

Administration of Fibrinogen (human) concentrate

ICD-10 Coordination and Maintenance Committee Update

March 2025

Octapharma USA

Bleeding is a major cause of death in the United States



Trauma

- ~ 2.6 million hospital admissions
- ~ 15% of these experience severe bleeding
- 40% of all trauma deaths are due to hemorrhage

Post-Partum Hemorrhage (PPH)

- ~ 3.6 million births in the US each year
- ~ 5% experience PPH
- 1-3% of these are severe
- PPH accounts for ~12% of maternal deaths

Cardiac Surgery

- ~ 400,000 cardiac surgeries requiring cardiopulmonary bypass (CPB)
- ~5-10% of these will experience major bleeding
- In addition, cardiac surgery patient can experience hypofibrinogenemia due to contact activation with the CPB circuit

Low Fibrinogen Levels Correlate with Poor Clinical Outcomes in Bleeding Patients



In trauma, patients presenting to the emergency room with levels under 1.5 g/dL, 28-day mortality increased 5-fold as compared to individuals presenting with fibrinogen levels > 2g/dL.



In bleeding obstetric patients, a serum fibrinogen level < 2.0 g/dL has an almost 100% positive predictive value for progression to severe PPH.



In cardiac surgery, low serum fibrinogen levels have been associated with increased transfusion requirements, increased postoperative bleeding and increased length of ICU stay.

For every minute of delay in the delivery of products, mortality increases by 5% in a patient with a major bleed.

Fast and effective fibrinogen replacement is critical to maintain hemostasis in these patients

What is Fibryga®?

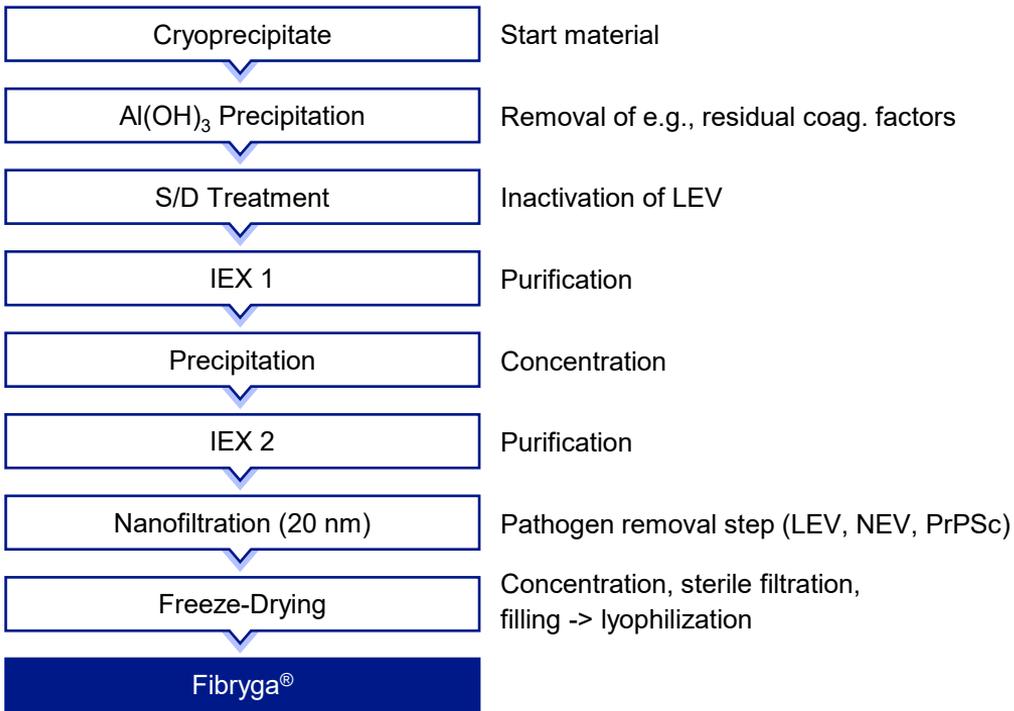
- Fibryga is a lyophilized powder for reconstitution and for intravenous use only. Fibryga® contains no preservatives. Each bottle contains approximately 1 g of fibrinogen. The diluent for reconstitution of the lyophilized powder is sterile Water for Injection.
- Fibryga® is a human fibrinogen concentrate indicated for:
 - fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency
 - treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.
 - Limitation of Use: Fibryga® is not indicated for dysfibrinogenemia.
- Generic name for Fibryga® is Fibrinogen (human).
- Administration could be documented in the medication administration records, physician's order sets, the patient progress notes, or anesthesia records.

