Ravulizumab-cwvz (ULTOMIRIS) for the Treatment of Neuromyelitis Optica Spectrum Disorder (NMOSD) National Drug Monograph Addendum November 2024

VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Indication Under Review in This Document

- Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive

Dosage Form Under Review

- Injection: 300 mg/mL (10mg/mL) in a single dose vial
- Dosing is weight-based:

Table 1 Ravulizumab-cwvz dosing for NMOSD

Weight	40 kg to less than 60 kg	60 kg to less than 100 kg	100 kg or more
Loading Dose	2,400 mg	2,700 mg	3,000 mg
Maintenance Dose (every 8 weeks starting 2 weeks after loading dose)	3,000 mg	3,300 mg	3,600 mg

REMS

- Ultomiris REMS – Prescribers must enroll in the program, counsel patients about the risk of meningococcal infections/sepsis, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines. This is the same program as with other indications for ravulizumab.

Clinical Evidence Summary

Efficacy Considerations

CHAMPION-NMOSD[2]

- Phase III, 50-week, open-label trial comparing ravulizumab to an external placebo group. The external placebo group was from eculizumab's phase III trial PREVENT.[3]
    - Open-label design may have influenced provider and patient views on the treatment effect of ravulizumab. This is particularly relevant as nearly all outcomes were based on provider or patient assessment and have some degree of subjectivity that could be influenced by bias. A separate committee reviewed "cases of interest", but this committee was also unblinded.
- Key inclusion criteria: AQP4-antibody positive, at least 1 relapse in the 12 months prior to screening, Expanded Disability Status Scale (EDSS) of 7 or less. Stable doses of immunosuppressive therapy could be continued, but patients were excluded if they were on other complement inhibitor therapy, if they had received mitoxantrone or rituximab 3 months prior to screening, or if they had received intravenous immunoglobulin 3 weeks prior to screening.
    - PREVENT had stricter inclusion criteria related to relapse history. It is possible that this may have led the historical placebo group to having a higher baseline annualized relapse rate (ARR) and worse baseline neurologic symptom severity. The impact of these baseline differences on the outcomes was assessed using propensity score–weighted analyses and it was determined these differences had an insignificant effect.
- Efficacy data are summarized in Table 2

Table 2: Efficacy results from CHAMPION-NMOSD

Outcome	Ravulizumab	Historical Placebo	p Value
Adjusted ARR (95% CI) – primary outcome	0 (0.044)	ARR was tested against the null hypothesis of 0.25	Poisson regression with 0 for ravulizumab not possible to run, though results considered significant.
No clinically important worsening in HAI (%)	56 (96.6)	36 (76.6)	0.0228
Mean change from baseline in EQ-5D (± SD)	0.005 ± 0.1522	-0.043 ± 0.2115	0.0567
Change from baseline in EQ-5D VAS (± SD)	2.6 ± 14.1	0.6 ± 16.4	n/a
No clinically important worsening in EDSS (%)	52 (89.7)	36 (76.6)	n/a

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; EQ-5D (VAS) = European Quality of Life-5 Dimensions (visual analog scale); HAI = Hauser Ambulation Index; SD = standard deviation. $p \leq 0.05$ considered statistically significant. As secondary endpoints tested in a hierarchical order, mean change form baseline in EQ-5D and on were not considered statistically significant.

Safety Results from NMOSD Clinical Trial[2]:

- Safety data from CHAMPION-NMOSD is summarized in Table 3

Table 3: Safety results from CHAMPION-NMOSD

Adverse Event Category	Events	Patients (%)
Any TEAE • **TEAE – severe severity**	328 • 13	53 (91.4) • 9 (15.5)
Any TEAE determined by investigator to be related to ravulizumab	38	26 (44.8)
TEAE leading to discontinuation of ravulizumab	3	1 (1.7)
Meningococcal infection (despite completing vaccination prior to starting ravulizumab)	2	2 (3.4)
TEAE in > 10% of patients • **COVID-19** • **Headache** • **Backpain** • **Arthralgia** • **Urinary Tract Infection**	 • 14 • 24 • 8 • 6 • 7	 • 14 (24.1) • 14 (24.1) • 7 (12.1) • 8 (13.8) • 3 (5.2)

TEAE = treatment-emergent adverse event

Other Therapeutic Options[1,4-7]

Alternative biologic treatments for NMOSD are listed in table 4 below

Table 4 Biologic Drug Treatment Options for NMOSD

Nonproprietary Drug	Maintenance dosing frequency and administration method	Other Considerations
Ravulizumab **Complement C5 Inhibitor**	Every 8-week intravenous infusion	REMS program for meningococcal infection risk
Eculizumab **Complement C5 Inhibitor**	Every 2-week intravenous infusion	REMS program for meningococcal infection risk
Inebilizumab **Anti-CD19 Antibody**	Every 6-month intravenous infusion	
Rituximab **Anti-CD20 Antibody**	Every 6-month intravenous infusion	Off-label for NMOSD
Satralizumab **IL-6 Receptor Antagonist**	Every 4-week subcutaneous injection	Self-administered option
Tocilizumab **IL-6 Receptor Antagonist**	Every 4-week intravenous infusion	Off-label for NMOSD

Projected Place in Therapy

- Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare CNS inflammatory demyelinating disease. Most people (>80%) with NMOSD have AQP4 antibody positive disease.[8] In 2024, there were 334 veterans with a diagnosis of NMOSD.
- No US clinical practice guidelines currently exist for NMOSD. The European Academy of Neurology (EAN) last revised clinical practice guidelines for NMOSD in 2010.[9] At that time, there were no pharmacologic treatments for NMOSD that were FDA approved; and rituximab was the only biologic medication described in the guideline. The German Neuromyelitis Optica Study Group (NEMOS) has recently published recommendations for treatment of NMOSD which are inclusive to the evidence for ravulizumab.[7]
- CHAMPION-NMOSD demonstrated a significant reduction in annualized relapse rate (ARR) compared to placebo. The open-label study design and use of a historical placebo group may present the potential for bias of this study's outcomes.
- The lack of a head-to-head comparison of ravulizumab with another NMOSD therapy, and the lack of head-to-head trials of most all the biologic therapies for NMOSD make assessing comparative efficacy difficult.
- A meta-analysis of complement C5 inhibitors, pooled the outcomes of PREVENT and CHAMPION-NMOSD for subgroup analysis of the class based on baseline characteristics of participants.[10] There were no characteristics that appeared to trend towards favoring placebo over complement C5 inhibitors. Another meta-analysis by Clardy et al. evaluated comparative efficacy of ravulizumab to FDA approved biologic therapies.[11] This meta-analysis did not include rituximab or tocilizumab. The results trended towards ravulizumab being more effective than other biologic therapies in ARR reduction. Both meta-analyses results could have been impacted by the design of the included trials (e.g., open-label trial design of CHAMPION-NMOSD). The latter meta-analysis was funded by Alexion Pharmaceuticals (manufacturer of eculizumab and ravulizumab-cwvz).
- Different from multiple sclerosis, NMOSD relapses tend to be associated with more of an incomplete recovery. Thus, evidence suggests biologic therapies may be preferred over oral immunosuppressive therapy (IST) for new diagnoses or patients who have relapsed on oral IST.[7] There is insufficient evidence to favor any one biologic therapy over another at this time. Ravulizumab may be considered as one of the biologic therapy options for NMOSD with positive AQP4 antibodies. Disease severity, risks, and patient specific considerations should be taken into account when choosing which therapy to start.

References

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