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PRODUCT: FESILTY (Fibrinogen BT524)

APPLICANT: Grifols Therapeutics, LLC

PROPOSED INDICATION: For treatment and prophylaxis in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency.

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EXECUTIVE SUMMARY:

FESILTY (BT524 fibrinogen) is a human fibrinogen concentrate derived from human plasma that is indicated as a complimentary therapy to the management of uncontrolled severe hemorrhage in individuals with congenital hypo- or afibrinogenemia with bleeding tendency. FESILTY (BT524 fibrinogen) is intended for intravenous (IV) administration and the recommended dose level is (b) (4)

with acquired fibrinogen deficiency. For individuals with congenital hypo- or afibrinogen the target plasma fibrinogen level is 100 mg/dL for minor bleeding and 150 mg/dL for major bleeding and, therefore, must be calculated on a case-by-case basis.

The nonclinical studies provided in this BLA submission evaluated the activity, thrombogenicity, local tolerance and safety pharmacology of FESILTY (BT524 fibrinogen) compared to an approved human fibrinogen product, Haemocomplettan P. Haemocomplettan P is the brand name in Europe and identical to the FDA approved product RiaSTAP. In vitro clot firmness was similar between both products when used at physiological relevant levels of 2.0-2.5 g/L. FESILTY (BT524 fibrinogen) and Haemocomplettan P also demonstrated similar clot activity in vitro. A single IV injection of FESILTY (BT524 fibrinogen) at 200 mg/kg in the ear vein of rabbits resulted in the formation of clots similar in frequency and size to those observed in animals administered Haemocomplettan P at the same dose level. This dose level is representative of a high dose given to humans in extreme situations such as severe hemorrhage. No differences in local tolerance or safety pharmacology were observed between FESILTY (BT524 fibrinogen) and Haemocomplettan P following IV administration in rabbits.

Studies to evaluate the developmental and reproductive toxicity and carcinogenicity/tumorigenicity of FESILTY (BT524 fibrinogen) were not conducted. These studies are not warranted based on product characteristics.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

Based on the review of the nonclinical data in this BLA submission (STN# 125833), no deficiencies were identified. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry:

FESILTY (BT524 fibrinogen) is a lyophilized, heat-treated fibrinogen concentrate manufactured from human plasma. It is a single use product containing 1 g of human fibrinogen that is to be reconstituted with 50 mL of sterile water for IV injection.

FESILTY (BT524 fibrinogen) is supplied in 100 mL type (b) (4) borosilicate glass vials closed with type (b) (4) bromobutyl stoppers, which are held in place with metal crimps covered with flip-off plastic caps. Sterile water is packaged separately in single-dose containers consisting of 20 mm neck type (b) (4) glass vials stoppered with a chlorobutyl rubber stopper, which is protected by an aluminum flip-off cap. The vials contain no antimicrobial agent or other added substance. The

device supplied for reconstitution of the product is the nextaro v, 20/20 5 µm, manufactured by SFM medical devices GmbH.

Abbreviations

AUC	Area under the curve
BLA	Biologics License Application
C _{max}	Maximum concentration
ECG	Electrocardiogram
FFP	Fresh frozen plasma
FIBTEM	Fibrin-based thromboelastometry with tissue factor activation and cytochalasin D
GLP	Good Laboratory Practice
IA	Intra-arterial
IM	Intramuscular
IV	Intravenous
MRT	Mean residence time
NIBSC	National Institute for Biological Standards and Control
PPQ	Process Performance Qualification
ROA	Route of administration
SC	Subcutaneous
STN	Submission tracking number
WHO	World Health Organization

Related File

PS007549: A lyophilized, heat-treated fibrinogen concentrate manufactured from human plasma. Product Name: BT524. Grifols, Therapeutics, LLC.

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INTRODUCTION

Fibrinogen is critical to the coagulation cascade in which thrombin converts fibrinogen to fibrin resulting in clot formation. Normal blood fibrinogen concentration is between 2.0 and 4.5 g/L although this range can vary among individuals. In cases of fibrinogen deficiencies, blood coagulation does not occur properly and can result in severe hemorrhagic events. The critical plasma fibrinogen level below which hemorrhages may occur is approximately 0.5 to 1.0 g/L.