What is Fibryga® ?

Fibryga® is extracted from large, multi-donor, pathogen inactivated pools of human plasma via fractionation. Fibryga fulfills an unmet need for a readily available, shelf-stable, precise, and safer source of fibrinogen to treat acquired fibrinogen deficiency resulting from bleeding.

Fibryga® is the first fibrinogen concentrate approved for the treatment of acquired hypofibrinogenemia due to major bleeding.

It is shelf-stable, dried-powder form of the clotting factor fibrinogen, a critical player in the final steps of blood clot formation



LEV: lipid-enveloped virus, NEV: non-enveloped virus, PrPSc: pathogenic prion protein, IEX: Ion-exchange chromatography

Fibryga[®] offers significant clinical advantages over cryoprecipitate, the current standard of care

Cryoprecipitate	Fibrinogen Concentrate
No viral inactivation, potential risk of pathogen transmission	Viral inactivation, minimal risk of pathogen transmission
Variable fibrinogen levels, accurate dosing not possible (>150 mg per unit)	Standardized fibrinogen content, accurate and consistent dosing (1g per vial)
Infusion volume higher than fibrinogen concentrate (150 mL)	Low infusion volume (50 mL)
Must be thawed before infusion (delays administration 30-45 minutes)	Rapidity of reconstitution and administration (5-10 minutes)
Requires ABO compatibility (blood-group specific)	No blood typing required
Shorter shelf life (1 year), greater possibility of wastage	Reconstitute for immediate use (↓ wastage), 4-year room temperature shelf life
Risk of thrombosis, factor VIII/VWF accumulation (contains FVIII, VWF and other factors)	Development of thrombosis is very rare (purified fibrinogen, avoids FVIII/VWF accumulation)
Risk of transfusion-related reactions (allergic reactions incidence reported to be ~5 per 100,000 units transfused per 2010-2012 NHSN report)	Potential lower risk of transfusion-related reactions

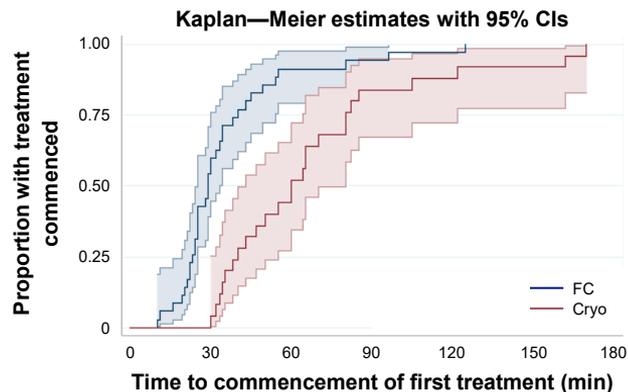
Fibrinogen Concentrates Like Fibryga® Can be Delivered to Bleeding Patients Faster in Emergency Situations

Fibryga® is a lyophilized powder that is stable at room temperature for 48 months permitting long-term storage in proximity to the point of care (i.e., trauma carts, maternal hemorrhage carts, anesthesia workstations, nursing Omnicell, area pharmacy).

For the first time, this combination of features allows clinicians access to a rapidly available fibrinogen source during this critical period in bleeding emergencies.

Figure 3. Time to commencement of first FC or Cryo treatment*

Patients receiving intervention	FC	Cryo
Patients with FIBTEM A5 ≤ 10 mm	35 (71%)	25 (51%)
Time to FC to Cryo, min	29 (23-40)	60 (40-80)
FIBTEM A5, mm	8 (7-9)	9 (5-10)
First dose of FC, g	3 (2-4)	—
First dose of Cryo, units	—	8 (8-14)



Patients awaiting first treatment

FC	35	16	3	2	1	0	0
Cryo	25	25	14	4	3	2	0

Winearls et al 2021

Cryo = cryoprecipitate. FC = fibrinogen concentrate. FIBTEM A5 = functional fibrinogen assessment at 5 minutes after clot formation. *Data in table are presented as number (percentage) or median (interquartile range).

