Zilucoplan (ZILBRYSQ) in Generalized Myasthenia Gravis
National Drug Mini-Monograph
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VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee 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[1]

Description / MOA	Complement C5 Inhibitor
Indication Under Review[1]	Generalized myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor antibody positive (AChR+).
Dosage Regimen	Once daily subcutaneous (SubQ) injection. Weight based dosing:

Actual Body Weight	Zilucoplan Dose
<56 kg	16.6 mg SubQ daily
≥56 kg to <77 kg	23 mg SubQ daily
≥77 kg	32.4 mg SubQ daily

Dosage Forms Under Review	Prefilled syringe
REMS Program	ZILBRYSQ REMS exists to reduce risk of meningococcal infections (see safety considerations below)

EFFICACY CONSIDERATIONS[2,3]

Trial	**Phase II trial**
Design	12-week multicenter, placebo-controlled, double-blind RCT.
Population	n=34 Key inclusion criteria: gMG, MGFA class II-IVa, AChR+,QMG ≥12. Pyridostigmine, steroids, and immunosuppressive therapy were allowed to be continued if stable for 4 weeks prior to start. Key exclusion criteria: thymectomy in past 6 weeks, IVIg or PLEX within 4 weeks of start (but was allowed for acute use during study), rituximab within 6 months of start.
Intervention	1:1:1 assigned to zilucoplan 0.1mg/kg daily, zilucoplan 0.3mg/kg daily, or placebo
Results	**Primary Outcome - Change in QMG score Mean Treatment Difference (SEM)** 0.3mg/kg: -2.8(1.7) p=0.05* 0.1mg/kg: -2.3(1.7) p=0.09* Between zilucoplan 0.3mg/kg and placebo, averages did start to diverge at week 1; differences not statistically significant until week 8. **Select Secondary Outcomes. Mean Treatment Difference (SEM):** MG-ADL: 0.3mg/kg: -2.3(1.3) p=0.04*; 0.1mg/kg: -2.2(1.3) p=0.05* MG-QoL 15r: 0.3mg/kg: -3.7(2.4) p=0.06*; 0.1mg/kg: -5.3(2.4) p=0.02*
Trial	**Phase III trial - RAISE**
Design	12-week multicenter, placebo-controlled, double-blind RCT.
Population	n=174 Key inclusion criteria: gMG, MGFA class II-IV, AChR+, MG-ADL≥6, QMG ≥12. Steroids and immunosuppressive therapy were allowed to be continued if stable for 30 days prior to start. Key exclusion criteria: thymectomy in past 12 months, IVIg or PLEX within 4 weeks of start (but was allowed for acute use during study), other complement inhibitor or rituximab within 12 months of start.
Intervention	1:1 assigned to zilucoplan 0.3mg/kg daily or placebo
Results	**Primary Outcome - Change in MG-ADL score Mean Treatment Difference (95% CI)** -2.09(-3.24,-0.95) p=0.0004* Averages between zilucoplan 0.3mg/kg and placebo did start to diverge at week 1 with statistical significance. **Select Secondary Outcomes. Mean Treatment Difference (95% CI):** QMG: -2.94(-4.39,-1.49) p<0.0001* MG-QoL 15r: -2.49(-4.45,-0.54) p=0.013*

*Statistically significant (Phase 2 p<0.1; Phase 3 p<0.05)

MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QoL 15r = Myasthenia Gravis Quality of Life Revised Scale; QMG = Quantitative Myasthenia Gravis

SAFETY[1]

Boxed Warnings	Meningococcal Infection Risk: Meningococcal vaccination should be completed at least 2 weeks prior to administering first dose of zilucoplan. Patients should be monitored for early signs of meningococcal infection and be evaluated immediately if infection is suspected. REMS program for this (see above).
Contraindications	Unresolved Neisseria meningitidis infection

