Human Fibrinogen Concentrate (RiaSTAP and Fibryna)

**Policy**

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

**Notes:** PRECERTIFICATION REQUIRED*

Aetna considers human fibrinogen concentrate (RiaSTAP and Fibryna) medically necessary for the treatment of acute bleeding episodes in persons with congenital fibrinogen deficiency including afibrinogenemia and hypofibrinogenemia when the diagnosis of congenital fibrinogen deficiency has been confirmed by blood coagulation testing.

Aetna considers RiaSTAP experimental and investigational for the treatment of the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established.

- Acquired hypofibrinogenemia
- Bleeding associated with aortic reconstruction and deep hypothermic circulatory arrest
- Dysfibrinogenemia
- Obstetric hemorrhage including post-partum haemorrhage in persons without congenital fibrinogen deficiency

**Policy History**

Last Review 08/01/2017  
Effective: 08/21/2009  
Next Review: 09/21/2017

**Definitions**

**Additional Information**

Clinical Policy Bulletin Notes
■ Peri-operative (pre-operative, intra-operative, and post-operative) hemorrhage in persons without congenital fibrinogen deficiency
■ Trauma-associated hemorrhage in persons without congenital fibrinogen deficiency.

* Precertification of human fibrinogen concentrate is required of all Aetna participating providers and members in applicable plan designs. For prior authorization of human fibrinogen concentrate, call (866) 503-0857, or fax (866) 267-3277.

**Background**

Fibrinogen, also known as Factor I, is synthesized in the liver and circulates in the blood with a normal plasma concentration of 250 to 400 mg/dL (2.5 to 4.0 g/L). It plays an important role in clotting of the blood. Diminished concentrations of fibrinogen limit the body's ability to form a clot. Congenital fibrinogen deficiency (CFD) is a rare, potentially life-threatening bleeding disorder. Individuals with CFD are unable to make sufficient amounts of fibrinogen. There are 2 types of hereditary fibrinogen disorders: (i) type I deficiencies (quantitative defects) such as afibrinogenemia and hypofibrinogenemia -- with low or unmeasurable levels of immunoreactive protein; and (ii) type II deficiencies (qualitative defects) such as dysfibrinogenemia and hypodysfibrinogenemia -- with normal or altered antigen levels associated with reduced coagulant activity. While dysfibrinogenemias are in most cases autosomal dominant disorders, type I deficiencies are generally inherited as autosomal recessive traits. Patients affected by congenital afibrinogenemia or severe hypofibrinogenemia may experience bleeding manifestations varying from mild to severe (Asselta et al, 2006).

Congenital fibrinogen deficiency affects an estimated 1 person per 1,000,000, with an estimated prevalence of 150 to 300 people in the United States. It is usually diagnosed at birth when newborns bleed from their umbilical cord site. al-Mondhiry and Ehmann (1994) noted that diagnosis of congenital afibrinogenemia is usually established by demonstrating trace or absent immunoreactive fibrinogen in the plasma. Patients with hypofibrinogenemia are usually asymptomatic, unless exposed to trauma. Furthermore, Berube (2009) stated that disorders involving fibrinogen are rare but should be considered in any
patient with a history of hemorrhage or thrombosis in whom most of the common causes have been ruled out. Blood coagulation tests such as prothrombin time (PT) that is often reported as the International Normalized Ratio (INR), activated partial thromboplastin time (APTT), and thrombin clotting time (TCT) or thrombin time (TT) all require the production of a fibrin clot as an end point, and will be abnormally prolonged in patients with hypofibrinogenemia or afibrinogenemia.

Abnormal laboratory results in patients with afibrinogenemia will correct completely following administration of normal plasma or purified fibrinogen. Accordingly, these tests are sensitive for the presence of a fibrinogen disorder, but lack specificity.

Verhovsek and colleagues (2008) provided examples of methods and findings for commonly used laboratory tests for afibrinogenemia and hypofibrinogenemia:

<table>
<thead>
<tr>
<th>Clinical Problem</th>
<th>Afibrinogenemia</th>
<th>Hypofibrinogenemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (normal: 11 to 14 sec)</td>
<td>No clot detected</td>
<td>14.2</td>
</tr>
<tr>
<td>INR (normal: 0.8 to 1.2)</td>
<td>No clot detected</td>
<td>1.2</td>
</tr>
<tr>
<td>APTT (normal: 22 to 35 sec)</td>
<td>No clot detected</td>
<td>32</td>
</tr>
<tr>
<td>TCT or TT (normal: 20 - 30 sec)</td>
<td>No clot detected</td>
<td>46</td>
</tr>
<tr>
<td>Reptilase time (normal: 15 - 27 sec)</td>
<td>&gt; 60</td>
<td>33</td>
</tr>
</tbody>
</table>
Clottable fibrinogen (normal: 160 - 420 mg/dL)  
Fibrinogen antigen (normal: 160 - 420 mg/dL)  
Ratio of fibrinogen antigen to clottable fibrinogen 

Individuals with CFD are advised to curtail physical activities because of risk of bleeding from minor trauma. If bleeding occurs in the brain or other organs and is left untreated, it may lead to blood loss, organ damage and death. The standard approach for replacement of fibrinogen in patients with CFD is cryoprecipitate; but more recently, a pasteurized human fibrinogen concentrate has become available.

