

**POLICY:** Hematology – Ceprothin® (protein C concentrate [human] injection for intravenous use – Baxalta/Shire)

**APPROVAL DATE:** 10/02/2019

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## OVERVIEW

Ceprothin is indicated for pediatric and adult patients with severe congenital protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans.<sup>1</sup>

## Disease Overview

Mutations in the *PROC* gene lead to deficiency of protein C, which is a natural anticoagulant.<sup>2</sup> Individuals with heterozygous *PROC* mutation present with milder disease but are at risk for development of venous thromboembolism. The milder form is present in about 1:200 to 1:500 people in the general population. Most individuals with mild protein C deficiency do not require treatment; anticoagulant therapy may be used for individuals with strong family history of venous thromboembolism. Those who have mutations in both *PROC* genes develop severe symptoms within a few hours to days after birth. In severe protein C deficiency, a complication called purpura fulminans may arise in which blood clots form throughout the body. Blood clots affect the extremities most often but can become widespread (disseminated intravascular coagulation), leading to tissue necrosis. Diagnosis is based on characteristic symptoms and detailed family history; molecular genetic testing is available at specialized laboratories but may not be necessary to perform. The prevalence of severe protein C deficiency is approximately 1:500,000 to 1:750,000 in the general population.

Xigris® (drotrecogin alfa [activated]), a recombinant form of human protein C, was previously marketed for the reduction of mortality in adults with severe sepsis; this was voluntarily withdrawn on October 25, 2011 after failure to show survival benefit vs. placebo.<sup>3</sup> Ceprothin is not labeled for use in this setting.

## Dosing Information

Dosing is highly individualized. Guidance specific to protein C 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).<sup>4</sup> 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:

- **Protein C Deficiency, Severe:** For routine prophylaxis, the maximum dose is 60 IU/kg once every 12 hours.<sup>1</sup> For acute episodes or perioperative prophylaxis, the prescribing information recommends a loading dose up to 120 IU/kg once, followed by 80 IU/kg every 6 hours for 3 doses, followed by 60 IU/kg every 6 hours thereafter.

### **POLICY STATEMENT**

Prior authorization is recommended for medical benefit coverage of Ceprotin. 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 Ceprotin as well as the monitoring required for adverse events and long-term efficacy, approval requires Ceprotin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Ceprotin is recommended in those who meet one of the following criteria:

#### **FDA-Approved Indications**

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- 1. Protein C Deficiency, Severe.** Approve for 1 year if Ceprotin is prescribed by or in consultation with a hematologist.

**Dosing.**<sup>1</sup> Approve up to 4,440 IU/kg intravenously per 28 days.

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#### **CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Ceprotin has 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.)

- Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

#### **REFERENCES**

- Ceprotin<sup>®</sup> injection for intravenous use [prescribing information]. Lexington, MA: Baxalta/Shire; December 2018.
- Protein C Deficiency. National Organization of Rare Disorders. Updated 2016. Available at: <https://rarediseases.org/rare-diseases/protein-c-deficiency/>. Accessed on June 10, 2019.
- Lilly announces withdrawal of Xigris<sup>®</sup> following recent clinical trial results [press release]. Indianapolis, IL: Eli Lilly; October 25, 2011. Available at: <https://investor.lilly.com/news-releases/news-release-details/lilly-announces-withdrawal-xigris-following-recent-clinical>. Accessed on June 10, 2019.
- MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2018). MASAC Document #253. Adopted on April 23, 2018. Available at: <https://www.hemophilia.org/node/3675>. Accessed on June 4, 2019.

**HISTORY**

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