FESILTY (BT524 fibrinogen) is a human fibrinogen concentrate product for fibrinogen supplementation for the treatment and prophylaxis of bleeding in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency. Congenital fibrinogen deficiency is a rare inherited coagulation disorder characterized by impaired hemostatic function because of reduced quantity and/or quality of circulating fibrinogen, resulting in mild to severe bleeding.

The current standard of care for fibrinogen deficiency consists of transfusion of allogenic blood products such as fresh frozen plasma (FFP) and cryoprecipitate. However, per the applicant, there remains an unmet need for fibrinogen supplementation due to the risks associated with allogenic blood products such as variable fibrinogen levels, presence of additional clotting factors, transfusion-related injuries, pathogen transmission, and immune reactions. Moreover, the availability of human fibrinogen concentrate in the United States is limited, as only two fibrinogen concentrate products are licensed for congenital fibrinogen deficiency, one of which is also licensed for acquired fibrinogen deficiency. Therefore, FESILTY (BT524 fibrinogen) was developed as an additional option for fibrinogen replacement.

NONCLINICAL STUDIES

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology studies were conducted to support the rationale for administration of FESILTY (BT524 fibrinogen) to treat the proposed clinical indication.

In Vitro Study

Study Number	Study Title / Publication Citation	Report Number
1	Primary and secondary pharmacodynamics of Fibrinogen Concentrate (BT524)	BE00824

Overview of Pharmacology Study

Overview of In Vitro Study

Study #1 Primary and secondary pharmacodynamics of Fibrinogen Concentrate (BT524)

Objective:

The objective of this study was to evaluate FESILTY (BT524 fibrinogen) clot formation in vitro.

Methods:

The applicant measured FESILTY (BT524 fibrinogen) and Haemocomplettan P activity using two standard assays: the (b) (4) assay and the (b) (4) assay. Both methods work by activating fibrinogen through thrombin-initiated coagulation. To evaluate clot firmness, the applicant also used the (b) (4) assay, which employs (b) (4) in which FESILTY (BT524 fibrinogen) was added to fibrinogen-depleted plasma at physiologically relevant concentrations ranging from (b) (4), and Haemocomplettan P was added at (b) (4).

For fibrinogen activity, the applicant used (b) (4) batches of FESILTY (BT524 fibrinogen) which included (b) (4) batches used in the clinical trials and (b) (4) batches of Haemocomplettan P as a comparator.

For clot firmness, the applicant used (b) (4) batches of FESILTY (BT524 fibrinogen), in which (b) (4) were added at 2.0 g/L, as well as the (b) (4) batches of Haemocomplettan P. Human plasma from various sources was used as a comparator for the (b) (4) assay.

Results:

FESILTY (BT524 fibrinogen) and Haemocomplettan P demonstrated similar fibrinogen activity in both the (b) (4), respectively) and (b) (4) assays (b) (4) respectively).

Average maximum clot firmness of FESILTY (BT524 fibrinogen) was 23 mm and Haemocomplettan P average clot firmness was less, at 13 mm. Of note, normal reference plasma was 23 mm, standard human plasma was 26 mm, and the WHO international standard fibrinogen plasma was 25 mm.

Reviewer's Conclusions:

- *This reviewer agrees that based on the data provided, activity of FESILTY (BT524 fibrinogen) as assessed by the (b) (4) and (b) (4) assays is similar to FDA approved Haemocomplettan P.*
- *FESILTY (BT524 fibrinogen)-mediated clot firmness was similar to the clot firmness of human plasma containing fibrinogen. However, Haemocomplettan P average clot firmness was decreased at 13 mm, which is likely due to a decreased product concentration of 2.0 g/L. This reviewer notes that (b) (4) batches of FESILTY (BT524 fibrinogen) were used at a product concentration of 2.0 g/L, resulting in an average clot firmness of 18 mm, suggesting that product concentration can affect clot firmness. Therefore, this reviewer considers that the differences in clot firmness between FESILTY (BT524 fibrinogen) and Haemocomplettan P may be influenced by the product concentration.*

SAFETY PHARMACOLOGY STUDIES

Summary List of Safety Pharmacology Studies

The following safety pharmacology study was conducted to evaluate cardiovascular and respiratory function in rabbits following FESILTY (BT524 fibrinogen) administration.