In an open, multi-center, non-controlled, retrospective study, Kreuz and co-workers (2005) examined the effectiveness and tolerability of a pasteurized human fibrinogen concentrate in patients with CFD. Hemostatic efficacy was assessed by laboratory investigation as well as clinical observation. A total of 12 patients (afibrinogenemia, n = 8; hypofibrinogenemia, n = 3; dysfibrinogenemia combined with hypofibrinogenemia, n = 1) were included in the study. Fibrinogen substitution was indicated for one of the following reasons: (i) to stop an ongoing bleed; (ii) as prophylaxis before surgery; or (iii) for routine prophylaxis to prevent spontaneous bleeding. A total of 151 fibrinogen infusions were recorded. The median single dosage was 63.5 mg/kg body weight of the drug for bleeding events or surgery and 76.9 mg/kg for prophylaxis. The median total dose per event for bleeding events or surgery was 105.6 mg/kg. Fibrinogen was administered in 26 bleeding episodes; 11 surgical operations; and 89 prophylactic infusions, of which 86 were received by 1
patient. The median response (n = 8) was 1.5 mg/dL per substituted mg of fibrinogen per kg body weight (0.8 to 2.3). The median in vivo recovery (n = 8) was 59.8 % (32.5 to 93.9). Clinical efficacy was very good in all events with the exception of one surgical procedure, where it was moderate. No intercurrent bleeding occurred during prophylaxis. All but 1 infusion was well-tolerated; the patient, who was administered 86 prophylactic infusions, experienced an anaphylactic reaction after the 56th infusion. In addition, one patient developed deep vein thrombosis and nonfatal pulmonary embolism with treatment for osteosynthesis after collum femoris fracture. Fibrinogen substitution could not be excluded as a contributing factor in this high-risk patient. The authors concluded that substitution with pasteurized human fibrinogen concentrate in patients with CFD is efficient and generally well tolerated.

A review by de Moerloose and colleagues (2013) stated that "Depending on the country of residence, patients receive fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrates. Fibrinogen concentrate preparation includes safety steps for inactivation/removal of viruses, so concentrates are safer than cryoprecipitate or FFP".

Bevan (2009) stated that congenital abnormalities of fibrinogen are rare disorders classified as quantitative (afibrinogenemia and hypofibrinogenemia) or qualitative types (dysfibrinogenemia and hypodysfibrinogenemia). Fibrinogen is essential to hemostasis as the substrate for fibrin clot formation and also acts in primary hemostasis as a key ligand in platelet aggregation. Quantitative deficiency of fibrinogen can result in severe bleeding, or arterial and venous thromboembolism, and poor wound healing. Dysfibrinogenemia is characterized by functional abnormalities of fibrinogen, which may be asymptomatic (in 50 % of cases), or cause bleeding (25 %) or thrombosis (25 %). Replacement of the deficient or abnormal fibrinogen with frozen plasma, cryoprecipitate, or fibrinogen concentrate has been found to be effective in practice in treating hemostatic complications of these disorders. Although cryoprecipitate is the most commonly used replacement material, pathogen-reduced fibrinogen concentrates have several advantages, most importantly a lower potential risk
of viral transmission and standardized fibrinogen content allowing accurate dosing. They also avoid transfusing unwanted clotting factors, platelet micro-particles and immunoglobulins, and can be administered rapidly without thawing. The use of fibrinogen concentrate to treat congenital fibrinogen disorders is strongly supported in principle and increasingly by practical experience and evidence.

Levy et al (2012) noted that there currently is a lack of awareness among physicians regarding the significance of fibrinogen during acute bleeding and, at many medical centers, fibrinogen is not monitored routinely during treatment. These investigators reviewed current studies that demonstrate the importance of considering fibrinogen replacement during the treatment of acquired bleeding across clinical settings. If depleted, the supplementation of fibrinogen is key for the rescue and maintenance of hemostatic function; however, the threshold at which such intervention should be triggered is currently poorly defined. Although traditionally performed via administration of fresh frozen plasma or cryoprecipitate, the use of lyophilized fibrinogen (concentrate) is becoming more prevalent in some countries. Recent reports relating to the efficacy of fibrinogen concentrate suggest that it is a viable alternative to traditional hemostatic approaches, which should be considered.

Levy et al (2014) stated that fibrinogen supplementation can be achieved using plasma or cryoprecipitate; however, there are a number of safety concerns associated with these allogeneic blood products and there is a lack of high-quality evidence to support their use. Additionally, there is sometimes a long delay associated with the preparation of frozen products for infusion. Fibrinogen concentrate provides a promising alternative to allogeneic blood products and has a number of advantages: it allows a standardized dose of fibrinogen to be rapidly administered in a small volume, has a very good safety profile, and is virally inactivated as standard. Administration of fibrinogen concentrate, often guided by point-of-care viscoelastic testing to allow individualized dosing, has been successfully used as hemostatic therapy in a range of clinical settings, including cardiovascular surgery, post-partum hemorrhage, and trauma.
Results showed that fibrinogen concentrate is associated with a reduction or even total avoidance of allogeneic blood product transfusion. Fibrinogen concentrate represents an important option for the treatment of coagulopathic bleeding; further studies are needed to determine precise dosing strategies and thresholds for fibrinogen supplementation.