Use of Fibrinogen Concentrates like Fibryga[®] may reduce the use of blood products as compared to standard of-care

In a meta-analysis by Wikkkelso et al., examining the use of fibrinogen concentrate in bleeding patients across several clinical scenarios, data indicated a reduction in the incidence of blood transfusions (RR 0.47, 95% CI 0.31 to 0.72)

A retrospective analysis in bleeding trauma patients comparing fibrinogen concentrate vs cryoprecipitate showed significant decreases in blood component usage in the first 24h across all types in the fibrinogen group. In addition, hospital length of stay and ICU length of stay were shorter in the fibrinogen group (6 vs 9 days; $p < 0.04$ and 4 vs 5 days; $p < 0.04$, respectively).

Reducing the amount of blood products patients receive is beneficial to healthcare:

- **Patient benefits include:**

- Reduced in-hospital mortality (OR 0.72; 95% CI 0.67–0.77; $p < 0.001$)
- Shorter hospital stays (IRR 0.85; 95% CI 0.84–0.87; $p < 0.001$)
- Lower rates of hospital-acquired infections (OR 0.79; 95% CI 0.73–0.86; $p < 0.001$)
- Decreased incidence of heart attacks and strokes (OR 0.69; 95% CI 0.58–0.82; $p < 0.001$)

Pathogen inactivation makes Fibryga® a safer source for Fibrinogen supplementation

- **Persistent Concern Over Bloodborne Pathogens:** Despite rigorous screening protocols, patients remain at risk of exposure to bloodborne infectious agents through blood transfusions. While transmission rates have been reduced to extraordinarily low levels, the risk is not eliminated.
- **FDA Recommendations for Enhanced Safety:** The FDA suggests using pathogen-inactivated blood products whenever possible to further minimize the risk of transmitting infectious agents.
- **Fibryga®'s Advanced Pathogen Inactivation:** Fibryga® undergoes a pathogen inactivation process that achieves a greater than **99.999% reduction in viral titers**, dramatically reducing patient risk compared to screening alone.

Virus Reduction Factor [\log_{10}]

Non-enveloped		Enveloped				
Product	Steps	HIV-1	PRV	BVDV	HAV	PPV
	S/D treatment	≥ 5.2	6.6	≥ 5.8	-	-
FIBRYGA ®	Nanofiltration (20 nm)	≥ 4.2	≥ 6.6	≥ 4.9	≥ 5.2	5.3
	Mean Cumulative Virus Reduction Factor	≥ 9.4	≥ 13.2	≥ 10.7	≥ 5.2	5.3

PRV = Pseudorabies Virus, model for large enveloped DNA viruses. BVDV = Bovine Virus Diarrhea Virus, model for HC. PPV = Porcine Parvovirus, model for B19V

Fibryga®: The Clinical Evidence

Research

JAMA | Original Investigation
Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery
The FIBRES Randomized Clinical Trial

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IMPORTANCE: Excessive bleeding is a common complication of cardiac surgery. An important cause of bleeding is acquired hypofibrinogenemia (fibrinogen level <1.52 g/L), for which guidelines recommend fibrinogen replacement with cryoprecipitate or fibrinogen concentrate. The 2 products have important differences, but comparative clinical data are lacking.

OBJECTIVE: To determine if fibrinogen concentrate is noninferior to cryoprecipitate for treatment of bleeding related to hypofibrinogenemia after cardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS: Randomized clinical trial at 11 Canadian hospitals enrolling adult patients experiencing clinically significant bleeding and hypofibrinogenemia after cardiac surgery from February 10, 2017, to November 1, 2018. Final 28-day follow-up visit was completed on November 28, 2018.

INTERVENTIONS: Fibrinogen concentrate (4 g, n = 415) or cryoprecipitate (30 units, n = 412) for each ordered dose within 24 hours after cardiopulmonary bypass.

MAIN RESULTS AND MEASUREMENTS: Primary outcome was blood components (red blood cells, platelets, plasma) administered during 24-hour post bypass. A 2-sample, 1-sided test for the ratio of the mean number of units was conducted to evaluate noninferiority (threshold for noninferiority ratio, <1.2).

