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Ceprotin™ FDA-Approved for Treatment of Rare Clotting Disorder

by Abby E. Kusnerik, Pharm.D. Candidate

On March 30, 2007, the U.S. Food and Drug Administration (FDA) approved Protein C Concentrate [Human] (Ceprotin™; Baxter International, Inc.). It is the first biologic available for the treatment of congenital Protein C deficiency.[1] Prior to its approval by the FDA, it was considered an orphan drug. Ceprotin™ has been approved for use by the European Medicines Evaluation Agency (EMEA) since 2001.[2]

Protein C is synthesized in the liver as a vitamin K-dependent plasma protein. It circulates in the blood as a zymogen (i.e., a pro-enzyme).[3-5] Normally, plasma levels of Protein C are between 4 to 5 mcg/ml.[6] Once Protein C is activated by the thrombin-thrombomodulin complex to activated Protein C (APC), it has an anticoagulant effect. Protein C is converted locally and on demand into APC at sites of intrinsic or extrinsic damage.[3] The actions of APC include regulation of hemostasis with negative feedback on thrombin generation, indirect profibrinolytic effects, and antiinflammatory activity. In combination with Protein S, APC down-regulates the blood coagulation pathways by proteolytic and irreversible inactivation of Factors Va and VIIIa. The exact mechanism for profibrinolytic activity is controversial. It has direct protective effects on endothelial cells by down-regulating inflammatory reactions.[3,5,6]

Congenital Protein C deficiency can be of two phenotypes: heterozygous or homozygous. Heterozygous disease is present in 1 out of every 200 to 300 adults but all may not exhibit symptoms; if symptoms are present, they are usually less severe than with homozygous disease, and do not occur until adulthood. The most common clinical features are deep and superficial venous thromboses, often at unusual sites. Severe cases of heterozygous disease can present like homozygous disease.[3,6]

Homozygous disease occurs in 1 out of every 160,000 to 360,000 births and prognosis is usually poor. The disease can manifest pre-term as miscarriage or intrauterine thrombosis, or symptoms may present soon after birth. The symptoms are directly related to the degree of Protein C deficiency. Severe clinical symptoms occur when Protein C is 20 to 25% of normal. Since higher concentrations of thrombomodulin exist in the microvasculature, the vessels of the skin, eyes, kidneys, and brain are at the greatest risk for thrombosis and necrosis.[3,5]

Current treatments for severe heterozygous and homozygous Protein C deficiency include fresh frozen plasma (FFP), oral anticoagulants, heparin, and prothrombin complex

concentrate (PCC). Guidelines for the treatment of Protein C deficiency are not currently available.[3,5]

Acquired Protein C deficiency occurs secondary to other conditions such as bacterial sepsis, disseminated intravascular coagulation (DIC), and conditioning therapy for bone marrow transplant. Disorders associated with Vitamin K deficiency (e.g., liver disease, malnutrition, and the use of warfarin) may also result in acquired Protein C deficiency.[5] Although not FDA-approved for acquired Protein C deficiency, some studies have demonstrated Ceprotin™ to be effective.[7]

Ceprotin™ is a monoclonal antibody-purified Human Protein C. Frozen plasma is initially tested for viral content, purified, and processed with two, independent, virus inactivation steps (i.e., intensive detergent treatment and vapor heating).[3,8]

Ceprotin™ is FDA-approved for prevention and treatment of venous thrombosis and purpura fulminans in patients with severe congenital Protein C deficiency.[1,9] Additionally, Ceprotin™ is approved for replacement therapy for pediatric and adult patients. It can be used for acute episodes, short-term prophylaxis, and long-term prophylaxis. The following conditions must be met to use for short-term prophylaxis in severe congenital Protein C deficiency: surgery or invasive therapy is imminent; initiation of coumarin therapy; coumarin therapy itself is insufficient; or coumarin therapy is not feasible. Ceprotin™ is not currently FDA-approved for use in patients with acquired Protein C deficiency.[9]