Elliott and Aledort (2013) stated that fibrinogen plays a key role in the coagulation process, and therefore maintaining adequate quantities of fibrinogen is an essential step in achieving satisfactory hemostasis in patients with acquired hypofibrinogenemia. Potential options for treating acquired hypofibrinogenemia in patients with uncontrolled bleeding include the use of cryoprecipitate or fibrinogen replacement therapy. These investigators provided a brief overview of the hemostatic process and the methods for assessing coagulopathy and discussed the safety and effectiveness of cryoprecipitate and fibrinogen concentrate in restoring fibrinogen levels, achieving hemostasis and reducing transfusion requirements in different patient populations requiring rapid hemostasis. Other issues relevant to the clinical use of these agents in restoring hemostasis, including variations in product composition, preparation time and cost, were also examined. The authors also noted that “Although it has been shown that fibrinogen concentrate offers a more rigorous viral inactivation process and has the potential for more rapid and predictable dosing than cryoprecipitate, there remains a clear need for prospective, randomized studies to establish the precise role of fibrinogen concentrate in achieving hemostasis, reducing transfusion requirements, and, more importantly, improving hard clinical outcomes such as morbidity and mortality in patients with acquired coagulopathies. Moreover, these studies need to further elucidate the threshold for fibrinogen concentrate treatment and the most appropriate dosages in different patient populations requiring rapid hemostasis. Finally, these prospective, randomized studies need to confirm the optimal timing of intervention with fibrinogen concentrate”.

An UpToDate review on "Disorders of fibrinogen" (Berube, 2014) states that "Sources of fibrinogen for clinical use include
cryoprecipitate, fresh frozen plasma (FFP), and fibrinogen concentrates; the latter, if available, is the preferred product”.

Fenger-Eriksen and colleagues (2008) noted that patients experiencing massive hemorrhage are at high risk of developing coagulopathy through loss, consumption, and dilution of coagulation factors and platelets. It has been reported that plasma fibrinogen concentrations may reach a critical low level relatively early during bleeding, calling for replacement fibrinogen therapy. These researchers audited the effects of fibrinogen concentrate therapy on laboratory and clinical outcome in patients with massive hemorrhage. They identified 43 patients over the previous 2 years to whom a fibrinogen concentrate had been administered as treatment for hypofibrinogenemia during serious hemorrhage. Platelet count, plasma fibrinogen, activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer, and volume of blood lost were obtained from medical and laboratory records. Numbers of units of red blood cells (RBC), fresh frozen plasma (FFP), and pooled platelet concentrates were recorded before and after fibrinogen substitution. A significant increase in plasma fibrinogen concentration was observed after fibrinogen concentrate therapy. Platelet counts and fibrin D-dimer values remained unchanged, whereas the APTT and PT improved significantly. Requirements for RBC, FFP, and platelets were significantly reduced; blood loss decreased significantly. The authors concluded that fibrinogen substitution therapy with a fibrinogen concentrate generally improved global laboratory coagulation results; and as supplementary intervention, appeared to reduce the requirements for RBC, FFP, and platelet substitution in this patient cohort.

On January 16, 2009, the Food and Drug Administration (FDA) licensed RiaSTAP (human fibrinogen concentrate) for the treatment of acute bleeding in patients with CFD. RiaSTAP is a purified fibrinogen concentrate made from the plasma of healthy human donors that undergoes virus inactivation and removal for safety assurance. It was developed under the FDA’s accelerated approval regulations for orphan drugs. There have been more than 1,000,000 units sold worldwide (outside the United States,
RiaSTAP is marketed under the trade name of Haemocomplettan. RiaSTAP is indicated for the treatment of acute bleeding episodes in patients with CFD including afibrinogenemia and hypofibrinogenemia; it is not indicated for dysfibrinogenemia.

The licensing of RiaSTAP was based on a phase II, prospective, open-label, safety and pharmacokinetic study using maximum clot firmness (MCF) as a surrogate endpoint for hemostatic efficacy. A total of 15 patients with afibrinogenemia achieved the target level of fibrinogen expected to prevent bleeding after they received 70 mg/kg body weight of the drug. In addition, plasma from 14 of the 15 patients showed a highly significant (p < 0.0001) mean improvement in MCF from baseline to 1 hour post-infusion following RiaSTAP treatment. The most serious adverse reactions that have been reported in clinical studies or through post-marketing surveillance following RiaSTAP treatment are allergic-anaphylactic reactions and thromboembolic episodes, including myocardial infarction, pulmonary embolism, deep vein thrombosis and arterial thrombosis. The most common adverse reactions that have been reported after RiaSTAP therapy are allergic reactions and generalized reactions such as chills, fever, headache, as well as nausea and vomiting.

In addition to the treatment of CFD, human fibrinogen concentrate has also been employed in the management of other hypofibrinogenemic conditions such as acquired hypofibrinogenemia and post-operative hemorrhage. Clinical data for the use of human fibrinogen concentrate in acquired hypofibrinogenemic states are scarce. Weinkove and Rangarajan (2008) evaluated the safety and effectiveness of Haemocomplettan in patients with acquired hypofibrinogenemia. Demographical and pre-treatment clinical data of patients treated with Haemocomplettan were retrospectively reviewed. Pre- and post-treatment fibrinogen levels, transfusion requirements, outcomes and adverse reactions were recorded. A total of 30 adult patients who received Haemocomplettan for acquired hypofibrinogenemia (plasma fibrinogen concentration less than 1.5 g/L) were included in the study. Causes of hypofibrinogenemia included placental abruption, disseminated
intravascular coagulation as a result of massive blood loss and transfusion, liver failure and cardiac surgery. Following a median dose of 4 g Haemocomplettan, median Clauss fibrinogen level rose from 0.65 to 2.01 g/L, with a median fibrinogen increment of 0.25 g/L per 1 g fibrinogen concentrate administered. It was reported that 46% of patients stopped bleeding with blood components and Haemocomplettan alone, and a further 29% stopped bleeding with surgical or endoscopic intervention. Inpatient mortality was 40%; no venous thromboses were observed. A total of 4 patients with massive perioperative hemorrhage and hypotension (including 3 post-cardiothoracic surgery) had arterial ischemic events, however, none of which was attributable to over-replacement of fibrinogen. The cost of Haemocomplettan was comparable with that of cryo-precipitate. The authors concluded that purified human fibrinogen concentrate appears effective in the management of acquired hypofibrinogenemia.

