

# Ravulizumab-cwvz (ULTOMIRIS) National Drug Monograph Addendum March 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.*

## FDA Approval Information

### Indication(s) Under Review in This Document

- Generalized Myasthenia Gravis (gMG) in patients who are anti-acetylcholine receptor antibody-positive (AChR+).

### Dosage Form(s) Under Review

- Injection: 300 mg/mL (10mg/mL) in a single dose vial
- Only the IV formulation is currently approved for myasthenia gravis
- Dosing is weight-based:

**Table 1 Ravulizumab-cwvz dosing for myasthenia gravis**

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 MG – Phase III trial

The phase III study (CHAMPION) for ravulizumab-cwvz in gMG was a 26-week randomized, double-blind, placebo-controlled trial.<sup>1</sup> A total of 175 patients with AChR+ gMG were randomized 1:1 to IV

ravulizumab or placebo. Most patients had mild to moderate symptoms represented by mostly Myasthenia Gravis Foundation of America (MGFA) classification II or III and average baseline Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 9. The study group had slightly more patients with oropharyngeal and/or respiratory muscle involvement than the placebo group. Almost all (90%) patients in this study were on concurrent immunosuppressive therapy, as stable-dose immunosuppressive therapies including oral glucocorticoids were permitted. Stable-dose oral cholinesterase inhibitor therapy was also permitted. Chronic immunomodulating therapies of plasma exchange, intravenous immunoglobulin (IVIg), rituximab, and other complement inhibitors (e.g. eculizumab) were not permitted. However, plasma exchange and IVIg could be used on a “rescue” basis in cases of clinical deterioration. Use of these rescue therapies could have some residual effect that impacted the end of study MG symptom evaluation in either the placebo or ravulizumab-cwvz group. More patients in the placebo group received rescue therapy than the ravulizumab group (14 vs. 8 patients).

The primary efficacy endpoint was the change of the MG-ADL total score from baseline to week 26. The total change in the ravulizumab group was -3.1 and treatment effect of ravulizumab was -1.6 versus placebo. Though this was found to be statistically significant, it should be noted that literature supports a 2 point difference on this scale to be considered the minimal clinically important difference (MCID).<sup>2</sup> This MCID was reached in the total change, but not in the placebo adjusted treatment effect. The first of the five hierarchical secondary endpoints was the change of the Quantitative Myasthenia Gravis (QMG) total score from baseline to week 26. The total change in the ravulizumab group was -2.8 and the treatment difference in this outcome for ravulizumab was -2 versus placebo. Again, though statistically significant vs. placebo, literature supports a MCID of 3 points on the QMG<sup>3</sup> score, which ravulizumab did not meet even before adjusting for placebo effect. Ravulizumab did have a statistically significant higher rate of patients who had a 5 or more point improvement on the QMG. The remaining three secondary outcomes did not reach statistical significance. See Table 1.

Though CHAMPION states that treatment with ravulizumab started to take effect at week one, it was noted there was variability in when ravulizumab reached statistically significant differences vs. placebo. For MG-ADL, there was significance at week 10, but then differences were insignificant at weeks 12 and 18 before returning to statistical significance at week 26. Comparably for QMG, there was significance at week 10, but then the difference was insignificant at week 12 before returning to statistical significance at weeks 18 and 26. This fluctuation in significance makes estimating time to effect more imprecise but based on the phase III trial, it appears that time to a sustained improvement may be 26 weeks or longer. A four-year open label extension to this trial is still ongoing (NCT03920293). This will be important to see what is the lasting clinical benefit of ravulizumab.

Comparatively to eculizumab’s, another complement inhibitor for gMG, phase III trial (REGAIN)<sup>4</sup>, the week 26 outcomes were milder for ravulizumab. For change in MG-ADL, the treatment difference was -1.9 for eculizumab and -1.6 for ravulizumab. For QMG, the treatment difference was -3 for eculizumab and -2 for ravulizumab. Furthermore, it should be noted that REGAIN required patients to be refractory to at least two immunotherapies. CHAMPION did not require use of prior immunotherapies, with only having 47% of participants that had failed two or more immunosuppressive therapies. Though eculizumab’s

better outcomes in a more refractory population may speak to the seemingly better efficacy with eculizumab, a head-to-head study would need to be done to prove this.