Other Warnings	Infection: patients may have increased susceptibility to infection, particularly with encapsulated bacteria. Vaccination for Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae are recommended. Even after vaccination, patients are still at increased risk for these infections. Pancreatitis and pancreatic cysts: Lipase and amylase levels should be obtained at baseline. Zilucoplan should be discontinued if pancreatitis is suspected and management initiated until pancreatitis is ruled out. Morphea: Open-label extension studies (still in progress) reported morphea in 10 (5%) patients. For most, onset was after 1 year of treatment. Severity was mild to moderate. One patient discontinued zilucoplan due to morphea.
Top 5 AEs	Injection site reactions, upper respiratory tract infection, diarrhea, urinary tract infection, nausea/vomiting
Drug Interactions	In vitro studies do not suggest any major pharmacokinetic drug-drug interactions as they found zilucoplan not to be a substrate, inhibitor, or inducer of any major CYP enzyme, uridine diphosphoglucuronosyl transferase, or transporter.

ALTERNATIVE BIOLOGIC THERAPIES FOR AChR+ gMG

Drug	Formulary status	Clinical Guidance	Administration Considerations
Zilucoplan (ZILBRYSQ) Complement C5 Inhibitor	TBD	Effective in generalized MG patients who are AChR+	SubQ injection daily. Can be self-administered.
Ravulizumab-cwvz (ULTOMIRIS) Complement C5 Inhibitor	NF, CFU	Effective in generalized MG patients who are AChR+	IV infusion with weight-based dosing every 8 weeks, starting 2 weeks after the loading dose.
Eculizumab (SOLIRIS) Complement C5 Inhibitor	NF, CFU	Effective in refractory generalized MG patients who are AChR+	IV infusion given weekly for 4 weeks then every 2 weeks.
Rozanolixizumab-noli (RYSTIGGO) Neonatal Fc Receptor Antagonist	NF, CFU	Effective in generalized MG patients who are AChR+ or MuSK+	SubQ infusion weekly for 6 weeks. Repeat cycles may be used. MG symptoms can return to baseline as soon as 8 weeks after stopping treatment.
Efgartigimod (VYVGART) Neonatal Fc Receptor Antagonist	NF, CFU	Effective in generalized MG patients who are AChR+ Studied in a very small number of other MG subtypes, improvement was minimal.	IV infusion given weekly for 4 weeks. Repeat cycles may be used. MG symptoms can return to baseline as soon as 8 weeks after starting a 4-week cycle.

VHA PLACE IN THERAPY

Potential Use in VHA

- Myasthenia gravis 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.
- The RAISE study showed that zilucoplan significantly improved MG-ADL and QMG scores at 12 weeks versus placebo.
- Zilucoplan's subQ self-administration is unique compared to other complement C5 inhibitors (eculizumab and ravulizumab) as well as other advanced biologic therapies for gMG (e.g., neonatal Fc receptor antagonists) as it can be administered at home.
- An indirect comparison of RAISE, CHAMPION[4] (ravulizumab phase III trial), and REGAIN[5] (eculizumab phase III trial) suggests that zilucoplan may have similar treatment difference (compared to placebo) as ravulizumab and eculizumab on MG-ADL and QMG. However, head-to-head trials do not exist for evaluation of comparative efficacy of zilucoplan to other complement C5 inhibitors or any other gMG treatment.
- Zilucoplan offers a steroid-sparing treatment option in patients with gMG who are AChR+. It can also be considered as add-on therapy when other traditional oral immunosuppressants like azathioprine, mycophenolate, and/or steroids, with or without acetylcholinesterase inhibitor (pyridostigmine), therapy is ineffective. Zilucoplan has not been studied with plasma exchange, intravenous immunoglobulin (IVIg), rituximab, neonatal Fc receptor antagonists (e.g., efgartigimod), or other complement inhibitors (e.g., ravulizumab) as chronic immunotherapy for gMG.
- There is no evidence to support the use of zilucoplan in other antibody types of MG including MuSK+, LRP4+ and seronegative disease.

References

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