MP 5.01.32  Eculizumab (Soliris)

Medical Policy

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Description

Eculizumab (Soliris) is a humanized monoclonal IgG antibody that selectively binds to complement protein C5 on the surface of human red blood cells. The high affinity bond protects against complement-mediated red blood cell hemolysis. Eculizumab antibody is used to treat patients with Paroxysmal Nocturnal Hemoglobinuria (PNH), which is an illness attributed to intravascular complement-mediated hemolysis. Treatment with eculizumab reduces hemolysis as a result of a high affinity bond with the red blood cell complement protein C5. The bond prevents enzymatic cleavage of C5 into C5a and C5b. This in turn prevents the generation of C5b-9. It is C5b-9 which causes intravascular red blood cell hemolysis.

With sufficient hemolysis, a patient may develop hemolytic anemia, hypercoagulation, thrombosis and bone marrow failure. Some patients are treated with repeated transfusions and/or anti-coagulation. Progression to myelodysplasia, aplastic anemia and acute leukemia can also occur.

Background

PNH is a form of hemolytic anemia secondary to a somatic mutation. A mutation of the X-linked phosphatidylinositol glycan class A (PIGA) gene, results in the absence of a protective protein. Without the glycosylphosphatidylinositol-linked protein, increased complement-mediated hemolysis occurs. The proportion of affected cells varies among patients.

The gold standard test for the diagnosis of PNH is flow cytometry. A peripheral blood sample is used. In addition to detecting small clones, the flow cytometry also has the ability to establish clonal size. Important in the PNH patient population, the test results are not affected by blood transfusions.

In the past, treatment of PNH has been in response to clinical manifestations of the hemolysis. The supportive options have included folic acid supplementation, hydration, anti-coagulation and red blood cell transfusions.

The recommended dose for eculizumab (Soliris) treatment is as follows:

- 600 mg every seven days for the first four weeks, followed by
- 900 mg for the fifth dose 7 days later, then
- 900 mg every 14 days thereafter.
Eculizumab (Soliris) received accelerated U.S. Food and Drug Administration (FDA) approval in March 2007. It is indicated for the treatment of patients with PNH to reduce hemolysis. (Dmytrijuk et al, 2008) Two clinical studies are cited in the prescribing information. Both studies used the recommended treatment schedule. The first study enrolled PNH patients with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and at least 100,000 platelets/microliter. Hemoglobin set-points of equal to or less than 9 g/dl and 7 g/dl for patients with and without symptoms respectively were used. Patient who did not need a transfusion during the three month “set-point” observation period were excluded. A total of 87 patients were randomized to eculizumab (43) or placebo (44) and treated for 26 weeks. In the twelve months prior to randomization, packed RBC units transfused per patient (median (Q1,Q3)) by group were eculizumab 18 (12, 24) and placebo 17 (14, 25). Concomitant anticoagulants used by members of each group were eculizumab 24 (56%) and placebo 20 (46%). Patients with a history of thrombosis by group were eculizumab 9 (16 events) and placebo 8 (11 events). By week 26, the patients treated with eculizumab received fewer transfused packed RBC units per patient. Mean number of transfused units was 3 for the treated group and 7 for the placebo group, whereas median units (range) transfused was 0 (0-16) compared to 10 (2-21) respectively. Transfusion avoidance by group was eculizumab 51% and placebo 0%. One patient in the placebo group had a thrombotic event. (Hillmen et al, 2006; Alexion Pharma, 2007) The second study enrolled PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter. A total of 97 patients were treated with eculizumab in an open-label, non-placebo controlled study for 52 weeks. Concomitant anticoagulants were used by 63% of the patients. There was a reduction in need for RBC transfusion. Two patients, of which one event was fatal, had thrombotic events. (Alexion Pharma, 2007) Hypercoagulation and thrombotic events are a known consequence for some patients with PNH. The risk of thrombosis seems to correlate to the PNH clonal size. The effect of eculizumab on the incidence of thrombotic events has not been answered by a prospective randomized study. Retrospective and observational data suggest a benefit with eculizumab treatment. Thromboembolism rate before treatment was approximately seven times greater per 100 patient years when compared to the thromboembolism rate while receiving treatment. (Hillmen et al, 2007) In another retrospective study, warfarin provided complete protection against thromboembolic events in PNH patients. (Hall, et al, 2003) The prescribing information warns that patients who discontinue treatment with eculizumab (Soliris) may be at increased risk for serous hemolysis. Patients who discontinue eculizumab (Soliris) treatment should be monitored for at least 8 weeks to detect serous hemolysis and other reactions. In contrast, Parker (2009) and the Canadian Agency for Technology Assessment in Health note the theoretical possibility of a rebound effect, cases have not been identified. (Parker, 2009; CADTH, 2010) Eculizumab is contraindicated in persons with unresolved serious Neisseria meningitidis infections, and in persons who are not currently vaccinated against Neisseria. Safely and effectiveness have not been established in patients below the age of 18. A minority of persons with PNH have a disease severity similar to that required to qualify for the pivotal eculizumab studies. In the eculizumab manufacturer’s submission to the National Health Service, it was anticipated that the drug would be used for the 15% of PHN patients that are most severely affected by the illness. (Alexion Pharma, 2008)

Policy
Eculizumab (Soliris) therapy may be considered **medically necessary** for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and thrombosis when all of the following criteria are met:

- Documented diagnosis of PNH (flow cytometric confirmation of at least 10% PNH type III red cells and platelet counts of at least 30,000/microliter prior to initiation of eculizumab treatment; and

- Member is either transfusion dependent (i.e., has at least 2 transfusions in the 12 months prior, one of which in the 3 prior months prior to initiation of eculizumab due to documented hemoglobin less than 7 g/dl in persons without anemic symptoms or less than 9 g/dl in persons with symptoms from anemia), or member has a documented history of major adverse vascular event from thromboembolism while on therapeutic anticoagulation therapy; and

- Member has been vaccinated against meningococcal infection (at least 2 weeks prior to eculizumab treatment, if not previously vaccinated).

Recurrent use of eculizumab (Soliris) therapy is **not medically necessary** for the treatment of PNH to reduce hemolysis when transfusion requirements are not significantly reduced. Recurrent use of eculizumab (Soliris) therapy is **not medically necessary** for the treatment of PNH to reduce thrombosis when thromboembolism events persist despite treatment. Reauthorization of eculizumab (Soliris) therapy may be considered **medically necessary** for the treatment of serious hemolysis after eculizumab (Soliris) discontinuation.

Eculizumab (Solaris) therapy is considered **investigational** when the criteria are not met and for all other indications not specifically mentioned above, including, but not limited to

- antibody-mediated rejection
- Guillain-Barré syndrome
- hemolytic uremic syndrome
- systemic lupus Erythematosus

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