Bleeding diathesis after aortic valve operation and ascending aorta replacement (AV-AA) is usually managed with FFP and platelet concentrates. In a pilot study, Rahe-Meyer et al (2009) compared hemostatic effects of conventional transfusion management and FIBTEM (thromboelastometry test)-guided fibrinogen concentrate administration. A blood-product transfusion algorithm was developed with retrospective data from 42 elective patients (group A). Two units of platelet concentrate were transfused after cardiopulmonary bypass, followed by 4 units of FFP if bleeding persisted, if platelet count was less than or equal to 100 x 10^3 microl(-1) when removing the aortic clamp, and vice versa if platelet count was greater than 100 x 10^3 microl(-1). The trigger for each therapy step was greater than or equal to 60 g blood absorbed from the mediastinal wound area by dry swabs in 5 mins. Assignment to two prospective groups was neither randomized nor blinded; group B (n = 5) was treated according to the algorithm, group C (n = 10) received Haemocomplettan/RiaSTAP before the algorithm-based therapy. A mean of 5.7 (0.7) g fibrinogen concentrate decreased blood loss to below the transfusion trigger level in all group C patients. Group C had reduced transfusion [mean of 0.7 (range of 0 to 4) units versus 8.5 (5.3) units in group A and 8.2
(2.3) units in group B] and reduced post-operative bleeding [366 (199) ml versus 793 (560) ml in group A and 716 (219) ml in group B]. The authors concluded that in this pilot study, FIBTEM-guided fibrinogen concentrate administration was associated with reduced transfusion requirements and 24-hr post-operative bleeding in patients undergoing AV-AA.

In a prospective randomised pilot study, Karlsson et al (2009) examined if prophylactic infusion of fibrinogen concentrate may reduce post-operative bleeding. A total of 20 elective coronary artery bypass graft (CABG) patients with pre-operative plasma fibrinogen levels of less than 3.8 g/L were included in this study. Patients were randomized to receive an infusion of 2 g fibrinogen concentrate (FIB group) or no infusion before surgery (control group). Primary endpoint was safety with clinical adverse events and graft occlusion assessed by multi-slice computed tomography. Pre-defined secondary endpoints were post-operative blood loss, blood transfusions, hemoglobin levels 24 hrs after surgery, and global hemostasis assessed with thromboelastometry, 2 and 24 hrs after surgery. Infusion of 2 g fibrinogen concentrate increased plasma levels of fibrinogen by 0.6 +/- 0.2 g/L. There were no clinically detectable adverse events of fibrinogen infusion. Computed tomography revealed 1 sub-clinical vein graft occlusion in the FIB group. Fibrinogen concentrate infusion reduced post-operative blood loss by 32 % (565 +/- 150 versus 830 +/- 268 ml/12 hrs, p = 0.010). Hemoglobin concentration was significantly higher 24 hrs after surgery in the FIB group (110 +/- 12 versus 98 +/- 8 g/L, p = 0.018). Prophylactic fibrinogen concentrate infusion did not influence global post-operative hemostasis as assessed by thromboelastometry. The authors concluded that in this pilot study pre-operative fibrinogen concentrate infusion reduced bleeding after CABG without evidence of post-operative hypercoagulability. They stated that larger studies are needed to ensure safety and confirm efficacy of prophylactic fibrinogen treatment in cardiac surgery.

Mercier and Bonnet (2010) reviewed the optimal use of blood products and clarified the indications for prohemostatic drugs in obstetric hemorrhage. The literature emphasizes the usefulness
of transfusing packed red blood cells, fresh frozen plasma and platelets earlier and in defined ratios to prevent dilutional coagulopathy during obstetric hemorrhage. It seems reasonable to use blood products for transfusion earlier and in a 1:1 fresh frozen plasma: red blood cell ratio during acute obstetric hemorrhage; however, this analysis is mainly based on trauma literature. Fibrinogen concentrate should be added if the fibrinogen plasma level remains below 1.0 g/L and perhaps even as soon as it falls below 1.5 to 2.0 g/L; the addition of tranexamic acid (1 g) is cheap, likely to be useful and appears safe. Data on the proactive administration of platelets are insufficient to recommend this practice routinely. Presently, recombinant factor VIIa (60 to 90 microg/kg) is advocated only after failure of other conventional therapies, including embolization or conservative surgery, but prior to obstetric hysterectomy. The authors stated that prospective randomized controlled trials are highly desirable to examine the use of clotting factors and other prohemostatic drugs for the management of obstetric hemorrhage.

