of Floseal was used in each rabbit. Due to the different product characteristic, the surgeon was not blinded to application of Spongostan. Reapplication of hemostatic agent was allowed until hemostasis was achieved. A maximum application of 4ml of Floseal variants would be allowed for each liver injury. A maximum application of 8 Spongostan would be allowed for each liver injury. For each of the test and control materials, evaluation was conducted in 12 animals. Animals in which hemostasis could not be achieved were sacrificed. The remaining animals were observed for rebleeding and sacrificed after 24 hours. Lesions were evaluated for time to hemostasis, rebleeding, and 24 hour rebleeding. Animals were also evaluated for 24 hour survival.

The median time to hemostasis was 360 seconds for Floseal Bovine Thrombin, 540 seconds for Floseal VH, 450 seconds for Floseal VH S/D, and greater than 900 seconds for Spongostan. At 15 minutes post-product application, 0 of 12 animals had rebleeding with Floseal Bovine Thrombin, 0 of 12 animals with Floseal VH, 1 of 12 animals with Floseal VH S/D, and 14 of 15 animals with Spongostan. The percentage of animals with 24 hour survival was 100% for Floseal Bovine Thrombin, 100% for Floseal VH, and 91.7% for Floseal VH S/D, while only one animal survived with Spongostan. At 24 hours, 8 of 12 animals had rebleeding with Floseal Bovine Thrombin, 6 of 12 animals with Floseal VH, 4 of 11 animals with Floseal VH S/D, and 1 of 1 animals with Spongostan.

All thrombin variants achieved statistically significant improvements in time to hemostasis compared to Spongostan. There was a statistically significantly (at the 5% level) lower percentage of animals with 15 minute bleeding with all three test items than with Spongostan. There was a statistically significant (at the 5% level) shorter time to hemostasis with all three test items than with Spongostan. However, this study was not designed to compare the effectiveness of the current and new versions of Floseal; therefore, data collected from this study cannot be used to conclude that no adverse effect on product effectiveness results from the additional manufacturing process for thrombin.

In a major deficiency letter (dated July 31, 2009), the sponsor was asked to provide additional animal study data to demonstrate that the new version of Floseal is as effective

as the current approved version. In response to this request, the sponsor submitted additional animal study data collected where the purpose of the study was to compare the hemostatic effectiveness, measured in time to hemostasis, of Floseal VH and Floseal VH S/D in the porcine liver abrasion model.

One hundred and twenty lesions per group (240 total) were performed in this study. Superficial liver abrasions were created, and the degree of bleeding pre-treatment was scored from 0-5. Two lesions were created at the same time, and each lesion was treated with either 2ml of Floseal VH or Floseal VH S/D (applied according to instructions for use) in a randomized order. Time to hemostasis was measured in seconds continuously after product application (up to 10 minutes) to assess non-inferiority of the hemostatic effectiveness of Floseal VH S/D to Floseal VH. Per product instructions, pressure was applied to Floseal using gauze for 120 seconds. Once hemostasis was achieved for a lesion, excess product was irrigated. At 10 minutes after product application, bleeding was assessed and a graded bleeding score was assigned.

The geometric mean ratio of Floseal VH to Floseal VH S/D in terms of seconds to hemostasis was 1.01. Its one-sided 97.5% lower confidence limit was 0.957, demonstrating Floseal VH S/D to be non-inferior to Floseal VH in this study. Hemostatic control and maintenance based on bleeding score success of Floseal VH and Floseal VH S/D were not significantly different from each other at 10 minutes post-treatment. Therefore, the new version of Floseal, Floseal VH S/D, which incorporates human thrombin that has been subjected to an additional solvent detergent process for viral inactivation, was demonstrated to have equivalent effectiveness in hemostasis to the current version of Floseal, Floseal VH.

Review of Proposed Labeling Changes

The sponsor states that the following changes have been made to the product labeling.

1. mention of the additional viral inactivation step
2. minor updates to the kit box format
3. include mention of additional viral inactivation step
4. minor updates to format
5. additional text revisions
6. new labeling for thrombin and calcium chloride vials
7. updated symbols on gelatin pouch
8. abbreviation for I.U. changed to units to avoid confusion with I.V. (this change is being implemented upon request from CBER)

Some of these changes are related to the additional viral inactivation steps while others are additional revisions to the text. Some text revisions result in additional emphasis to an existing warning, precaution, or instruction for use. Most of the proposed changes further clarify the intent of the statements that appear in the current version of the labeling. However, there are several changes that required further supportive data or rationale from the sponsor to justify these changes. These are described in further detail below.

The following three contraindications were removed and written in the draft labeling as warnings:

1. Do not inject or compress Floseal Matrix into blood vessels. Do not apply Floseal Matrix in the absence of active blood flow, e.g., to clamped or bypassed vessels while the vessel is clamped or bypassed. Extensive intravascular clotting and even death may result.
2. To avoid a risk of allergic anaphylactoid reaction and/or thromboembolic events, which may be life threatening, do not inject Floseal Matrix into a vessel or tissue.
3. Do not use Floseal Matrix in the closure of skin incisions because it may interfere with the healing of the skin edges due to mechanical interposition of gelatin.

The sponsor states that they consider these statements to be more applicable as warnings as they do not apply to individuals with a particular condition that may otherwise cause harm to the patient. This is not adequate rationale to support the removal of a contraindication and placement under the warnings section. Contraindications are descriptive of situations in which the device should not be used because the risk of use clearly outweighs any possible benefit, including known hazards. Therefore, contraindications are not specific only to applications related to susceptible individual conditions. In a major deficiency letter (dated July 31, 2009), the sponsor was requested to either provide clinical evidence to support removal of the above cited contraindications or not remove these contraindications. The sponsor responded that they agree with FDA's position that contraindications are descriptive of situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. Therefore, the sponsor will not remove these contraindications.