Study Number	Study Title / Publication Citation	Report Number
2	Effects of cardiovascular and respiratory functions following intravenous administration in the anesthetized rabbit	AB04588

Overview of Safety Pharmacology Study

Overview of In Vivo Study

Study #2 Effects of cardiovascular and respiratory functions following intravenous administration in the anesthetized rabbit

Report Number	AB04588
Date Report Signed	June 27, 2012

Title		BT-524- Effects of cardiovascular and respiratory functions following intravenous administration in the anesthetized rabbit
GLP Status		No
Testing Facility		(b) (4)
Objective		Evaluate effects of BT-524 on cardiovascular and respiratory functions following a single intravenous administration in the anesthetized rabbit.
Study Animals	Strain/Breed	(b) (4)
	Species	(b) (4)
	Age	10-13 weeks
	Body Weight	2.4-2.6 kg
	#/sex/group	6 males/group
	Total #	24
Test Article		BT-524 (Batch# (b) (4) ; this batch was manufactured to supply nonclinical studies and clinical trials and, per the applicant, is comparable to commercial manufacturing).
Control Article		Haemocomplettan P (Batch# (b) (4)
Route of Administration		IV
Description of product administration procedure		Injection was performed using a syringe pump and an implanted catheter into the left jugular vein. The test or control article was infused at a rate of 5 mL/minute at a volume of 2.5 or 10 mL/kg for low or high doses, respectively.
Study Groups and Dose Levels		Group A – BT-524, 50 mg/kg (n=6) Group B – BT-524, 200 mg/kg (n=6) Group C – Haemocomplettan P, 50 mg/kg (n=6) Group D – Haemocomplettan P, 200 mg/kg (n=6) Note: Groups A and C received 2.5 mL/kg and Groups B and D received 10 mL/kg, which is identical to their respective administered product.
Dosing Regimen		Single
Randomization		Yes
Description of Masking		Not indicated
Scheduled Sacrifice Time Points		30 minutes post product administration

Key Evaluations and Assessments:

Animals were monitored beginning with a 15-minute baseline period prior to simulation with Ringer lactate solution, continuing through product administration, and concluding with termination at 30 minutes post-dose.

Hemodynamic and pulmonary parameters including arterial blood pressure, electrocardiogram (ECG), respiratory flow, and esophageal pressure were measured per the following timeline:

Hemodynamic, airway mechanics, and respiratory metrics were recorded for approximately 30 seconds at the following timepoints: baseline (15, 10, 5 and 2 minutes before treatment simulation); control simulation which entailed IV administration of Ringer lactate solution at the same dose volume and infusion rate used for the test or control item in each group (30 seconds and 1 minute after simulation start); after control simulation (30 seconds and 2, 5 and 10 minutes

after the end of the simulation); test article or control article administration (2 minutes prior to, 30 seconds and 1 minute after administration); and after test article or control article administration (30 seconds, 2, 5, 10, 15, 20, 25 and 30 minutes after the end of administration).

Electrocardiogram data was obtained from the mean of values of the 10 best quality ECG recordings at the following timepoints: baseline (15, 10, and 5 minutes before control simulation); control simulation (1 minute following simulation); test article or control article administration (1 minute after administration); and after test article or control article administration (30 seconds, 2, 5, 10, 15, 20, and 30 minutes after the end of administration).

Key Results:

No animals died during the study.

Statistically significant differences in blood pressure, heart rate, ECG, respiratory rate, and pulmonary metrics were observed between measurements following control simulation and product administration. However, no statistically significant differences were observed among intergroup comparisons, suggesting comparable hemodynamics, respiratory, and cardiac effects among animals administered FESILTY (BT524 fibrinogen) and Haemocomplettan P.

Reviewer's Conclusions:

- *This reviewer agrees that FESILTY (BT524 fibrinogen) and Haemocomplettan P demonstrated similar safety pharmacology profiles in anesthetized rabbits.*

PHARMACOKINETIC STUDIES

Summary List of Pharmacokinetics Studies

The following pharmacokinetic studies were conducted to evaluate the pharmacokinetic profile of FESILTY (BT524 fibrinogen) following administration in rabbits.