Wikkelsoe and colleagues (2012) described the protocol of a randomized controlled trial (FIB-PPH trial) to examine the effects of fibrinogen concentrate as initial treatment for post-partum hemorrhage (PPH). In this placebo-controlled, double-blind, multi-center trial, parturients with primary PPH are eligible following vaginal delivery in case of manual removal of placenta (blood loss [greater than or equal to] 500 ml) or manual exploration of the uterus after the birth of placenta (blood loss [greater than or equal to] 1,000 ml). Caesarean sections are also eligible in case of peri-operative blood loss [greater than or equal to] 1,000 ml. The exclusion criteria are known inherited hemostatic deficiencies, pre-partum treatment with anti-thrombotics, pre-pregnancy weight less than 45 kg or refusal to receive blood transfusion. Following informed consent, patients will be randomly allocated to either early treatment with 2 g fibrinogen concentrate or 100 ml isotonic saline (placebo). Hemostatic monitoring with standard laboratory coagulation tests and thrombo-elastography (TEG, functional fibrinogen and RapidTEG) is performed during the initial 24 hours. Primary outcome is the need for blood transfusion. To examine a 33 % reduction in the need for blood transfusion a total of 245 patients
will be included. Four university affiliated public tertiary care hospitals will include patients during a 2-year period. Adverse events including thrombosis are assessed in accordance with International Conference on Harmonisation (ICH) - good clinical practice (GCP). The authors concluded that a widespread belief in the benefits of early fibrinogen substitution in cases of PPH has led to increased off-label use. The FIB-PPH trial is investigator-initiated and aims to provide an evidence-based platform for the recommendations of the early use of fibrinogen concentrate in PPH.

Schochl et al (2010) reported the treatment of major trauma using mainly coagulation factor concentrates. This retrospective analysis included trauma patients who received greater than or equal to 5 units of red blood cell concentrate within 24 hours. Coagulation management was guided by thromboelastometry (ROTEM). Fibrinogen concentrate was given as first-line hemostatic therapy when maximum clot firmness (MCF) measured by FibTEM (fibrin-based test) was less than 10 mm. Prothrombin complex concentrate (PCC) was given in case of recent coumarin intake or clotting time measured by extrinsic activation test (EXTEM) greater than 1.5 times normal. Lack of improvement in EXTEM MCF after fibrinogen concentrate administration was an indication for platelet concentrate. The observed mortality was compared with the mortality predicted by the trauma injury severity score (TRISS) and by the revised injury severity classification (RISC) score. Of 131 patients included, 128 received fibrinogen concentrate as first-line therapy, 98 additionally received PCC, while 3 patients with recent coumarin intake received only PCC. Twelve patients received FFP and 29 received platelet concentrate. The observed mortality was 24.4 %, lower than the TRISS mortality of 33.7 % (p = 0.032) and the RISC mortality of 28.7 % (p > 0.05). After excluding 17 patients with traumatic brain injury, the difference in mortality was 14 % observed versus 27.8 % predicted by TRISS (p = 0.0018) and 24.3 % predicted by RISC (p = 0.014). The authors concluded that ROTEM-guided hemostatic therapy, with fibrinogen concentrate as first-line hemostatic therapy and additional PCC, was goal-directed and fast. A favorable survival rate was observed. Moreover, they stated that prospective, randomized trials to
investigate this therapeutic alternative further appear warranted.

Wafaisade et al (2012) examined if blood component transfusion and hemostatic drug administration during acute trauma care have changed in daily practice during the recent years. The multi-center trauma registry of the German Society for Trauma was retrospectively analyzed for primarily admitted patients older than 16 years with an Injury Severity Score greater than or equal to 16 who had received at least 5 red blood cell (RBC) units between emergency room arrival and intensive care unit admission. Administration of FFP and platelet units has been documented since 2002, and use of hemostatic drugs since 2005. From 2002 to 2009 (n = 2,813), the FFP:RBC ratio increased from 0.65 to 0.75 (p = 0.02) and the platelet:RBC ratio from 0.04 to 0.09 (p < 0.0001). A constant increase was also observed regarding the overall use of hemostatic drugs (n = 1,811; 2005 to 2009) as these were administered to 43.4 % of the patients in 2005 and to 60.7 % in 2009 (p < 0.0001). In particular, the administration of fibrinogen concentrate (2005: 17.0 %, 2009: 45.6 %; p < 0.0001) and recombinant factor VIIa (2005: 1.9 %, 2009: 6.3 %; p = 0.04) showed a marked increase. However, mortality rates remained unchanged during the 8-year study period. The authors concluded that therapy of bleeding trauma patients has changed in Germany during the recent years toward more aggressive coagulation support. This development continues although grades of evidence are still low regarding most of the changes reported in this study. They stated that randomized controlled trials are needed with respect to blood component therapy using pre-defined ratios and to the administration of hemostatic drugs commonly used for the severely injured.

Grottke (2012) noted that trauma-induced coagulopathy is a frequent complication in severely injured patients. To correct coagulopathy and restore hemostasis, these patients have traditionally been treated with fresh frozen plasma, but in the last decade, there has been a shift from empirical therapy to targeted therapy with coagulation factor concentrates and other hemostatic agents. This investigator highlighted emerging therapeutic options and controversial topics. Early administration
of the anti-fibrinolytic medication tranexamic acid was shown in the multi-center CRASH-2 trial to be an effective and inexpensive means of decreasing blood loss. Numerous retrospective and experimental studies have shown that the use of coagulation factor concentrates decreases blood loss and may be useful in reducing the need for transfusion of allogeneic blood products. In particular, early use of fibrinogen concentrate and thrombin generators has a positive impact on hemostasis. However, the use of prothrombin complex concentrate to correct trauma-induced coagulopathy has also been associated with a potential risk of serious adverse events. The author concluded that current evidence in trauma resuscitation indicated a potential role for coagulation factor concentrates and other hemostatic agents in correcting trauma-induced coagulopathy. They stated that despite a shift towards such transfusion strategy, there remains a shortage of data to support this approach.