There are a very limited number of published studies evaluating Ceprotin™. However, the prescribing information for Ceprotin™ references data that are expected to be published in the summer of 2007.[10] Efficacy and safety data were collected retrospectively due to the rarity of severe congenital Protein C deficiency. Patients were administered Ceprotin™ for not only acute episodes, but also short- and long-term prophylaxis. Treatment outcomes included improved or healed purpura fulminans and coumarin-induced skin necrosis. The patients who received Ceprotin™ for short- or long-term prophylaxis experienced no significant thrombotic events or complications.[9] Serious and common adverse reactions observed in clinical trials were rash, itching, and lightheadedness. However, hemothorax and hypotension have been reported in post-marketing surveillance. To date, there have been no reports of the development of inhibiting antibodies to Ceprotin™. Concurrent use with anticoagulants may increase the risk of severe bleeding episodes. Although there are no reports to date, Ceprotin™ still carries a risk of transmitting infectious organisms.[9]

In one published study, Moritz and associates retrospectively assessed efficacy and safety of Ceprotin™ in the treatment of severe congential Protein C deficiency. Twenty-two patients were evaluated for regression of any skin lesions present at entry and dissolution of thrombotic occlusions after administration of Ceprotin™. Of the 22 patients studied, 14 patients presented with either purpura fulminans or coumarin-induced skin necrosis with some patients having more than one acute episode (See Table 1).[11] Safety analysis included an additional 57 subjects that were administered Ceprotin™ for other types of Protein C deficiency. The most common side effects in this trial were fever, increased C-reactive protein (CRP), itching, and rash. Viral safety was evaluated and no viral transmission or seroconversion was observed. Also, no inhibitory antibody formation was observed in 15 patients evaluated. The authors concluded that Ceprotin™ was safe and effective in the treatment of patients with severe congenital Protein C deficiency.[11]

Pharmacokinetic data reported in the prescribing information evaluated Ceprotin™ in 21 asymptomatic and symptomatic

Table 1. Summary of Treatment Outcome Results[11]

		Improvement				
Clinical Presentation (n=patients)	**Total Episodes**	**Marked/ Healed**	**Moderate**	**Slight**	**None**	**Not Evaluated**
Purpura fulminans (n=10)*	16	16	0	0	0	0
Coumarin-induced skin necrosis (n=4)*	6	6	0	0	0	0
Cerebral thrombosis (n=1)	1	0	0	0	1	0
Retinal/vitreous hemorrhage/thrombosis (n=1)	8	1	0	1	5	1
Deep vein thrombosis (n=1)	1	1	0	0	0	0
Hematoma (n=2)	3	1	0	0	0	2
Catheter thrombosis (n=1)	1	0	0	0	0	1
Osteonecrosis (n=1)	1	0	1	0	0	0
TOTAL	37	25	1	1	6	4

*FDA-approved indications
Note: The 22 patients evaluated had 37 clinical presentations

subjects with Protein C deficiency. The median half-life was 9.9 hours (range of 4.9 to 14.7 hours) based on a non-compartmental method.[9] Data available from Moritz and associates demonstrated half-lives that varied between 1.7 and 18.7 hours using a non-compartmental model. The researchers noted that variance could be caused by age, race, gender, weight, plasma volume, and phase of therapy (acute versus maintenance). For these reasons, patient specific half-lives should be determined.[11]

Each international unit of Ceprotin™ corresponds to the activity of Protein C in 1 ml of normal plasma. Therefore, patient specific laboratory assessment of a Protein C deficit is necessary to determine the dose of Ceprotin™. For children and adults with severe Protein C deficiency, the initial dose for acute episodes and short-term prophylaxis is 100 to 120 international units/kg (for determination of recovery and half-life).[9] For the subsequent three doses, the recommendation is 60 to 80 international units/kg every 6 hours that should be adjusted to maintain peak Protein C activity of 100%. The recommended maintenance dose is 45 to 60 international units/kg every 6 or 12 hours that should be adjusted to maintain recommended maintenance trough Protein C activity levels >25%.[9] For long-term prophylaxis, the recommended maintenance dose is 45 to 60 international units/kg every 12 hours and adjusted to maintain trough Protein C activity levels >25% (Note: There is NO initial dose followed by three subsequent doses.).[9] Ceprotin™ is continued until desired anticoagulation is achieved. Ceprotin™ should be administered by intravenous infusion at a rate no greater than 2 ml/min. In children with a body weight <10 kg, the infusion rate should not exceed 0.2 ml/min.[3]

Ceprotin™ is available in single-dose vials that contain 500- or 1000-international units of human Protein C and are reconstituted with 5- or 10-mL of sterile water for injection, respectively.[9] This provides a single dose of human Protein C at a concentration of 100 international units/mL. It is important to note that Ceprotin™ contains trace amounts of heparin.[8,9] Additionally, at maximum daily doses, it contains > 200 mg of sodium; therefore, Ceprotin™ should be used with caution in sodium restricted patients.[9] Unreconstituted, the product is stable for 3 years when refrigerated.[9] After reconstitution, Ceprotin™ should be used immediately since it is only chemically and physically stable for 6 hours at room temperature.[8,9] Baxter has not yet released pricing information for Ceprotin™. Baxter anticipates Ceprotin™ to be commercially available in the summer of 2007. Ceprotin™ has not yet been evaluated for addition to the Formulary at the Cleveland Clinic.