RESULTS: Of 827 randomized patients, 735 (372 fibrinogen concentrate, 363 cryoprecipitate) were treated and included in the primary analysis (median age, 64 [interquartile range, 53-72] years; 30% women, 72% underwent complex operations, 95% moderate to severe bleeding, and pretreatment fibrinogen level, 1.16 [interquartile range, 1.3-1.9] g/L). The trial met the a priori stopping criterion for noninferiority at the interim analysis after 827 of planned 1200 patients were randomized. Mean 24-hour postbypass allogeneic transfusions were 16.3 (95% CI, 14.9 to 17.8) units in the fibrinogen concentrate group and 17.0 (95% CI, 15.6 to 18.6) units in the cryoprecipitate group (ratio, 0.96 [1-sided 97.5% CI, 0.84 to 1.09, P = .001] for noninferiority [2-sided 95% CI, 0.84 to 1.09, P = .50 for superiority]). Thromboembolic events occurred in 26 patients (7.0%) in the fibrinogen concentrate group and 35 patients (9.6%) in the cryoprecipitate group.

CONCLUSIONS AND RELEVANCE: In patients undergoing cardiac surgery who develop clinically significant bleeding and hypofibrinogenemia after cardiopulmonary bypass, fibrinogen concentrate is noninferior to cryoprecipitate with regard to number of blood components transfused in a 24-hour period post bypass. Use of fibrinogen concentrate may be considered for management of bleeding in patients with acquired hypofibrinogenemia in cardiac surgery.

TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03374234

Visual Abstract
Editorial
Supplemental content

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- Five separate clinical trials have shown Fibryga® is safe and efficacious in the adult and pediatric populations in both congenital and acquired fibrinogen deficiency
- FIBRES Trial (Fibrinogen Replacement in Cardiac Surgery) results demonstrated that in 735 cardiac surgery patients Fibryga® was safe and effective as compared to cryoprecipitate (17.0+17.7 vs 17.4+17.0 units transfused, respectively; unadjusted odds ratio 0.98). Fibryga® group (37 thromboembolic events) versus cryoprecipitate (50)
- In the FORMA-05 study examining Fibryga® in major abdominal surgery it was similar found to be efficacious and safe in promoting hemostasis as compared to cryoprecipitate. It arrived in the operating room 46 minutes faster and patients receiving Fibryga® had fewer thromboembolic events (0 versus 7)

Adverse Events Reported in more than 5% of patients in the FIBRES trial

System Organ Class Preferred Term	FIBRYGA® Patients (N=372) n (%)	Cryoprecipitate Patients (N=363) n (%)
Cardiac disorders		
Atrial fibrillation	108 (29.0%)	122 (33.6%)
Blood and lymphatic system disorders		
Anemia	58 (15.6%)	52 (14.3%)
Thrombocytopenia	15 (4.0%)	20 (5.5%)
Psychiatric disorders		
Delirium	56 (15.1%)	54 (14.9%)
Renal and urinary disorders		
Acute kidney injury	29 (7.8%)	29 (8.0%)
Renal failure	19 (5.1%)	19 (5.2%)
Hepatobiliary disorders		
Hepatic function abnormal	27 (7.3%)	26 (7.2%)
Infections and infestations		
Pneumonia	18 (4.8%)	19 (5.2%)

Adverse Reactions

- The most serious adverse reactions that may be observed with Fibryga® are thromboembolic episodes and anaphylactic-type reactions.
- The most common adverse reactions observed in clinical studies with Fibryga® in acquired fibrinogen deficiency (> 5% of patients) were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium and renal failure.
- The most common adverse reactions observed in clinical studies with Fibryga® in congenital fibrinogen deficiency (> 5% of patients) were nausea, vomiting, pyrexia (fever), and thrombocytosis.

In summary:

Fibryga® is the first and only fibrinogen concentrate indicated in bleeding patients with acquired fibrinogen deficiency (hypofibrinogenemia)

It provides fast access to a fibrinogen source in acutely bleeding patients not previously available to clinicians (5-10 min preparation vs 45 min cryoprecipitate)

- For every minute of delay in the delivery of products, mortality increases by 5% in a patient with a major bleed

Fibryga® is a shelf-stable dried powder form of fibrinogen with a 4-year room temperature stability, which can help with blood product wastage/shortages

It has a high purity and contains known amounts of fibrinogen with low levels of other clotting factors

Its pathogen inactivation technology (nanofiltration and solvent/detergent treatments) provides patients with a higher margin of safety than the current standard of care