Soliris® – Clinical Rationale Request for Consideration
Alexion Pharmaceuticals

On behalf of Alexion Pharmaceuticals, thank you for the opportunity to provide a response to the Drug Class Review with New Drug Evaluation: Biologics for Autoimmune Disorders-Neuromyelitis Optica Spectrum Disorder. The information summarized below is intended to help you in making a fully informed decision to benefit patient care in Oregon. To this aim, we have highlighted evidence demonstrating 1) the devastating consequences of NMOSD relapse and the importance of relapse prevention; 2) the role of complement in the pathophysiology of anti-AQP4 antibody positive NMOSD; and 3) recent eculizumab clinical data demonstrating its long-term safety and efficacy in the treatment of anti-AQP4 antibody positive NMOSD as well as its efficacy across a broad range of patient populations. Beginning with FY2021 IPPS, Centers for Medicare & Medicaid Services (CMS) has granted eculizumab (Soliris) a New Technology Add-on Payment (NTAP) designation for the NMOSD indication.

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, severe, disabling, autoimmune CNS disease which is mediated by complement activation and is typically characterized by inflammation of the optic nerve or spinal cord.[1–3] NMOSD is a relapse-driven disease, whereby unpredictable transverse myelitis and/or optic neuritis attacks lead to the accumulation of neurological disability.[1] Approximately 90% of NMOSD cases are relapsing,[4] with up to 50% of patients experiencing at least 1 relapse per year.[2,5] Within 5 years of the first attack, 50% of NMOSD patients are wheelchair-dependent and functionally blind, and one-third will have died.[6] Because of the significant impact of relapse on mortality, patients' quality of life, and healthcare resource utilization, prevention of relapse is the principal treatment goal in NMOSD.[7]

Activation of the complement pathway is an important driver of neuronal damage in anti-AQP4 antibody positive NMOSD.[6] Binding of anti-AQP4-IgG to the AQP4 water channel protein, which is expressed in the optic nerve and spinal cord, activates the complement cascade.[8–10] In particular, complement activation leads to the cleavage of the C5 complement protein and the subsequent formation of the multi-unit C5b-9 aggregate (the membrane attack complex, or MAC), which forms a transmembrane pore on cell membranes.[11,12] In addition to C5b, cleavage of C5 leads to the production of C5a, a potent chemotactic factor and pro-inflammatory molecule.[13] Ultimately, MAC-mediated and inflammation-driven tissue injury leads to astrocyte and oligodendrocyte damage, demyelination, and neuronal death.[14]

Analysis of patient samples shows evidence of complement deposition in NMOSD lesions,[15] accompanied by complement-mediated astrocyte loss.[16] Relapsing NMOSD patients have significantly higher C5b-9 levels in the CSF compared to patients with MS or other neurological disorders, and there is a positive correlation between levels of C5b-9 and Expanded Disability Status Scale (EDSS) score.[17] Additionally, high levels of pro-inflammatory C5a protein are present in the cerebrospinal fluid of patients with NMOSD during acute exacerbations and are correlated with the number of enhanced lesions and with the worsening of EDSS score.[17,18]

Eculizumab (Soliris®) is a humanized monoclonal antibody and the first approved medication for the treatment of adult patients with NMOSD who are anti-AQP4 antibody positive.[19] Eculizumab binds to terminal complement protein C5, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9 and the release of C5a. Eculizumab carries a boxed warning for risk of meningococcal infection, and patients must receive meningococcal vaccination according to country-level guidance prior to treatment initiation. Please see the full prescribing information for the complete boxed warning.

In the Phase III PREVENT trial, 143 adult patients with anti-AQP4-Ab+ NMOSD were randomized 2:1 to receive eculizumab (n=96) or placebo (n=47).[20] A significant effect on the time to first adjudicated on-trial relapse was observed for eculizumab compared to placebo (P<0.0001), confirming that the primary endpoint of the trial was met.[21] In the eculizumab arm, adjudicated relapses occurred in 3 of 96 patients (3%) compared to 20 of 47 patients (43%) in the placebo arm, corresponding to a 94% reduction in the risk of relapse. The reduction in relapse risk with eculizumab translated into reduced rates of hospitalization and acute relapse treatment.[22] The rate of AEs was 745 events per 100 patient-years (PY) in the eculizumab arm and 1,127 events per 100 PY in the placebo arm.[20] The rate of SAEs was 27 events per 100 PY in the eculizumab arm and 55 events per

100 PY in the placebo arm. No reports of SAEs leading to treatment discontinuation were observed in the eculizumab-treated arm, and no cases of meningococcal infection were reported.

