

- POLICY:** Hematology – Fibrinogen Products
- Fibryga® (fibrinogen [human] for intravenous use – Octapharma USA)
 - RiaSTAP® (fibrinogen concentrate [human] for intravenous use – CSL Behring)

APPROVAL DATE: 10/02/2019

OVERVIEW

Fibryga and RiaSTAP, human fibrinogen concentrates, are indicated for treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.^{1,2} Fibryga prescribing information notes that it is not indicated for dysfibrinogenemia.

Disease Overview

Congenital fibrinogen deficiencies are caused by mutations in the *FGA*, *FGB*, and *FGG* genes.^{3,4} These genes are responsible for creating the polypeptide chains which form the functional fibrinogen (also known as Factor I) hexamer. Afibrinogenemia and hypofibrinogenemia are known as Type I or quantitative deficiencies due to low or absent circulating fibrinogen levels. Afibrinogenemia is very rare (estimated prevalence 1:1,000,000) and is caused by homozygous null mutations. It is often diagnosed in infancy with prolonged umbilical cord bleeding, although later age of onset is possible. Hypofibrinogenemia is caused by heterozygous null mutation and is therefore likely much more prevalent than afibrinogenemia, although the exact incidence is difficult to determine because many patients are asymptomatic.

Dysfibrinogenemia, also known as Type II or qualitative deficiency, is characterized by normal levels of fibrinogen but low functional activity.^{3,4} It is caused by missense mutations. Clinical presentation is widely variable and can range from asymptomatic to bleeding or even thromboembolism. Increased thromboembolic risk may be explained by inability of defective fibrinogen to bind thrombin, leading to elevated circulating thrombin levels. Additionally, abnormal fibrinogen may form a fibrin clot that is resistant to plasmin degradation.

Diagnosis is made by routine coagulation tests in addition to fibrinogen assays.⁵ An accurate diagnosis is crucial to distinguish between quantitative/type I and qualitative/type II disorders and guide appropriate treatment. Treatment of fibrinogen deficiency is generally on-demand for acute bleeding episodes, although effective prophylaxis has been used in high-risk patients (e.g., secondary prevention after cerebral hemorrhage, primary prevention during pregnancy to prevent miscarriage).^{6,7} Fibrinogen concentrates are preferred over fresh frozen plasma or cryoprecipitate due to the ability for more precise dosing, less volume overload, and decreased risk of viral contamination.^{3,6,7}

Dosing Information

Dosing is highly individualized. Guidance specific to congenital fibrinogen deficiency is limited. The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).⁸ The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Congenital Fibrinogen Deficiency, Including Afibrinogenemia and Hypofibrinogenemia:** Doses of Fibryga and RiaSTAP are individualized based on patient-specific characteristics (e.g., extent of bleeding, clinical condition, laboratory values).^{1,2} Treatment with fibrinogen products is repeated as needed to maintain target levels. Based on the product half-lives of approximately three days^{1,2}, it is not anticipated that doses more frequent than once daily would typically be needed. On-demand doses up to 100 mg/kg are supported.⁷ Prophylactic dosing is not well established; doses up to 100 mg/kg and intervals as frequent as once weekly have been reported.⁷

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of fibrinogen products (Fibryga, RiaSTAP). Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with fibrinogen products as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fibryga or RiaSTAP is recommended in those who meet the following criteria:

FDA-Approved Indications

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- 1. Congenital Fibrinogen Deficiency (Factor I Deficiency), Including Afibrinogenemia and Hypofibrinogenemia.** Approve for 1 year if the patient meets the following criteria (A and B):
 - A) The diagnosis is confirmed by the following laboratory testing (i and ii):**
 - i. Prolonged activated partial thromboplastin time and prothrombin time at baseline, as defined by the laboratory reference values; AND**
 - ii. Lower than normal plasma functional and antigenic fibrinogen levels at baseline, as defined by the laboratory reference values; AND**
 - B) The requested agent is prescribed by or in consultation with a hematologist.**

Dosing. Approve up to 700 mg/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Fibrinogen products have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Concomitant Use of Fibryga and RiaSTAP.** There are no data to support concomitant use of these products.

- 2. Dysfibrinogenemia.** In dysfibrinogenemia, patients have adequate levels of fibrinogen but dysfunctional clotting.^{3,4} Prescribing information for Fibryga notes that it is not indicated in dysfibrinogenemia.² RiaSTAP should also not be used in these patients due to risk for thromboembolism.⁴
- 3.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. RiaSTAP® for intravenous use [prescribing information]. Kankakee, IL: CSL Behring; October 2017.
2. Fibryga® for intravenous use [prescribing information]. Hoboken, NJ: Octapharma USA; July 2017.
3. De Moerloose P, Casini A, Neerman-Arbez M. Congenital fibrinogen disorders: an update. *Semin Thromb Hemost.* 2013;39(6):585-595. Available at: <https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0033-1349222#TB01978-1>. Accessed on June 10, 2019.
4. Factor I (Fibrinogen) Deficiency. National Hemophilia Foundation. Available at: <https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other-Factor-Deficiencies/Factor-I>. Accessed on June 10, 2019.
5. Casini A, Unda A, Palla R, et al. Diagnosis and classification of congenital fibrinogen disorders: communication from the SSC of the ISTH. *J Thromb Hemost.* 2018;16(9). Available at: <https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14216>. Accessed on June 11, 2019.
6. Congenital afibrinogenemia. National Organization for Rare Disorders. Updated 2018. Available at: <https://rarediseases.org/rare-diseases/afibrinogenemia-congenital/>. Accessed on June 10, 2019.
7. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood.* 2015;125(13):2052-2061.
8. Kreuz W, Meili E, Peter-Salonen K, et al. Efficacy and tolerability of a pasteurized human fibrinogen concentrate in patients with congenital fibrinogen deficiency. *Transfus Apher Sci.* 2005;32(3):247-253.

HISTORY

Type of Revision	Summary of Changes	Approval Date
New policy	--	10/02/2019