Primary Study

Study Number	Study Title / Publication Citation	Report Number
3	Pharmacokinetic study following intravenous administration in the rabbit.	AB09129

Supplementary Study

Study Number	Study Title / Publication Citation	Report Number
4	Validation of determination of fibrinogen in rabbit plasma according to SV-T:EA-155-04	ABE-00009-01

Note: Study #4 is not reviewed in depth in this memo because it contains data on the validation of methodologies used in Study #3 and does not provide data regarding the pharmacokinetics of FESILTY (BT524 fibrinogen).

Overview of Pharmacokinetic Study

Overview of In Vivo Study

Study #3: Pharmacokinetic study following intravenous administration in the rabbit.

Objective:



The objective of this study was to determine the pharmacokinetic profile of FESITLY (BT524 fibrinogen) and the reference item, Haemocomplettan P, in the rabbit after a single IV administration.

Methods:

Male (b) (4) rabbits weighing 2.5 to 2.8 kg and approximately 12-14 weeks of age received a single IV administration of FESITLY (BT524 fibrinogen) (n=6) or Haemocomplettan P (n=6) at 200 mg/kg, which is the same dose level used in the applicant's toxicology study. Animals were observed daily and weighed on days -3, 0, 7, and 15. Blood was collected from the ear artery (approximately 1 mL). Blood collection followed two staggered schedules: 3 animals from each treatment group were sampled immediately following product administration and at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours post-administration, while the remaining 3 animals from each group were sampled at the end of injection and at 0.5, 2, 8, 24, 72, 144, 216, 288, and 360 hours post-administration. Plasma was isolated from whole blood for pharmacokinetic analyses^{1,2}. Animals were euthanized on day 15, except for 4 animals which remained at the testing facility for staff training purposes.

Results:

¹(b) (4)



No unscheduled deaths occurred during the study.

The maximum plasma concentrations (C_{\max}) observed were 5025 µg/mL for FESILTY (BT524 fibrinogen) (30 minutes) and 5388 µg/mL (1 minute) for Haemocomplettan P. Plasma concentrations were quantifiable up to 72 hours post- FESITLY (BT524 fibrinogen) administration and 144 hours post-Haemocomplettan P administration. The mean residence time (MRT; average time product stays in the body) for FESILTY (BT524 fibrinogen) and Haemocomplettan P was 58.4 hours and 41.6 hours, respectively. Similarly, the half-life of FESILTY (BT524 fibrinogen) was 41.8 hours, whereas Haemocomplettan P was 27.5 hours. The applicant notes that the validity of the nonclinical pharmacokinetics data may be limited because the extrapolated area under the curve (AUC) is more than 20% of the $AUC_{0-\infty}$ and therefore does not comply with criteria set by the test facility.

Reviewer's Conclusion:

- The applicant has provided pharmacokinetic data from their Phase I/II clinical trial in which children, adolescents, and adults with congenital fibrinogen deficiency (Trial 984) received a single IV infusion of FESILTY (BT524 fibrinogen) at 70 mg/kg. It is this reviewer's opinion that these data are more relevant in characterizing the pharmacokinetics of FESILTY (BT524 fibrinogen) than data collected from rabbits due to potential species-specific differences. This reviewer defers to clinical pharmacology for an in-depth review of the human data.*

TOXICOLOGY STUDIES

Summary List of Toxicology Studies

The following toxicology studies were conducted to evaluate the safety of FESILTY (BT524 fibrinogen) following administration in rabbits.

Toxicology Studies

Study Number	Study Title / Publication Citation	Report Number
5	BT-524 - Thrombogenic effect in the anesthetized rabbit after a single intravenous administration.	AB04757

Other Safety/Toxicology Studies

Study Number	Study Title / Publication Citation	Report Number
6	BT-524 – Local tolerance study in the rabbit after a single subcutaneous, intramuscular, intra-arterial, or intravenous administration, followed by a 3- or 7-day observation period.	AB04758

Note: All listed studies are summarized in this review memo under ‘Overview of Toxicology Studies.