Ceprotin™ is a novel treatment for complications of severe congenital Protein C deficiency. Although data are limited because of the rare nature of this disease, Ceprotin™ use appears to be effective and well tolerated. Until pricing data are available, cost comparisons to other treatments can not be determined. Finally, additional research is necessary to determine efficacy and safety in acquired Protein C deficiency.

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Proper Disposal of Expired or Unwanted Medications

Expired or unwanted medications should be disposed of properly to keep them away from children and pets as well as to prevent drug diversion. There are currently several options for disposing of expired or unwanted medications. New federal prescription drug disposal guidelines recommend the following:

- The patient should take unused, unneeded, or expired prescription drugs out of their original containers and throw them in the trash.
- Patients can mix the prescription drugs with an undesirable substance such as used coffee grounds or kitty litter. This combination should be placed in non-descript containers and thrown away.
- Prescription medications may be flushed down the toilet *only* if the patient information or prescribing information recommends disposing in this manner.
- Although limited in the United States, some communities have pharmaceutical take-back programs that allow the general public to bring unused drugs to a central location for proper disposal.

Within these new guidelines, which can be found at http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf, there are specific drugs that should be flushed down the toilet instead of being disposed of in the trash. The following table lists select medications and their special disposal instructions:

Drug	Special Dosage Instructions
Actiq® (oral transmucosal fentanyl citrate)	• Do not flush entire unused units, handles, or blister packages down the toilet. • If there is any medication remaining after the dose, place the handle under hot running water until the medication is gone and discard the handle where it is out of reach of children and pets. • For unopened/unused Actiq® units: 1. Remove one Actiq® unit from its blister package and hold the Actiq® by its handle over the toilet bowl. 2. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet. 3. Discard the handle in a place out of reach of children and pets. 4. Repeat steps 2 and 3 for each Actiq® unit. 5. Flush the toilet twice after 5 Actiq® units have been cut. Do not flush more than 5 Actiq® units at one time.
AndroGel® (testosterone gel)	• Unused gel should be disposed of by thoroughly rinsing down the sink or placing in the trash in a manner to avoid accidental exposure or ingestion by household members or pets.
Duragesic® (fentanyl)	• Fold the sticky sides of the patch together and flush down the toilet.
Fentora™ (fentanyl buccal tablets)	• Call Cephalon at 1-800-896-5855 or flush unneeded tablets down the toilet. • Do not flush blister packages or cartons down the toilet.
Oxycontin® (oxycodone)	• Flush tablets down the toilet.
Reyataz® (atazanavir)	• Flush capsules down the toilet.
Videx®/Videx® EC (didanosine)	• Flush tablets or capsules down the toilet or pour oral liquid down the sink.

Adapted from: Tom WC, Pharmacist's Letter 2007; 23 (230401).

When disposing of any medication, patients should follow the specific instructions from the manufacturer. Many Schedule II medications (e.g., Percocet®, Oxycontin®) have special instructions to flush the drug down the toilet or pour its liquid down the sink. Additionally, unless otherwise specified, most patches are to be folded in half so that the sticky sides are together and discarded in the trash so as to prevent accidental ingestion by children or pets. Finally, please see the Department of Pharmacy policy #05-070 for further information on disposing of controlled substances.

Formulary Update

The Cleveland Clinic Pharmacy and Therapeutics Committee met on Tuesday, April 3, 2007, and the following decisions were made:

Formulary Additions:

1. **Apomorphine (Apokyn®)**: Apomorphine is a morphine derivative with potent dopaminergic activity, but is devoid of opioid activity. Subcutaneous apomorphine is FDA-approved for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease. Due to the risk of profound hypotension and loss of consciousness, concomitant administration with 5HT3 receptor antagonists (e.g., ondansetron [Zofran®] or palonosetron [Aloxi®]) is contraindicated. In addition, it should be administered cautiously in patients at risk for QT/QTc prolongation or taking other medications that can prolong the QT/QTc interval. Because of its potential to cause nausea and vomiting, trimethobenzamide (Tigan®) should be administered orally three times daily 3 days prior to initiating therapy and continued for 2 months. The recommended starting dose of apomorphine is 2 mg (0.2 mL) administered subcutaneously. All patients should be administered a 2 mg (0.2 mL) test dose in a setting where blood pressure can be monitored closely. Supine and standing blood pressures should be checked at baseline and 20-, 40-, and 60-minutes following the dose. Patients developing clinically significant orthostatic hypotension should not be continued on apomorphine therapy. If the test dose is tolerated, the patient can be continued on 2 mg (0.2 mL) administered subcutaneously on an as needed basis. If needed, the dose can be increased in 1 mg (0.1 mL) increments to a maximum dose of 6 mg (0.6 mL). Apomorphine is available as 10 mg/mL - 3 mL cartridges with a pen injector device. Its use is ***restricted*** to the Movement Disorder Clinic.

2. **Glutamine Powder for Oral Solution (Sympt-X®)**: Glutamine is an amino acid that regulates gastrointestinal cell growth, function, and regeneration. Glutamine is available as 10-gram powder packets for oral solution. Each packet should be mixed with 8 oz. of liquid or with semisolid food. Doses of glutamine 2 gm/m^2 should be swished and swallowed twice daily. Therapy should begin on day one of chemotherapy and continued for 14 days post-chemotherapy and up to 28 days post-bone marrow transplant. Oral glutamine use is ***restricted*** to pediatric patients for the prevention and treatment of mucositis/stomatitis caused by chemotherapy or radiation.

3. **iLEX Skin Protectant Paste**: iLEX is a topical skin barrier used in the prevention and treatment of skin irritations and excoriations resulting from procedures such as ileostomy, colostomy, fistula, G-tube placements, excoriation resulting from incontinence in the perianal region, fecal fistula, and surgical and traumatic wounds with drainage causing dermal irritation and skin breakdown. It is available in 60 gm tubes.

4. **Paliperidone (Invega™)**: Paliperidone extended-release tablets are FDA-approved for the treatment of schizophrenia. Paliperidone is the major active metabolite of risperidone and antagonizes both dopamine Type 2 and serotonin Type 2A receptors. Due to its CNS effects, paliperidone should be used cautiously in combination with other centrally-acting medications. Paliperidone is available in 3-, 6-, and 9-mg extended-release tablets. The recommended dose is 6 mg once daily administered in the morning. The maximum recommended dose is 12 mg daily. Patients with renal impairment require dosage adjustments. **Initiation of paliperidone therapy is restricted** to the Department of Psychiatry. Patients may be continued on paliperidone if they were receiving it as an outpatient.

Drug Restriction Changes:

1. **Factor VIIa recombinant (NovoSeven®)**: The restriction criteria have been expanded to include Staff Physicians from Cardiothoracic Surgery and Cardiothoracic Anesthesiology. The full restriction is as follows:
Restricted to the Departments of Hematology/Medical Oncology, Vascular Medicine, Neurology, Neurosurgery, Medical Staff from the Liver Transplant Team, and Cardiothoracic Surgery/Anesthesiology.

2. **Quadrivalent Human Papillomavirus Vaccine (Gardasil®)**: The restriction has been changed to permit use in pediatric inpatients. The full restriction is as follows:
Restricted to outpatient use in adults. May be used in both pediatric inpatients and outpatients.

Drug Withdrawals:

1. On March 29, 2007, all generic pergolide tablets and brand Permax® tablets used to manage symptoms associated with Parkinson's disease were removed from the market because of the risk of serious damage to heart valves. Two recent studies confirmed that patients receiving pergolide had increased chance of regurgitation of the mitral, tricuspid, and aortic valves. This adverse effect was not seen with other dopamine agonists. Patients currently receiving pergolide should be tapered off therapy and switched to other available therapeutic alternatives.

Drug Withdrawals (continued):

2. Due to an increased risk of cardiovascular side effects including angina, heart attacks, and strokes associated with the use of tegaserod (Zelnorm®), Novartis voluntarily suspended marketing the agent on March 30, 2007.

For more detailed information on the above medications, please consult the Formulary on the Intranet (under Clinical Resources/ Drug Information), specifically under Lexi-Drugs Online. Furthermore, please call the Drug Information Center at 4-6456, option #1 if you have any questions.

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Department of Pharmacy/Hb-03
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