Ziegler et al (2013) stated that use of allogeneic blood products to treat pediatric trauma may be challenged, particularly in relation to safety. These researchers reported successful treatment of a child with severe abdominal and pelvic injuries with preemptive fibrinogen supplementation followed by rotational thromboelastometry (ROTEM)-guided, goal-directed hemostatic therapy. Fibrinogen concentrate was administered (total dose: 2 g), while transfusion of fresh frozen plasma and platelet concentrate was avoided. Activated partial thromboplastin time was prolonged and Quick values were low but ROTEM clotting time values remained normal, therefore, no thrombin-generating drugs were considered necessary. The authors concluded that this case showed the potential for hemostatic treatment with coagulation factor concentrates to be applied to pediatric trauma.

Wafaisade et al (2013) examined if the administration of fibrinogen concentrate (FC) in severely injured patients was associated with improved outcomes. Patients documented in the Trauma Registry of the German Society for Trauma Surgery (primary admissions, Injury Severity Score [ISS] greater than or equal to 16) who had received FC during initial care between emergency department (ED) arrival and intensive care unit admission (FC+) were matched with patients who had not
received FC (FC-). The matched-pairs analysis yielded two comparable cohorts (n = 294 in each group) with a mean ISS of 37.6 ± 13.7 (FC+) and 37.1 ± 13.3 (FC-) (p = 0.73); the mean age was 40 ± 17 versus 40 ± 16 (p = 0.72), respectively. Patients were predominantly male (71.1% in both groups, p = 1.0). On ED arrival, hypotension (systolic blood pressure, less than or equal to 90 mm Hg) occurred in 51.4% (FC+) and 48.0% (FC-) (p = 0.41), and base excess was -7.4 ± 5.3 mmol/L for FC+ and was -7.5 ± 6.2 mmol/L for FC- (p = 0.96). Patients were administered 12.8 ± 14.3 (FC+) versus 11.3 ± 10.0 (FC-) packed red blood cell units (p = 0.20). Thromboembolism occurred in 6.8% (FC+) versus 3.4% (FC-) (p = 0.06), and multi-organ failure occurred in 61.2% versus 49.0% (p = 0.003), respectively. Whereas 6-hour mortality was 10.5% for FC+ versus 16.7% for FC- (p = 0.03), the mean time to death was 7.5 ± 14.6 days versus 4.7 ± 8.6 days (p = 0.006). The overall hospital mortality rate was 28.6% versus 25.5% (p = 0.40), respectively. The authors concluded that this was the first study to investigate the effect of FC administration in bleeding trauma. In this large population of severely injured patients, the early use of FC was associated with a significantly lower 6-hour mortality and an increased time to death, but also an increased rate of multi-organ failure. A reduction of overall hospital mortality was not observed in patients receiving FC.

In a single-center, prospective, placebo-controlled, double-blind study, Rahe-Meyer et al (2013) examined if fibrinogen concentrate can reduce blood transfusion when given as intra-operative, targeted, first-line hemostatic therapy in bleeding patients undergoing aortic replacement surgery. Patients aged 18 years or older undergoing elective thoracic or thoraco-abdominal aortic replacement surgery involving cardiopulmonary bypass were randomized to fibrinogen concentrate or placebo, administered intra-operatively. Study medication was given if patients had clinically relevant coagulopathic bleeding immediately after removal from cardiopulmonary bypass and completion of surgical hemostasis. Dosing was individualized using the fibrin-based thrombo-elastometry test. If bleeding continued, a standardized transfusion protocol was followed. A total of 29 patients in the fibrinogen concentrate group and 32 patients in the placebo group were eligible for the efficacy
analysis. During the first 24 hours after the administration of study medication, patients in the fibrinogen concentrate group received fewer allogeneic blood components than did patients in the placebo group (median, 2 versus 13 U; p < 0.001; primary endpoint). Total avoidance of transfusion was achieved in 13 (45 %) of 29 patients in the fibrinogen concentrate group, whereas 32 (100 %) of 32 patients in the placebo group received transfusion (p < 0.001). There was no observed safety concern with using fibrinogen concentrate during aortic surgery. The authors concluded that hemostatic therapy with fibrinogen concentrate in patients undergoing aortic surgery significantly reduced the transfusion of allogeneic blood products. Moreover, they stated that larger multi-center studies are needed to confirm the role of fibrinogen concentrate in the management of peri-operative bleeding in patients with life-threatening coagulopathy.

In a prospective, randomized, open-label study, Tanaka et al (2014) compared hematologic and transfusion profiles between the first-line acquired fibrinogen (FIB) replacement and platelet transfusion in post-cardiac surgical bleeding. A total of 20 adult patients who underwent valve replacement or repair and fulfilled preset visual bleeding scale were randomized to 4 g of FIB or 1 unit of apheresis platelets. Primary end-points included hemostatic condition in the surgical field and 24-hour hemostatic product usage. Hematologic data, clinical outcome, and safety data were collected up to the 28th day post-operative visit. In patients who received the first-line FIB concentrate (n = 10), the visual bleeding scale improved after intervention, and the incidence of platelet transfusion and total plasma donor exposure were lower compared to the platelet group (n = 10). Post-intervention FIB level was statistically higher (209 mg/dL versus 165 mg/dL) in the FIB group than in the platelet group, but platelet count and prothrombin were lower. There were no statistical differences in the post-operative blood loss and red blood cell transfusion between 2 groups. The authors concluded that these preliminary data indicated that the primary FIB replacement may potentially reduce the incidence of platelet transfusion and the number of donor exposures. These preliminary findings need to be validated by well-designed studies.
Gielen et al (2014) performed a systematic review and meta-analysis to define the association between fibrinogen levels and blood loss after cardiac surgery. A database search (January 2013) was performed on publications assessing the association between pre- and post-operative fibrinogen levels and post-operative blood loss in adult patients undergoing cardiac surgery. Cohort studies and case-control studies were eligible for inclusion. The main outcome was the pooled correlation coefficient, calculated via Fisher’s Z transformation scale, in a random-effects meta-analysis model stratified for the time-point at which fibrinogen was measured. A total of 20 studies were included. The pooled correlation coefficient of studies (n = 9) concerning pre-operative fibrinogen levels and post-operative blood loss was -0.40 (95 % confidence interval [CI]: -0.58 to -0.18), pointing towards more blood loss in patients with lower pre-operative fibrinogen levels. Among papers (n = 16) reporting on post-operative fibrinogen levels and post-operative blood loss, the pooled correlation coefficient was -0.23 (95 % CI: -0.29 to -0.16). The authors concluded that the findings of this meta-analysis indicated a significant but weak-to-moderate correlation between pre- and post-operative fibrinogen levels and post-operative blood loss in cardiac surgery. They stated that this moderate association calls for appropriate clinical studies on whether fibrinogen supplementation will decrease post-operative blood loss.

