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Review Article

Caplacizumab: First FDA-approved therapy in 2019 for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura

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ABSTRACT

The U.S. Food and Drug Administration in February 2019 approved Cablivi (Caplacizumab) injection, the first therapy specifically indicated, in combination with plasma exchange and immunosuppressive therapy, for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), a rare and life-threatening disorder that causes blood clotting. Patients with aTTP endure hours of treatment with daily plasma exchange, which requires being attached to a machine that takes blood out of the body and mixes it with donated plasma and then returns it to the body. Even after days or weeks of this treatment, as well as taking drugs that suppress the immune system, many patients will have a recurrence of aTTP.

This is the first targeted treatment that inhibits the formation of blood clots. It provides a new treatment option for patients that may reduce recurrences as per the USFDA officials.

INTRODUCTION

Patients with aTTP develop extensive blood clots in the small blood vessels throughout the body. These clots can cut off oxygen and blood supply to the major organs and cause strokes and heart attacks that may lead to brain damage or death. Patients can develop aTTP because of conditions such as cancer, HIV, pregnancy, lupus or infections, or after having surgery, bone marrow transplantation or chemotherapy.[1-4]

The efficacy of Caplacizumab was studied in a clinical trial of 145 patients who were randomized to receive either Caplacizumab or a placebo. Patients in both groups received the current standard of care of plasma exchange and immunosuppressive therapy. The results of the trial demonstrated that platelet counts improved faster among patients treated with Caplacizumab, compared to placebo. Treatment with Caplacizumab also resulted in a lower total number of patients with either aTTP-related death and recurrence of aTTP during the treatment period, or at least one treatment-emergent major thrombotic event (where blood clots form inside a blood vessel and may then break free to travel throughout the body). The proportion of patients with a recurrence of aTTP in the overall study period (the drug treatment period plus a 28-day follow-up period after discontinuation of drug treatment) was lower in the Caplacizumab group (13 percent) compared to the placebo group (38 percent), a finding that was statistically significant.[1]

Common side effects of Caplacizumab reported by patients in clinical trials were bleeding of the nose or gums and headache. The prescribing information for Caplacizumab includes a warning to advise health care providers and patients about the risk of severe bleeding. Health care providers are advised to monitor patients closely for bleeding when administering Caplacizumab to patients who currently take anticoagulants.[1]

This article consists of brief Pharmacotherapeutics review of Caplacizumab.

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Cablivi (Caplacizumab)

The FDA granted the approval of Cablivi to Ablynx.

Caplacizumab is produced in *Escherichia coli* by recombinant DNA technology and has an approximate molecular weight of 28 kDa.[1]

Dosage form:

Injection for intravenous or subcutaneous use.[1]

Indication and Uses:

It is a von Willebrand factor (vWF)-directed antibody fragment indicated for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.[1]

Dosage and administration:

It should be administered upon the initiation of plasma exchange therapy. The recommended dose of Caplacizumab is as follows:

First day of treatment: 11 mg bolus intravenous injection at least 15 minutes prior to plasma exchange followed by an 11 mg subcutaneous injection after completion of plasma exchange on day one.

Subsequent treatment during daily plasma exchange: 11 mg subcutaneous injection once daily following plasma exchange.

Treatment after the plasma exchange period: 11 mg subcutaneous injection once daily for 30 days beyond the last plasma exchange; If after the initial treatment course, sign(s) of a persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days. Discontinue Caplacizumab if the patient experiences more than 2 recurrences of aTTP, while on Caplacizumab.[1,5,6]

[ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, also known as von Willebrand factor-cleaving protease (VWFCP)—is a zinc-containing metalloprotease enzyme that cleaves von Willebrand factor (vWf), a large protein involved in blood clotting.]

Missed Dose:

If a dose of Caplacizumab is missed during the plasma exchange period, it should be given as soon as possible. If a dose of Caplacizumab is missed after the plasma exchange period, it can be administered within 12 hours of the scheduled time of administration. Beyond 12 hours, the missed dose should be skipped and the next daily dose administered according to the usual dosing schedule.[1]

Dosage forms and strengths:

For injection: 11 mg as a white lyophilized powder in a single-dose vial[1]

Contraindications:

It is contraindicated in patients with a previous severe hypersensitivity reaction to Caplacizumab or to any of the excipients. Hypersensitivity reactions have included urticaria.