A post-hoc analysis of PREVENT data evaluated the efficacy of eculizumab across several clinically relevant subgroups.[23] The significant reduction in relapse risk observed for eculizumab versus placebo was consistently maintained across subgroups based on the following: 1) concomitant immunosuppressive therapy (IST) and previous rituximab use; 2) age, sex, region, race; 3) time since clinical onset of NMOSD; 4) historical annualized relapse rate; 5) baseline EDSS score; and 6) history of another autoimmune disorder. The serious infection rate was lower with eculizumab than placebo regardless of rituximab use in the previous year, concomitant IST use, or history of another autoimmune disorder.

An interim analysis of the ongoing PREVENT open-label extension study (OLE) (interim data cut, July 31, 2019) demonstrated the sustained ability of long-term eculizumab treatment to reduce relapse risk in patients with anti-AQP4-Ab+ NMOSD.[24] Across PREVENT and the OLE, 137 patients received eculizumab and were monitored for a median of 133.3 weeks (range 5.1–276.9 weeks). At 192 weeks (3.7 years), 94.4% of patients remained adjudicated relapse-free. The adjudicated annualized relapse rate was 0.025 in all eculizumab-treated patients versus 0.350 in the PREVENT placebo group. During the OLE, 37% of patients stopped or decreased background immunosuppressive therapy use. Serious infection rates were 10.2 per 100 PY in eculizumab-treated patients versus 15.1 per 100 PY in the PREVENT placebo group. No patient developed meningococcal infection.

Eculizumab use has produced extensive, long-term legacy safety data from other therapeutic indications in paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). In a 10-year pharmacovigilance safety analysis including postmarketing safety data collected from March 2007 through October 2016, the cumulative exposure of eculizumab was 21,016 PY in patients with PNH and 7,502 PY for patients with aHUS.[25] Seventy-six cases of meningococcal infection were reported at a rate of 0.25 per 100 PY (0.24 per 100 PY for PNH, and 0.29 per 100 PY for aHUS). The rate of meningococcal infection decreased over time (from 0.57 per 100 PY in 2007 to 0.16 per 100 PY in 2016). Additionally, in this pharmacovigilance study, eculizumab exposure was reported in a total of 434 pregnant women with PNH or aHUS.[25] Seventy percent of pregnancies with reported outcomes resulted in live births, and the rates of pregnancy loss and fetal malformation were similar to those of the general population.

Taken together, these results demonstrate the significant efficacy of eculizumab for the treatment of anti-AQP4-Ab+ NMOSD and the extensive long-term clinical safety data across multiple disorders. The significant reduction in risk of relapse with eculizumab observed in the PREVENT trial was sustained for nearly 4 years.[24] Eculizumab selectively targets terminal complement protein C5, which plays a critical role in the pathogenesis of anti-AQP4-Ab+ NMOSD, while preserving important functions of the immune system. There was a low incidence of adverse events, severe adverse events, and infections with eculizumab in NMOSD clinical studies, and its safety profile is consistent with long-term safety data in other indications.[20,24]

Thank you for your consideration and please feel free to contact us directly if you require any additional information.

Sincerely,

Yuriy Edwards, MD, PhD
Medical Director, Neurology
U.S. Medical Affairs
yuriy.edwards@alexion.com

Katie Wray, PharmD
Post-Doctoral Fellow
U.S. Medical Affairs
katie.wray-consultant@alexion.com

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Medical Director, Neurology
U.S. Medical Affairs
yuriy.edwards@alexion.com

Katie Wray, PharmD
Post-Doctoral Fellow
U.S. Medical Affairs
katie.wray-consultant@alexion.com

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