Aubron et al (2014) summarized the available literature evaluating the use of FC in the management of severe trauma. Studies reporting the administration of FC in trauma patients published between January 2000 and April 2013 were identified from MEDLINE and from the Cochrane Library. The systematic review identified 12 articles reporting FC usage in trauma patients: 4 case reports, 7 retrospective studies, and 1 prospective observational study; 3 of these were not restricted to trauma patients. The authors concluded that despite methodological flaws, some of the available studies suggested that FC administration may be associated with a reduced blood product requirement. They stated that randomized controlled trials (RCTs) are needed to determine whether FC improves outcomes in pre-hospital management of trauma patients or whether FC is superior to another source of fibrinogen in early
hospital management of trauma patients.

In June 2017, Fibryna, a human fibrinogen concentrate, was approved by the U.S Food and Drug Administration for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. However, Fibryna is not indicated for dysfibrinogenemia.

Two clinical trials (FORMA 01 and FORMA 02) formed the basis for the safety and efficacy for Fibryna. The FORMA 01 was a randomized, phase 2 crossover study in which 22 subjects (ranging in age 12 to 53 years; 6 adolescents and 16 adults) with congenital fibrinogen deficiency compared the pharmacokinetics (PK) and pharmacodynamics (PD) of Fibryna to the comparable U.S. licensed fibrinogen concentrate product, RiaSTAP. Each subject received a single intravenous 70 mg/kg dose of Fibryna and the comparator product. Blood samples were drawn from the subjects to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The incremental in vivo recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was a 1.8 mg/dL (range 1.1 – 2.6 mg/dL) increase per mg/kg. The median in vivo recovery indicated that a dose of 70 mg/kg will increase patients’ fibrinogen plasma concentration by approximately 125 mg/dL. No difference in fibrinogen activity was observed between males and females. There was no difference in the pharmacokinetics of Fibryna between adults and adolescents (12-17 years of age) (FDA, 2017).

An interim analysis of the FORMA 02 was used for the FDA-approved indications of Fibryna. The FORMA 02 is an ongoing prospective, uncontrolled phase 3, open-label, multicenter clinical study involving 13 patients (ranging in age 13 to 53 years; 2 adolescents and 11 adults) with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia), and was used to establish safety and efficacy of Fibryna. Of the 22 evaluable bleeding events, 21 (95%) were rated as having a good or excellent efficacy. For 1 bleeding event, the investigator’s assessment was missing. The median number of infusions for the
bleeding events was 1. Two (9%) bleeding events required 2 infusions. None of the bleeding events required more than 2 infusions. The most common adverse reactions observed in more than one subject in the clinical study (> 5%) were vomiting, weakness and pyrexia (FDA, 2017).

According to the prescribing information, the dosing, duration, and frequency of administration for Fibryna should be individualized based on the extent of bleeding, laboratory values, and the clinical condition of the patient. The recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding and 150 mg/dL for major bleeding. The patient’s fibrinogen level should be monitored during treatment with Fibryna. Additional infusions of Fibryna should be administered if the plasma fibrinogen level is below the accepted lower limit (80 mg/dL for minor bleeding, 130 mg/dL for major bleeding) of the target level until hemostasis is achieved. (FDA, 2017). See appendix for additional dosing information.

Post-Partum Hemorrhage:

In a multi-center, double-blinded, parallel RCT, Wikkelso and colleagues (2015) hypothesized that pre-emptive treatment with FC reduces the need for RBC transfusion in patients with PPH. These investigators assigned subjects with severe PPH to a single dose of FC or placebo (saline). A dose of 2 g or equivalent was given to all subjects independent of body weight and the FC at inclusion. The primary outcome was RBC transfusion up to 6 weeks post-partum; secondary outcomes were total blood loss, total amount of blood transfused, occurrence of re-bleeding, hemoglobin of less than 58 g/L, RBC transfusion within 4 hours, 24 hours, and 7 days, and as a composite outcome of “severe PPH”, defined as a decrease in hemoglobin of greater than 40 g/L, transfusion of at least 4 units of RBCs, hemostatic intervention (angiographic embolization, surgical arterial ligation, or hysterectomy), or maternal death. Of the 249 randomized subjects, 123 of 124 in the fibrinogen group and 121 of 125 in the placebo group were included in the intention-to-treat analysis. At inclusion the subjects had severe PPH, with a mean blood loss of 1,459 (S.D. of 476) ml and a mean FC of 4.5 (S.D. of 1.2) g/L. The
intervention group received a mean dose of 26 mg/kg FC, thereby significantly increasing FC compared with placebo by 0.40 g/L (95 % CI: 0.15 to 0.65; p = 0.002). Post-partum blood transfusion occurred in 25 (20 %) of the fibrinogen group and 26 (22 %) of the placebo group (relative risk [RR], 0.95; 95 % CI: 0.58 to 1.54; p = 0.88). These researchers found no difference in any pre-defined secondary outcomes, per-protocol analyses, or adjusted analyses. No thromboembolic events were detected. The authors concluded that there is no evidence to support the use of 2 g FC as pre-emptive treatment for severe PPH in patients with normo-fibrinogenemia.