The following two statements have been deleted from the "For Nasal/Sinus Applications" section:

1. Floseal Matrix does not have to be removed postoperatively as it is bioresorbed.
2. The use of Floseal Matrix for mechanical support has not been studied.

The sponsor states that the statement about Floseal not having to be removed is contradictory to the warnings regarding removal of excess Floseal. Therefore, the sponsor is removing this statement. This is acceptable as it is contradictory to the warning.

The sponsor states that the statement regarding unstudied use for mechanical support is being removed so that attention will not be called to this unsupported use. However, further clarification was needed to support the removal of this statement. There are instances where this type of a statement is included in the labeling, such as in the case where a common belief may exist where the product is effective for a particular use but there is no accepted data to support such a use. In a major deficiency letter (dated July 31, 2009), the sponsor was requested to either provide evidence that the Floseal product is not believed to be useful for mechanical support in nasal/sinus applications or not remove this statement from labeling. The sponsor responded that Baxter is not aware of a common belief among physicians/surgeons that absorbable hemostats can be used for mechanical support in nasal or sinus applications. Two cited publications concluded that Floseal is not useful when used as a mechanical support in nasal surgery. Based on this information, Baxter believes that inclusion of the statement "The use of Floseal Matrix for mechanical support has not been studied" does not align with the

directions for use included in the IFU, specifically the labeled application technique to irrigate any excess Floseal away from the hemostatic clot.

Both these publications present data on patients who experience mucosal adhesions after use of Floseal to provide hemostasis during endoscopic sinus surgery. One publication makes mention of the lack of utility of Floseal as a surgical stent. Although these publications do not promote the use of Floseal to provide mechanical support during nasal surgery, the existence of such studies imply that people may consider the use of Floseal as a surgical stent to provide mechanical support during nasal surgery. In addition, it does not appear that the statement that Floseal was not studied for use as mechanical support contradicts with a statement that excess Floseal should be removed from the site of application. Rather this statement does align with the statement that excess Floseal should be removed since the utility of Floseal as a packing agent for providing mechanical support has not been studied. The sponsor was asked (via e-mail on December 16, 2009) to provide additional information as a follow-up to this response, specifically the original reason for having included this statement in the labeling. The sponsor stated that this statement was included in the instructions for use when Floseal was approved for use in nasal sinus application in order to clarify the use of Floseal in nasal/sinus surgeries for hemostasis and not as a means of mechanical support. The sponsor was then asked (via e-mail on December 18, 2009) to not remove this statement from the labeling. The sponsor agreed to keep this statement in the labeling and submitted revised draft labeling via e-mail on December 22, 2009.

Summary of Interactive Review and Correspondence

Following the review of the original submission, a major deficiency letter was issued on July 31, 2009.

On December 16, 2009, the sponsor was asked, via e-mail, to provide information regarding the original basis for including the statement “The use of Floseal Matrix for mechanical support has not been studied” in the instructions for use.

On December 17, 2009, the sponsor clarified, via e-mail, that the statement “The use of Floseal Matrix for mechanical support has not been studied” was included in the instructions for use as part of the PMA supplement approval for use of the product in nasal sinus application.

On December 18, 2009, the sponsor was asked, via e-mail, to keep the statement “The use of Floseal Matrix for mechanical support has not been studied” within their instructions for use in order to further support the warning that excess Floseal should be removed from site of application and to reinforce that the use of Floseal for mechanical support has not been studied.

On December 22, 2009, the sponsor agreed to keep the statement “The use of Floseal Matrix for mechanical support has not been studied” within their instructions for use and provided revised draft labeling via e-mail.

Conclusion

The supplement is being submitted to seek approval for a new version of Floseal, which incorporates human thrombin that has been subjected to an additional solvent detergent process for viral inactivation. In order to demonstrate that there are no adverse effects on product effectiveness from this additional manufacturing step, a study of time to hemostasis was evaluated on bleeding wounds on the surface of the liver in rabbits that have been treated to compromise the clotting time. However, this study was not designed to compare the effectiveness of the current and new versions of Floseal; therefore, data collected from this study cannot be used to conclude that no adverse effect on product effectiveness results from the additional manufacturing process for thrombin. The sponsor was asked to provide additional animal study data to demonstrate that the new version of Floseal is as effective as the currently approved version.

In amendment 01, the sponsor submitted data collected from a porcine study where the effectiveness of Floseal VH S/D was compared to Floseal VH in 120 lesions (on the surface of liver) per group. The geometric mean ratio of Floseal VH to Floseal VH S/D in terms of seconds to hemostasis was 1.01. Its one-sided 97.5% lower confidence limit was 0.957, demonstrating Floseal VH S/D to be non-inferior to Floseal VH in this study. The hemostatic control and maintenance based on bleeding score success of Floseal VH and Floseal VH S/D were not significantly different from each other at 10 minutes post-treatment.

The sponsor also proposed labeling changes that require further supportive data. In amendment 01, the sponsor has agreed to not relocate the three contraindications statements that they had originally drafted to move to the warnings section. The sponsor has also agreed to not remove from labeling the statement that Floseal has not been studied for use as mechanical support during nasal sinus surgery.

Recommendation - I recommend that the supplement be **Approved**.

(b) (6) (b)(6) (b) (6) , Ph.D. Date
Reviewer, Plastic and Reconstructive Surgery Devices Branch

(b) (6) (b)(6) Ph.D., Date
Chief, Plastic and Reconstructive Surgery Devices Branch