

From: [Do Yu](#)
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Tuesday, October 10, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Tuesday, October 03, 2017 5:16:16 PM
Attachments: [image001.png](#)
[FDA Annotated Labeling Text Version October 3 2017 IG.docx](#)
[BLA 125640 Container Label 10 mL.pdf](#)

Dear Ms. Robertson:

We are reviewing your original November 3, 2016, submission to BLA 125640 for Fibrin Sealant (Human). We have the following comments and requests for additional information to continue our review:

We hereby provide our comments, regarding the Prescribing Information and other labeling components, in the attached files and as follows:

Please revise the Prescribing Information and carton (box) label according to the attached annotated versions of the labeling. Please accept all those tracked changes with which you agree, but insert your own comments where further discussion is warranted. Please be sure to submit both clean and annotated versions of the revised labeling (including the carton label) in Word and PDF files in your response. Also, please indicate clearly, point by point, whether you would accept each change or not. If not, please provide briefly your rationale or justification. For those comments/requests whose scope reaches beyond the Prescribing Information, please provide more detailed responses.

Please note FDA may have additional comments, based on review of the revised labeling included in your response.

General

- Use active voice and command language throughout the **FULL PRESCRIBING INFORMATION** wherever possible.
- Periods are not acceptable after the numbers for the section or subsection headings. Please delete the periods throughout the **FULL PRESCRIBING INFORMATION**.
- Do not number pages of the prescribing information.

HIGHLIGHTS

- In the absence of a proprietary name, the parentheses should be omitted, and the chemical component portion of the nonproprietary name should be in UPPER CASE. For example: **FIBRIN SEALANT (Human)**. Please replace all references to VeraSeal with FIBRIN SEALANT (Human).
- Please delete “(b) (4) [REDACTED]” from the indication statement. Should the BLA be approved, the indication statement may be modified to include (b) (4) [REDACTED] completed with results supporting the revision.
- Please delete the **DRUG INTERACTIONS** section. This section is not required in the absence of information.
- In the **USE IN SPECIFIC POPULATIONS** section, the Pregnancy statement is no longer used in the **HIGHLIGHTS** in the absence of information. See guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* for more information.

CONTENTS

- Ensure that the Table of Contents aligns with the sections and subsections of the **FULL PRESCRIBING INFORMATION**.

FULL PRESCRIBING INFORMATION

1 INDICATION AND USAGE

Please delete “(b) (4)” from the indication statement. Should the BLA be approved, the indication statement may be modified to include (b) (4) completed with results supporting the revision.

2 DOSAGE AND ADMINISTRATION

Only the route of administration, with a bolded sentence case directive, belongs beneath the section heading:
For topical use only.

Delete Line 10 (“**Do not inject.**”), as this may be inadvertently misinterpreted as another route of administration.

2.1 Dosage

- Provide basic dosing information first, followed by other information relevant to dosage and administration. The sequence of information should reflect the relative importance of the information to administer the drug safely and effectively. For example:

Individualize application of the fibrin sealant (individual dosages typically ranged from 0.3 to 18.0 ml in the clinical studies). For other procedures, larger volumes may be required.

As an approximate guide, the surface area that can be covered by one kit is as follows:

Table 1. Surface area coverage

Pack size	Surface area coverage (cm²) Application by dripping or spray (1 mm thick layer)
2 mL	14-20
4 mL	28-40
6 mL	42-60
10 mL	70-100

The applied dose is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

The initial volume of the product applied at a chosen anatomic site or target surface area should entirely cover the intended application area. Apply as a thin layer. Application can be repeated, if necessary.

2.2 Preparation and Handling

- Use active voice and command language wherever possible. For example:
 - Thaw product at room temperature (20 °C - 25 °C, [68 – 77 °F]) for approximately eighty (80) minutes for the 2 mL and the 4 mL presentations and one hundred twenty (120) minutes for the 6 mL and the 10 mL presentations.
 - Use product immediately once the packaging is opened.
 - Do not use solutions that are cloudy or have deposits.
- Enhance readability by providing step-by-step directions for preparation and administration. Numbered steps are also helpful. Please include explanatory figures showing different connection operations, and the device completely assembled before being used.
- Please specify if movements during connection with the applicator tip should be conducted with the syringe body or with syringe luer connectors for the most user-friendly assembly, and specify movement direction:

clockwise or counterclockwise to ensure connection and avoid disconnection.

5 WARNINGS AND PRECAUTIONS

The **5.4 Application precautions** subsection does not belong in the **5 WARNINGS AND PRECAUTIONS** section. This information belongs in the **2 DOSAGE AND ADMINISTRATION** section.