Bleeding:

It increases the risk of bleeding. In clinical studies, severe bleeding adverse reactions of epistaxis, gingival bleeding, upper gastrointestinal hemorrhage, and metrorrhagia were each reported in 1% of subjects. Overall, bleeding events occurred in approximately 58% of patients on Caplacizumab versus 43% of patients on placebo. The risk of bleeding is increased in patients with underlying coagulopathies (e.g. hemophilia, other coagulation factor deficiencies). It is also increased with concomitant use of Caplacizumab with drugs affecting hemostasis and coagulation.

Interrupt use of Caplacizumab if clinically significant bleeding occurs. If needed, von Willebrand factor concentrate may be administered to rapidly correct hemostasis. If Caplacizumab is restarted, monitor closely for signs of bleeding.

Withhold Caplacizumab for 7 days prior to elective surgery, dental procedures or other invasive interventions. If emergency surgery is needed, the use of von Willebrand factor concentrate may be considered to correct hemostasis. After the risk of surgical bleeding has resolved, and Caplacizumab is resumed, monitor closely for signs of bleeding.[1]

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Drug interactions:

Concomitant use of Caplacizumab with any anticoagulant may increase the risk of bleeding.[1]

Use in specific populations:

Pregnancy:

It may increase the risk of bleeding in pregnant women, fetus, and neonate. Monitor neonates for bleeding.

Lactation:

There is no information regarding the presence of Caplacizumab in human milk, the effects on the breastfed child or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Caplacizumab and any potential adverse effects on the breastfed child from Caplacizumab, or from the underlying maternal condition.

Pediatric Use:

The safety and effectiveness of Caplacizumab in pediatric patients have not been established.

Geriatric Use:

Clinical studies of Caplacizumab did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Overdosage:

In case of overdose, based on the pharmacological action of Caplacizumab, there is the potential for an increased risk of bleeding. Close monitoring for signs and symptoms of bleeding is recommended. If needed, the use of von Willebrand factor concentrate could be considered to correct hemostasis.[1]

Mechanism of Action:

Caplacizumab targets the A1-domain of vWF, and inhibits the interaction between vWF and platelets, thereby reducing both vWF-mediated platelet adhesion and platelet consumption.[1]

Pharmacokinetics:

Absorption:

The bioavailability of subcutaneous Caplacizumab is approximately 90%.

The maximum concentration was observed 6 to 7 hours after subcutaneous dosing of 10 mg Caplacizumab once daily in healthy subjects.

Distribution:

Caplacizumab central volume of distribution is 6.33 L in patients with aTTP.

Elimination:

The half-life of Caplacizumab is concentration and target-level dependent.

Metabolism:

The available data suggest target-bound Caplacizumab is metabolized within the liver. Because Caplacizumab is a monoclonal antibody fragment, it is expected to be catabolized by various proteolytic enzymes.

Excretion:

The available nonclinical data suggest unbound Caplacizumab is cleared renally.

Antidrug Antibodies:

No clinically significant differences in the pharmacokinetics of Caplacizumab were observed in patients with pre-existing or treatment-emergent anti-drug antibodies.

Specific Populations:

No clinically significant differences in the pharmacokinetics of Caplacizumab were observed based on age (18 to 79 years), sex (66% females), race (White (83%) and Black (17%)), blood group (O (41%) and other groups (59%)), or renal impairment (mild [CrCl: 60 to 90 mL/min], moderate [CrCl: 30 to 60 mL/min] or severe [CrCl: 15 to 30 mL/min]). The effect of hepatic impairment on the pharmacokinetics of Caplacizumab is unknown.[1,7]

Storage:

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Unopened vials may be stored in the original carton at room temperature up to 30°C (86°F) for a single period of up to 2 months. Do not return Caplacizumab to the refrigerator after it has been stored at room temperature.[1]

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Patient counseling information:

Advise patients that bruising and bleeding may occur more easily, that nose bleeds and bleeding of gums may occur and that it may take them longer than usual to stop bleeding. Advise patients to contact their healthcare provider immediately if excessive bleeding or bruising occurs.

Advise patients to inform their healthcare provider before scheduling any elective surgery, dental procedure or other invasive interventions.[1]

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