**Table 2: Efficacy results from CHAMPION MG**

Study	Design	Results																																								
<b>CHAMPION MG Phase III N=175</b>	26-week randomized 1:1, double blind, placebo controlled study  <u>Key Inclusion Criteria:</u> <ul style="list-style-type: none"> <li>• Diagnosis of MG 6 months or more prior to screening</li> <li>• MGFA class II – IV</li> <li>• MG-ADL total of 6 or more</li> <li>• AChR+</li> </ul> <u>Key Exclusion Criteria:</u> <ul style="list-style-type: none"> <li>• Active or untreated thymoma, history of thymic carcinoma, or thymectomy in 12 months prior to screen</li> <li>• History of <i>Neisseria meningitidis</i> infection</li> <li>• IVIg or plasma exchange in 4 weeks prior to randomization</li> <li>• Rituximab in 6 months prior to randomization</li> <li>• Previous treatment with complement inhibitor</li> </ul>	All results described as least-squares mean change from baseline to week 26:  <u>Primary:</u> <table border="1"> <thead> <tr> <th></th> <th>Ravulizumab-cwvz</th> <th>PBO</th> <th>PBOTD (95% CI)</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>MG-ADL</td> <td>-3.1±0.38</td> <td>-1.4±0.37</td> <td>-1.6 (-2.6, -0.7)</td> <td>p = 0.0009</td> </tr> </tbody> </table> <u>Secondary:</u> <table border="1"> <thead> <tr> <th></th> <th>Ravulizumab-cwvz</th> <th>PBO</th> <th>PBOTD (95% CI)</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>QMG</td> <td>-2.8±0.46</td> <td>-0.8±0.45</td> <td>-2 (-3.2, -0.8)</td> <td>p=0.0009</td> </tr> <tr> <td>% with 5 or more point improvement on QMG</td> <td>30</td> <td>11.3</td> <td>2.7 (1.4, 5.3) <i>Absolute percentage difference</i></td> <td>p=0.0052</td> </tr> <tr> <td>MG-QOL15r</td> <td>-3.3±0.71</td> <td>-1.6±0.7</td> <td>-1.7 (-3.4, 0.1)</td> <td>p=0.0636</td> </tr> <tr> <td>Neuro-QoL Fatigue</td> <td>-7±1.92</td> <td>-4.8±1.87</td> <td>-2.2 (-6.9, 2.6)</td> <td>n/a</td> </tr> <tr> <td>% with 3 or more point improvement on MG-ADL</td> <td>56.7</td> <td>34.1</td> <td>1.6 (1.2, 2.3) <i>Absolute percentage difference</i></td> <td>n/a</td> </tr> </tbody> </table> MG-QOL15r – 15-item Myasthenia Gravis Quality of Life Neuro QoL – Neurological Quality of Life		Ravulizumab-cwvz	PBO	PBOTD (95% CI)	p value	MG-ADL	-3.1±0.38	-1.4±0.37	-1.6 (-2.6, -0.7)	p = 0.0009		Ravulizumab-cwvz	PBO	PBOTD (95% CI)	p value	QMG	-2.8±0.46	-0.8±0.45	-2 (-3.2, -0.8)	p=0.0009	% with 5 or more point improvement on QMG	30	11.3	2.7 (1.4, 5.3) <i>Absolute percentage difference</i>	p=0.0052	MG-QOL15r	-3.3±0.71	-1.6±0.7	-1.7 (-3.4, 0.1)	p=0.0636	Neuro-QoL Fatigue	-7±1.92	-4.8±1.87	-2.2 (-6.9, 2.6)	n/a	% with 3 or more point improvement on MG-ADL	56.7	34.1	1.6 (1.2, 2.3) <i>Absolute percentage difference</i>	n/a
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## Safety Considerations

The safety profile of ravulizumab has been fully discussed in the monograph reviewing use of ravulizumab in paroxysmal nocturnal hemoglobinuria (PNH) and complement-mediated thrombotic microangiopathy (TMA) in patients with atypical hemolytic uremic syndrome (aHUS).

In CHAMPION MG, the rate of total adverse events were similar between ravulizumab and placebo. There were two deaths in the ravulizumab-cwvz group; both were determined to be unrelated to the study drug (COVID-19 and cerebral hemorrhage). Headache, diarrhea, and nausea were the most commonly reported adverse events during the trial.