6 ADVERSE REACTIONS

Include the statement of the most common adverse reactions, with their cutoff frequency, beneath the heading of section **6 ADVERSE REACTIONS** section (before subsection 6.1). For example:

The most common adverse reactions (reported in = 1% of clinical trial subjects) were nausea and procedural pain.

6.1 Clinical Trials Experience

- Avoid referencing MedDRA as sources for terminology.
- Please provide description of overall clinical trial database from which the adverse reactions have been drawn, including overall exposure (number of patients, dosage, duration), demographics of exposed population, designs of trial, and any critical exclusions from safety database.
- Please expand Section 6.1, Clinical Trials Experience, to include adverse reactions, categorized by the types of surgery (vascular, liver resection, and soft tissue) and provide a Table that summarizes the frequency of adverse reactions by system organ class from the clinical trials.

7 DRUG INTERACTIONS

Delete the **DRUG INTERACTIONS** section. It is not required in the absence of information.

8 USE IN SPECIFIC POPULATIONS

In the **8.1 Pregnancy** subsection, delete the statement “VERASEAL should be given to a pregnant woman only if clearly needed.” This statement is not informative and is no longer recommended.

11 DESCRIPTION

- Structure this section as follows: general description of the combination product; composition of biological components; source of the starting materials; and brief overview of the manufacturing processes. Follow with measures to ensure product safety with regard to adventitious viruses.
- Please verify if the manufacturing pools are tested for B19V. This testing is not stated as an in-process control test in the Appendix to Production Procedure IG_MP-000026_ING.
- Please add tables with overall virus reduction factors for Fibrinogen and Thrombin.

12 CLINICAL PHARMACOLOGY

Add subsection **12.2 Pharmacodynamics** which is required per 21 CFR 201.57(c)(13)(i). For information on preparing this subsection, please refer to guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products - Content and Format* (available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf>).

13.2 Animal Toxicology and/or Pharmacology

Delete this section when there are no data.

14 CLINICAL STUDIES

Avoid terms such as “primary endpoint” or “secondary endpoint.” Instead, please describe only those

- endpoints that were found to be both statistically and clinically significant OR demonstrated a meaningful lack of effect.
- While subsectioning is permissible in this section, it is done with numbering (14.1, 14.2, etc.) Lettering is meaningless in Structured Product Labeling. Most often, there is no subsectioning in this section. Instead, information is sorted under italicized or underlined subheadings.
- Present results up to three significant figures.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Please provide a more accurate description of the kit as suggested in the annotated version.
- Use command language wherever possible. For example: Use the product immediately once the package is opened.
- If possible, please define “immediately” in the following statement: “Once the packaging is opened, use FIBRIN SEALANT (Human) immediately.”
- To support the proposed storage before use, you conducted the in-use stability study (Report IG_IE-000222_ING) which tested potency and purity of the two components and functionality of the final product. In addition, please provide your justification that sterility of the components or integrity of the packaging will also be maintained within 24 or 48 hours of storage at room or refrigerated temperature.

BLISTER LABEL

Delete the proprietary name VeraSeal.

PACKAGE (CARTON/BOX) LABEL

- Each package label containing a product shall include the name, address, and license number of the manufacturer. Please add the address to the package label.
- Delete the proprietary name VeraSeal.
- Consider increasing the font size for Lot No., Expiration Date, and Address for better readability.

ADDITIONAL COMMENTS REGARDING SECTION 2.2 AND 2.3 (Instructions for Preparation, Handling, and Administration)

In the submitted Usability/Human Factors study (Report IG_ITEC-002779_ING), all of the participants had comments to improve the description of connection operations in preparation instructions and to supplement it with explanatory figures that show the different connection steps until the application system is fully assembled for use. The participants also did not agree that the “thawing procedure is clear and easy to understand” and commented that the thawing instructions need to be clarified. The product thawing time was considered too long, even at 37 °C and not feasible in case of emergency. The participants also felt that the term “immediately” should be better defined for use of the product once the packaging is opened. As these steps are critical for the effectiveness of the device and for the timeliness of patients in critical condition receiving treatment, please evaluate possible improvements to the labeling and/or instructions for use that would provide useful details for the user to complete these tasks with less difficulty or confusion.

The review of this submission is ongoing, and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit your response as an amendment to this file by October 10, 2017, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is November 3, 2017.

Please acknowledge receipt of this request and contact me at (240) 402-8343 or Yu.Do@fda.hhs.gov if you have any questions.

Sincerely,

Yu Do, M.S.
Regulatory Project Manager
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
Office of Medical Products and Tobacco
Food and Drug Administration
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