Overview of Toxicology Studies

Overview of In Vivo Studies*Study #5: BT-524 - Thrombogenic effect in the anesthetized rabbit after a single intravenous administration*

Report Number		AB04757
Date Report Signed		June 7, 2012
Title		BT-524 - Thrombogenic effect in the anesthetized rabbit after a single intravenous administration.
GLP Status		Yes
Testing Facility		(b) (4)
Objective		To evaluate any possible thrombogenic effect of the test item in the anesthetized rabbit after a single intravenous administration.
Study Animals	Strain/Breed	(b) (4)
	Species	(b) (4)
	Age	Approximately 13 weeks
	Body Weight	2.2-2.5 kg
	#/sex/group	6 males/group
	Total #	12
Test Article		BT524 (Batch# (b) (4) ; this batch was manufactured to supply nonclinical studies and clinical trials and, per the applicant, is comparable to commercial manufacturing).
Control Article		Haemocomplettan P (Batch# (b) (4)
Route of Administration		IV; femoral vein
Description of product administration procedure		Injection was performed using a syringe pump and an implanted catheter into a femoral vein. The jugular vein was clamped for 10 minutes following administration of test and control articles to monitor thrombogenic events.
Study Groups and Dose Levels		Group 1 – 200 mg/kg BT-524 Group 2 – 200 mg/kg Haemocomplettan P Note: The dose level of 200 mg/kg was intended to represent a high dose given to humans in extreme situations such as severe hemorrhage.
Dosing Regimen		Single
Randomization		Yes
Description of Masking		Not indicated
Scheduled Sacrifice Time Points		Days 0 and 1

Key Evaluations and Assessments:

Animals were observed for morbidity/mortality twice a day.

Anesthetized animals received a single IV infusion via a cannulated femoral vein of 200 mg/kg of FESILTY (BT524 fibrinogen) or Haemocomplettan P at a rate of 5 mL/minute. Thrombogenic events were evaluated by clamping the animal's exposed jugular vein beginning 15 seconds after completion of the infusion and maintaining for 10 minutes. The venous segment was removed, and its content was emptied into a Petri dish containing 30 mL of 5% sodium citrate solution. Clots were assessed on a scale of 0-4, and defined as 0 for no clot formation, 1 for a few macroscopic strands of fibrin, 2 for several small thrombi, 3 for two or more large thrombi, and 4 for a single large thrombus forming a cast.

Key Results:

No unscheduled deaths occurred during the study.

Several small thrombi (score 2) were observed for all animals administered FESILTY (BT524 fibrinogen) and all but one administered Haemocomplettan P, in which no clots (score 0) were observed. Overall, no significant differences in clot scoring between FESILTY (BT524 fibrinogen) and Haemocomplettan P were observed.

Reviewer's Conclusions:

- *This reviewer agrees that these data suggest comparable thrombogenicity risk between products.*
- *Repeat dosing of human fibrinogen in an animal model is not feasible because it would elicit the production of anti-fibrinogen antibodies.*

Study #6: BT-524 – Local tolerance study in the rabbit after a single subcutaneous, intramuscular, intra-arterial, or intravenous administration, followed by a 3- or 7-day observation period.

Report Number		AB04758
Date Report Signed		June 7, 2012
Title		BT-524 – Local tolerance study in the rabbit after a single subcutaneous, intramuscular, intra-arterial, or intravenous administration, followed by a 3- or 7-day observation period.
GLP Status		Yes
Testing Facility		(b) (4)
Objectives		To evaluate the local tolerance of the test item in the rabbit after a single subcutaneous, intramuscular, intra-arterial, or intravenous administration and to evaluate the recovery of possible changes at the injection sites, 3 days, and 7 days after dosing.
Study Animals	Strain/Breed	(b) (4)
	Species	(b) (4)
	Age	Approximately 15 weeks
	Body Weight	2.8-3.1 kg
	#/sex/group	3 males/group
	Total #	12
Test Article		BT524 (Batch# (b) (4))
Control Article		Haemocomplettan P (Batch# (b) (4))

Route of Administration	<p>Subcutaneous (SC), Intramuscular (IM), Intravenous (IV), Intra- arterial (IA)</p> <p>SC – Single bolus (1 mL/injection) in the anterior dorsal region using sterile syringe.</p> <p>IM – Single bolus (1 mL/injection) in the dorsal lumbar muscles using sterile syringe.</p> <p>IV – Single injection (10 mL/injection at 2mL/minute) in the marginal ear vein using an infusion pump.</p> <p>IA – Single injection (10 mL/injection at 2mL/minute) in the central ear artery using an infusion pump.</p> <p>Note: Healthy animals received the test article on the left side and the control article on the right side. Rationale for including ROAs other than the proposed clinical IV ROA was to address the risks of accidental IA, IM, and SC administration of FESITLY (BT524 fibrinogen) that may occur in humans.</p>
Study Groups and Dose Levels	<p>Group 1 – SC and IM</p> <p>Group 2 – SC and IM</p> <p>Group 3 – IV and IA</p> <p>Group 4 – IV and IA</p>
Dosing Regimen	Single
Randomization	Yes
Description of Masking	Not indicated
Scheduled Sacrifice Time Points	Days 3 (Groups 1 & 3) and 7 (Groups 2 & 4)