As with its other indications, ravulizumab has a REMS program for the purposes of safety on this medication. 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.<sup>5</sup>

## Other Therapeutic Options

Alternative treatments for AChR+ gMG are listed in tables 3 and 4 below:

**Table 3 Treatment Alternatives – newer MG agents**

Drug	Formulary status	Clinical Guidance	Other Considerations
<b>Ravulizumab-cwvz (Ultomiris®)</b>  Complement C5 Inhibitor	TBD	Effective in AChR Ab+ generalized MG	Infusion-related reactions, severe meningococcal infection (vaccination prior to therapy required), other infections, diarrhea, headache  IV infusion: initial loading dose followed by every 8 week infusions starting 2 weeks after loading dose. Weight-based dosing.
<b>Eculizumab (Soliris®)</b>  Complement C5 Inhibitor	NF, CFU	Effective in refractory AChR Ab+ generalized MG	Infusion-related reactions, severe meningococcal infection (vaccination prior to therapy required), other infections, headaches, musculoskeletal pain  IV infusion given weekly for 4 weeks then every 2 weeks.
<b>Efgartigimod (Vyvgart®)</b>  Neonatal Fc Receptor Antagonist	NF, CFU	Effective in AChR Ab+ generalized MG  Studied in a very small number of other MG subtypes and improvement was minimal. As a subgroup, it was too small to be evaluated for statistical significance.	Allergic reactions, headache, infections, leukopenia, myalgia  IV infusion given weekly for 4 weeks. Repeated as needed no more than 50 days from start of previous cycle. Repeat cycles are common as MG symptoms can return to baseline as soon as 8 weeks after starting a 4-week cycle. Efficacy and safety of long-term chronic therapy not studied.

**Table 4 Treatment Alternatives – Other Chronic Immunotherapies**

Drug	Formulary status	Time to onset of effect	Time to maximal effect
<b>Azathioprine</b>	F	12 months	1-2 years
<b>Cyclosporine</b>	F	6 months	7 months
<b>Mycophenolate mofetil</b>	F	6-12 months	1-2 years
<b>Prednisone</b>	F	2-3 weeks	5-6 months
<b>Rituximab (stronger evidence in MuSK+ gMG)</b>	F (biosimilar rituximab-pvvr)	6-12 months	7-16 months
<b>Tacrolimus</b>	F	6 months	12 months
<b>IVIg</b>	F	immediate	
<b>Plasma exchange</b>	Non-pharmacy product	immediate	

## Projected Place in Therapy

- Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disorder. The disease is characterized by fatigable weakness cause by antibodies that interfere with skeletal muscle

signaling at the neuromuscular junction. Symptoms can be limited to the eyes (ocular MG) or systemic (generalized MG, gMG). In its most severe case, gMG can result in respiratory depression or respiratory failure.

- It is estimated that the prevalence of MG is between 14 and 20 per 100,000 people in the US<sup>6</sup>. In FY22, there were 6,396 Veterans with MG who sought care at VA.
- The most current guideline, the 2020 Update to the International Consensus Guidance for Management of Myasthenia Gravis, does not address ravulizumab.<sup>7</sup>
- The CHAMPION study showed ravulizumab to be superior to placebo on MG-ADL and QMG at 26 weeks.
- As another complement inhibitor for gMG, it offers a less frequent infusion schedule compared to eculizumab. However, head-to-head trials do not exist for comparative efficacy to eculizumab or any other gMG treatment.
- Other chronic immunosuppressant therapies including corticosteroids, are associated with various side-effects such as glucose intolerance, weight gain, arterial hypertension, osteoporosis, gastrointestinal issues, bradycardia, and renal dysfunction. Except for steroids, they also are characterized by a longer time to onset and maximal effect.
- Ravulizumab offers a steroid-sparing treatment option in patients with gMG who are anti-acetylcholine receptor antibody-positive (AChR+). It can also be considered as add-on therapy when other traditional oral immunosuppressants like azathioprine, mycophenolate, and/or steroids, with or without additional acetylcholinesterase inhibitor (pyridostigmine) therapy is ineffective. Ravulizumab has not been studied with plasma exchange, intravenous immunoglobulin (IVIg), rituximab, efgartigimod, and other complement inhibitors (e.g. eculizumab).
- There is no evidence to support the use of ravulizumab in other antibody types of MG including MuSK+, LRP4+ and seronegative disease.

## References

1. Vu T, Meisel A, Mantegazza R, et al. Terminal complement inhibitor ravulizumab in generalized myasthenia gravis. *NEJM*. 2022;1(5)
2. Muppidi S. The myasthenia gravis–specific activities of daily living profile. *Ann N Y Acad Sci* 2012;1274:114-119.
3. Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. *Muscle Nerve* 2014;49:661-665.
4. Howard JF, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): a phase 3, randomized, double-blind, placebo-controlled, multicentre study. *Lancet Neurol*. 2017;16(12):976-986
5. Ultomiris® [Prescribing Information] Alexion Pharmaceuticals. Boston, MA; July 2022
6. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. *BMC Neurol*. 2010;10:46.

7. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis 2020 Update. *Neurology*. 2021;96:114-122

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