Bleeding Associated with Aortic Reconstruction and Deep Hypothermic Circulatory Arrest:

Hanna and associates (2016) noted that human FC (HFC) is approved by the FDA for use at 70 mg/kg to treat congenital afibrinogenemia. In a prospective, pilot, off-label study, these researchers examined if this dose of HFC increases fibrinogen levels in the setting of high-risk bleeding associated with aortic reconstruction and deep hypothermic circulatory arrest (DHCA). A total of 22 patients undergoing elective proximal aortic reconstruction with DHCA were administered 70 mg/kg HFC upon separation from cardio-pulmonary bypass (CPB). Fibrinogen levels were measured at baseline, just before, and 10 minutes after HFC administration, on skin closure, and the day after surgery. The primary study outcome was the difference in fibrinogen level immediately after separation from CPB, when HFC was administered, and the fibrinogen level 10 minutes following HFC administration. Additionally, post-operative thromboembolic events were assessed as a safety analysis. The mean baseline fibrinogen level was 317 ± 49 mg/dL and fell to 235 ± 39 mg/dL just before separation from CPB. After HFC administration, the fibrinogen level rose to 331 ± 41 mg/dL (p < 0.001) and averaged 372 ± 45 mg/dL the next day. No post-operative thromboembolic complications occurred. The authors concluded that administration of 70 mg/kg HFC upon separation from CPB raised fibrinogen levels by approximately 100 mg/dL without an apparent increase in thrombotic complications during proximal aortic reconstruction with DHCA. Moreover, they stated
that further prospective study in a larger cohort of patients will be needed to definitively determine the safety and evaluate the effectiveness of HFC as a hemostatic adjunct during these procedures.

Appendix

RiaSTAP is available as single-use vials containing 900 to 1,300 mg lyophilized fibrinogen concentrate powder for reconstitution. Actual fibrinogen potency for each lot is printed on vial label and carton. The dosing of RiaSTAP is as follows (Israels, 2009; CSL Behring US Package Insert, 2009):

Adult:

- Administer intravenously, not to exceed injection rate of 5 ml/min.
- Dose (mg/kg) = (Target level [mg/dL] - measured level [mg/dL]) divided by 1.7; if fibrinogen level unknown, use 70 mg/kg body weight.
- Maintain target fibrinogen level of 100 mg/dL until hemostasis is obtained.

Pediatric:

- Data limited; clinical trials included 4 children less than 16 years of age.
- Children exhibited shorter half-life (69.9 +/- 8.5 hrs) and faster clearance (0.7 +/- 0.1 mg/L) than adults (half-life = 82.3 +/- 20.1 hrs; clearance = 0.53 +/- 0.1 mg/L), but limited number of children restricts statistical interpretation of these data.

Fibryna is available as lyophilized powder in single-use bottles containing approximately 1 g fibrinogen concentrate per bottle. The dosing of Fibryna is as follows (FDA, 2017):

Adult:

- Administer intravenously, not to exceed injection rate 5 mL/min.
• Dose (mg/kg) = [Target level (mg/dL) – measured level (mg/dL)] divided by 1.8 (mg/dL per mg/kg body weight); if fibrinogen level unknown, use 70 mg/kg body weight.
• Maintain target fibrinogen level of 100 mg/dL for minor bleeding, and 150 mg/dL for major bleeding.

Pediatric:
• Data limited; an ongoing prospective phase 3 trial included 2 adolescents
• There was no difference in the pharmacokinetics of Fibryna between adults and adolescents (12-17 years of age).

### CPT Codes / HCPCS Codes / ICD-10 Codes

**Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":**

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>85384</td>
<td>Fibrinogen; activity</td>
</tr>
<tr>
<td>85385</td>
<td>antigen</td>
</tr>
<tr>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
</tr>
<tr>
<td>96375</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96376</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96379</td>
<td>Unlisted therapeutic; prophylactic, or diagnostic intravenous or intra-arterial injection or infusion</td>
</tr>
</tbody>
</table>

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7178</td>
<td>Injection, human fibrinogen concentrate, 1mg</td>
</tr>
</tbody>
</table>
ICD-10 codes covered if selection criteria are met:
D68.2 Hereditary deficiency of other clotting factors

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):
D65 Disseminated intravascular coagulation [defibrination syndrome]
D78.01 - D78.21 Hemorrhage and hematoma complicating a procedure
D78.22 E36.01 - E36.02
G97.31 - G97.32 G97.51
- G97.52 G97.61
- G97.64H59.111 - H59.129
H59.311 - H59.312
O72.0 - O72.3 Postpartum hemorrhage
O86.0, O90.2 Other complications of obstetrical surgical wounds

The above policy is based on the following references:


30. Berube C. Disorders of fibrinogen. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2014.


Amendment to
Aetna Clinical Policy Bulletin Number: 0792 Human Fibrinogen Concentrate (RiaSTAP and Fibryna)

This bullet only applies to persons without congenital fibrinogen deficiency in the Pennsylvania Medical Assistance plan.