Key Evaluations and Assessments:

Animals were observed for morbidity/mortality at least twice a day. On the day of product administration, clinical observations occurred prior to and three times following dosing. Physical examinations were performed prior to administration of FESILTY (BT254 fibrinogen) and Haemocomplettan P and at termination. Body weights were measured on days -3, 0, 3, and 7.

Injection sites were visually assessed prior to and twice after dosing (approximately 3- and 7 hours post product administration) along with once daily observations thereafter to evaluate local tolerance. Local reactions including erythema and eschar formation (i.e., redness of the skin due to inflammation and dry, dead layer of skin), oedema formation (i.e., excessive buildup of fluid), induration (i.e., thickening or hardening of tissue), and hematoma/hemorrhagic infiltration (i.e., bruising) were scored 0-4, in which increased numerical scores were representative of increased severity.

At the scheduled sacrifice timepoints, tissue was collected at injection sites and the surrounding areas for macroscopic and histopathological evaluations. Peer review of the histopathological data was conducted by a pathologist.

Key Results:

No unscheduled deaths occurred during the study. Body weights were similar among groups.

There were no observable differences in the severity of local injection site reactions among animals that received either FESILTY (BT524 fibrinogen) or Haemocomplettan P. Small hematomas ($\leq 1\text{ cm}^2$) were observed following IV administration, which occurred in 2-3 animals and resolved between days 4 and 7. All local reactions were observed following IA administration, with induration and hematoma lasting up to day 7. Very slight oedema and/or very small to small hematomas ($\leq 1\text{ cm}^2$ to $\leq 2\text{ cm}^2$) were noted in 1 or 2 animals after SC and IM administrations of both the test and control articles which resolved by day 3.

There were no histopathological findings attributable to FESILTY (BT524 fibrinogen) or Haemocomplettan P following IV administration. SC administrations of FESILTY (BT524 fibrinogen) and Haemocomplettan P were primarily characterized by acute dermal hemorrhage and inflammatory cell infiltration with partial resolution in both groups by day 7. IM injections of FESILTY (BT524 fibrinogen) or Haemocomplettan P were characterized by slight to moderate macrophagic cell infiltration of multifocal distribution in the muscle tissue with an unresolved state of slight inflammation on day 7. IA administrations of FESILTY (BT524 fibrinogen) or Haemocomplettan P were characterized by minimal perivascular inflammation on day 3 with minimal to slight multifocal perivascular or subcutaneous inflammation and slight subcutaneous fibrin deposits noted in 1/3 males given FESILTY (BT524 fibrinogen) on day 7.

Reviewer's Conclusions:

- *This reviewer agrees that minimal differences in local tolerance and histopathological findings were observed in animals that received FESILTY (BT524 fibrinogen) and Haemocomplettan P, suggesting similar tolerance safety profiles between the two products.*
- *Mild but unresolved inflammation was observed in animals that received IM or IA administration of FESILTY (BT524 fibrinogen), and Haemocomplettan P. Based on these results, administration of FESILTY (BT524 fibrinogen) other than the intended ROA (IV) may result in persistent local inflammation in humans.*

APPLICANT'S PROPOSED LABEL

Section 13 ('Nonclinical Toxicology') was omitted from the proposed label for FESILTY. The nonclinical toxicology studies for this product are not informative to clinical prescribing decisions because safety concerns were not identified in the nonclinical studies. This omission is consistent with product labels of other approved fibrinogen concentrate products.

CONCLUSION OF NONCLINICAL STUDIES

Review of the available nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data support approval of the license application.

KEY WORDS/TERMS

FESILTY, BT524, acquired fibrinogen deficiency, congenital fibrinogen deficiency, bleeding, fibrinogen replacement, clot formation, thrombogenesis