



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Fibrinogen Concentrate (RiaSTAP®)

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Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers fibrinogen concentrate (RiaSTAP®) as medically necessary for the treatment of acute bleeding episodes in individuals with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to fibrinogen concentrate (RiaSTAP®) therapy.

FDA Approved Indications

RiaSTAP, Fibrinogen Concentrate (Human) is indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. RiaSTAP is not indicated for dysfibrinogenemia.

FDA Recommended Dosing

RiaSTAP dosing, duration of dosing and frequency of administration should be individualized based on the extent of bleeding, laboratory values, and the clinical condition of the patient. RiaSTAP dose when baseline fibrinogen level is known - dose should be individually calculated for each patient based on the target plasma fibrinogen level based on the type of bleeding, actual measured plasma fibrinogen level and body weight.

RiaSTAP dose when baseline fibrinogen level is not known - If the patient's fibrinogen level is not known, the recommended dose is 70 mg per kg of body weight administered intravenously. Monitoring of patient's fibrinogen level is recommended during treatment with RiaSTAP. A target fibrinogen level of 100 mg/dL should be maintained until hemostasis is obtained.

Drug Availability

RiaSTAP is supplied in a single-use vial. Each carton contains one vial of RiaSTAP. The components used in the packaging for RiaSTAP are latex-free. The actual potency of fibrinogen concentrate in milligram (mg) is stated on each RiaSTAP vial label and carton.

General Background

Pharmacology

Fibrinogen is found in normal human plasma and is required for blood to clot. Fibrinogen concentrate is used to replace low or absent levels of fibrinogen in patients with congenital fibrinogen deficiency. Plasma fibrinogen activity reaches a maximum level within 1 hour of infusion. Half-life is approximately 78 hours.

Clinical Efficacy

Fibrinogen concentrate was approved using FDA's accelerated approval program. This special process allows drugs for serious or life-threatening conditions to be approved using only surrogate markers, but requires manufacturers to conduct post-approval studies to confirm the drug's clinical benefit. A pharmacokinetic study evaluated a single dose of fibrinogen concentrate 70 mg/kg using the surrogate endpoint of maximum clot firmness (MCF), measured by thromboelastometry. Maximum clot firmness measures the blood's ability to coagulate and is used to assess hemostatic efficacy of fibrinogen concentrate. Clot firmness depends on fibrinogen concentration of the plasma sample, activation of coagulation, and polymerization and crosslinking of the fibrin matrix. The 1 hour change in MCF from baseline was significant (8.9 ± 4.4 mm, $p < 0.0001$).

Older studies of fibrinogen concentrate, specifically those studies utilizing Haemocomplettan (the same CSL Behring product as RiaSTAP but under a different tradename), were submitted as part of the accelerated approval process. A physician survey was conducted to determine what treatments were given to patients with congenital fibrinogen deficiency and target fibrinogen levels. Data were collected from 34 physicians from 10 countries. Patients ranged in age from 7 days to 75 years and were generally treated with fibrinogen, cryoprecipitate, or a combination of both. Products were given as "on demand treatment" or for prophylaxis. All agents were judged by physicians to be equally effective for controlling hemostasis. Median target fibrinogen levels were 100 mg/dL, maintained for 1 – 7 days for prophylaxis and minor bleeding events. A target level of 150 mg/dL, maintained for 4 – 14 days, was generally used for major bleeding events.

In an observational, follow-up study, the efficacy of fibrinogen concentrate was evaluated in 12 patients with afibrinogenemia, hypofibrinogenemia, or dysfibrinogenemia. Clinical efficacy of fibrinogen concentrate was judged to be "very good" in 36 of 37 bleeding episodes where fibrinogen concentrate was used.

In one case report, fibrinogen concentrate was given to one patient with congenital afibrinogenemia in separate bleeding episodes. In both episodes, bleeding was resolved with fibrinogen concentrate given with red blood cells and tranexamic acid.

Adverse Drug Reactions

Fever and headache are the most common adverse reactions reported in clinical studies. Chills, fever, nausea, vomiting, and allergic reactions are the most common reactions reported in postmarketing studies. Serious adverse events reported with fibrinogen concentrate use include allergic and anaphylactic reactions and thromboembolic events.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
J1680	Injection, human fibrinogen concentrate, 100 mg

ICD-9-CM Diagnosis Codes	Description
286.3	Congenital deficiency of other clotting factors
286.6	Defibrination syndrome

References

1. Acharya SS, Dimichele DM. Rare inherited disorders of fibrinogen. *Haemophilia*. Nov 2008;14(6):1151-1158.
2. Bell SF, Rayment R, Collins PW, Collis RE. The use of fibrinogen concentrate to correct hypofibrinogenaemia rapidly during obstetric haemorrhage. *Int J Obstet Anesth*. Apr;19(2):218-223.
3. Brenni M, Worn M, Bruesch M, Spahn DR, Ganter MT. Successful rotational thromboelastometry-guided treatment of traumatic haemorrhage, hyperfibrinolysis and coagulopathy. *Acta Anaesthesiol Scand*. Jan;54(1):111-117.
4. Center for Biologic Evaluation and Research. Blood Products Advisory Committee Human Fibrinogen Concentrate (RiaSTAP) Briefing Document. Available online at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4410B1-1.pdf>. Accessed on August 09, 2010. Chevy Chase, MD.: Food and Drug Administration; 2009.
5. Center for Drug Evaluation and Research. Search Orphan Drug Designations and Approvals: Riastap. Available online at: <http://www.accessdata.fda.gov/scripts/opdlisting/oodp/index.cfm>: Food and Drug Administration; 2010.
6. CSL Behring. RiaSTAP (fibrinogen concentrate, human) injection [product information]. Kankakee, IL: CSL Behring LLC. 2010.
7. Danes AF, Cuenca LG, Bueno SR, Mendarte Barrenechea L, Ronsano JB. Efficacy and tolerability of human fibrinogen concentrate administration to patients with acquired fibrinogen deficiency and active or in high-risk severe bleeding. *Vox Sang*. Apr 2008;94(3):221-226.
8. de Moerloose P, Neerman-Arbez M. Treatment of congenital fibrinogen disorders. *Expert Opin Biol Ther*. Jul 2008;8(7):979-992.
9. Dzieczkowski J, Anderson K. Transfusion Biology and Therapy. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. New York, NY: McGraw Hill; 2008.
10. Ejby-Poulsen P, Brandt-Nielsen E. Five cases of hypofibrinogenaemic haemorrhage in pregnancy treated with fibrinogen manufactured from human plasma. *Acta Obstet Gynecol Scand*. 1958;37(4):472-481.
11. Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sorensen B. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. *Br J Anaesth*. Dec 2008;101(6):769-773.

12. Haberer JP, Obstler C, Samama CM, et al. Postoperative deep venous thrombosis in a woman with congenital afibrinogenaemia treated with fibrinogen concentrates. *Eur J Anaesthesiol.* Jun 2008;25(6):519-521.
13. Hoffman R, ed. *Hoffman: Hematology: Basic Principles and Practice.* 5th ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2009.
14. Inamoto Y, Terao T. First report of case of congenital afibrinogenemia with successful delivery. *Am J Obstet Gynecol.* Dec 1 1985;153(7):803-804.
15. Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Skrtic S, Jeppsson A. Prophylactic Fibrinogen Infusion in Cardiac Surgery Patients: Effects on Biomarkers of Coagulation, Fibrinolysis, and Platelet Function. *Clin Appl Thromb Hemost.* Jun 7.
16. Kobayashi T, Kanayama N, Tokunaga N, Asahina T, Terao T. Prenatal and peripartum management of congenital afibrinogenaemia. *Br J Haematol.* May 2000;109(2):364-366.
17. Kreuz W, Meili E, Peter-Salonen K, et al. Efficacy and tolerability of a pasteurised human fibrinogen concentrate in patients with congenital fibrinogen deficiency. *Transfus Apher Sci.* Jun 2005;32(3):247-253.
18. MacKinnon HH, Fekete JF. Congenital afibrinogenemia. Vascular changes and multiple thromboses induced by fibrinogen infusions and contraceptive medication. *Can Med Assoc J.* Apr 3 1971;104(7):597-599.
19. Majerus P, Tollefsen D. Blood Coagulation and Anticoagulant, Thrombolytic, and Antiplatelet Drugs. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 11th ed. New York, NY: McGraw-Hill; 2006.
20. Manco-Johnson MJ, Dimichele D, Castaman G, et al. Pharmacokinetics and safety of fibrinogen concentrate. *J Thromb Haemost.* Dec 2009;7(12):2064-2069.
21. Negrier C, Rothschild C, Goudemand J, et al. Pharmacokinetics and pharmacodynamics of a new highly secured fibrinogen concentrate. *J Thromb Haemost.* Sep 2008;6(9):1494-1499.
22. Parameswaran R, Dickinson JP, de Lord S, Keeling DM, Colvin BT. Spontaneous intracranial bleeding in two patients with congenital afibrinogenaemia and the role of replacement therapy. *Haemophilia.* Nov 2000;6(6):705-708.
23. Peyvandi F, Haertel S, Knaub S, Mannucci PM. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. *J Thromb Haemost.* Jul 2006;4(7):1634-1637.
24. Peyvandi F. Results of an international, multicentre pharmacokinetic trial in congenital fibrinogen deficiency. *Thromb Res.* Dec 2009;124 Suppl 2:S9-11.
25. Rahe-Meyer N, Pichlmaier M, Haverich A, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. *Br J Anaesth.* Jun 2009;102(6):785-792.
26. Schmitt H. Indications and clinical effect of fibrinogen preparations. *Vox Sang.* Apr 1969;16(4):412-417.
27. Schochl H, Forster L, Woidke R, Solomon C, Voelckel W. Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. *Anaesthesia.* Feb;65(2):199-203.
28. Solomon C, Pichlmaier U, Schoechl H, et al. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. *Br J Anaesth.* May;104(5):555-562.

29. Toledano A, Lachassinne E, Roumegoux C, et al. Treatment of congenital afibrinogenemia in a premature neonate. *Ann Pharmacother.* Jul 2008;42(7):1145-1146.
30. Tziomalos K, Vakalopoulou S, Perifanis V, Garipidou V. Treatment of congenital fibrinogen deficiency: overview and recent findings. *Vasc Health Risk Manag.* 2009;5:843-848.
31. Weinkove R, Rangarajan S. Fibrinogen concentrate for acquired hypofibrinogenemic states. *Transfus Med.* Jun 2008;18(3):151-157.
32. Yamanaka Y, Takeuchi K, Sugimoto M, Sato A, Nakago S, Maruo T. Dysfibrinogenemia during pregnancy treated successfully with fibrinogen. *Acta Obstet Gynecol Scand.* Oct 2003;82(10):972-973.

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