New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Rystiggo® (rozanolixizumab-noli) [UCB, Inc.]**
Dosage Formulations:	Sterile, preservative-free, clear to slightly opalescent, colorless to pale brownish yellow solution, administered as a subcutaneous infusion that delivers 280 mg/2 mL (140 mg/mL) of rozanolixizumab-noli.
FDA Approval Date: **FDB File Date:**	FDA: June 26, 2023 FDB: July 2, 2023
Indication:	Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive (Ab+).
Mechanism of Action:	Rystiggo is a humanized IgG4 monoclonal antibody that binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG (including fewer harmful antibodies), which reduces the symptoms of gMG.
Dose/ Administration:	• Before initiation of a new treatment cycle with Rystiggo, evaluate the need to administer age-appropriate vaccines according to immunization guidelines. Rystiggo causes transient reduction in IgG levels; therefore, immunization with live-attenuated or live vaccines is not recommended during treatment with Rystiggo. • The recommended dosage is based on patient body weight and is administered as a subcutaneous infusion using an infusion pump rate of up to 20 mL/hour once weekly for 6 weeks.

Body Weight	Dose	Volume to be Infused
Less than 50 kg	420 mg	3 mL
50 kg to less than 100 kg	560 mg	4 mL
100 kg and above	840 mg	6 mL

- Missed doses may be administered up to 4 days after the scheduled time point. Thereafter, resume the original dosing schedule until the treatment cycle is completed.
- Administer subsequent treatment cycles based on clinical evaluation; the safety of initiating subsequent cycles sooner than 63 days from the start of the previous treatment cycle has not been established.
- Preparation and Administration
  - Allow vials to reach room temperature for approximately 30 minutes. Keep vials in original carton to protect from light until ready to use. Vials should be inspected visually for particulate matter and discoloration prior to administration.
  - Infuse Rystiggo within 4 hours of puncturing the vial and administer immediately after priming the infusion set.
  - Infuse at a constant flow rate up to 20 mL/hour.
    - Choose an infusion site in the lower right or lower left part of the abdomen below the navel. Avoid infusing into tattoos, scars, or stretch marks. Rotate infusion sites for subsequent administrations.
    - Monitor during administration and for 15 minutes after completion for clinical signs and symptoms of hypersensitivity reactions.
    - When the infusion is complete, do not flush the infusion line as the volume of infusion has been adjusted taking into account the losses in the line.

Disease State Clinical Highlights:	• Myasthenia gravis (MG) is an autoimmune neuromuscular transmission disorder characterized by fluctuating weakness in ocular, bulbar, limb, and/or respiratory muscles due to an antibody-mediated immunologic attack directed at acetylcholine receptors (AChR) or muscle-specific tyrosine kinase (MuSK) receptors. There are two clinical forms of MG: ocular and generalized. In ocular MG, weakness is limited to the eyelids and extraocular muscles. In generalized MG (gMG), weakness involves a variable combination of ocular, bulbar, limb and respiratory muscles.
	• Approximately 71,000 people are diagnosed with MG in the United States – 85% gMG
	• The International Consensus Guidance for Management of Myasthenia Gravis has not been updated since 2020 (before the approval of the first FcRn antagonist). Recommendations from the most recently updated guidance are as follows:
	  ○ Pyridostigmine for initial treatment
	  ○ Corticosteroids for patients with MG who have not met treatment goals after adequate trial of pyridostigmine. Corticosteroids should be considered as an initial agent for ocular MG.
	  ○ Nonsteroidal immunosuppressive agents when corticosteroids are contraindicated (azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus)
	  ○ Plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) for patients with refractory MG or with life-threating signs (respiratory insufficiency or dysphagia)
	  ▪ PLEX may be more effective in MusK-MG
	  ○ Rituximab for MuSK Ab+ MG who have unsatisfactory response to initial immunotherapy
	  ○ Eculizumab should be considered for treatment of severe, refractory, AChR Ab+ gMG after trials of other immunotherapies have been unsuccessful

Drug Clinical Highlights:	• Rystiggo is the first and only FDA-approved treatment for patients with anti-MuSK Ab+ gMG.
	
	<u>Contraindications</u>
	• None
	
	<u>Warnings/Precautions</u>
	• Infections
	  ○ Rystiggo may increase risk of infection.
	  ○ Delay administration in patients with an active infection.
	  ○ Monitor for signs and symptoms of infection in patients treated with Rystiggo.
	  ○ If serious infection occurs, administer appropriate treatment and consider withholding Rystiggo until the infection has resolved.
	• Aseptic Meningitis
	  ○ Serious adverse reactions of aseptic meningitis have been reported in patients treated with Rystiggo.
	  ○ If symptoms consistent with aseptic meningitis develop, diagnostic workup and treatment should be initiated according to the standard of care.
	• Hypersensitivity Reactions
	  ○ Hypersensitivity reactions, including angioedema and rash, were observed in patients treated with Rystiggo.
	  ○ Monitor patients during treatment with Rystiggo and for 15 minutes after the administration is complete for clinical signs and symptoms of hypersensitivity reactions.
	  ○ If a hypersensitivity reaction occurs, the healthcare professional should institute appropriate measures if needed or the patient should seek medical attention.
	
	<u>Pregnancy and Lactation</u>
	• There are limited data on Rystiggo use in pregnant women. Following administration of rozanolixizumab-noli to pregnant monkeys at doses greater than those used clinically,

increases in embryonic death, reduced body weight, and impaired immune function were observed in offspring.
- There are no data on the presence of rozanolixizumab-noli in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk.

Renal and Hepatic Impairment

- No dedicated pharmacokinetic studies have been conducted in patients with renal or hepatic impairment. Renal or hepatic impairment is not expected to affect the pharmacokinetics of rozanolixizumab-noli, and no dosage adjustment is required.

Clinical Studies

- MycarinG (NCT03971422): a Phase 3, multicenter, randomized, double-blind, placebo-controlled study conducted to demonstrate the efficacy of Rystiggo for the treatment of gMG in adults who are anti-AChR Ab+ or anti-MuSK Ab+
- The study included a 4-week screening period and a 6-week treatment period, followed by 8 weeks of observation. During the treatment period, Rystiggo or placebo were administered as a SC infusion once a week for 6 weeks.

MycarinG (NCT03971422) Study Design Summary	
Study Population (n = 200)	Median age: 52 years (range, 18–89 years) Median time since diagnosis: 6 years 61% female 68% White; 11% Asian; 3% Black or African American; 1% American Indian or Alaska Native 7% Hispanic or Latino ethnicity Median Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score: 8 Median Quantitative Myasthenia Gravis (QMG) total score: 15 89.5% (n=179) were positive for AChR antibodies; 10.5% (n=21) were positive for anti-MuSK antibodies At baseline, more than 83% of patients received AChE inhibitors, more than 56% received steroids, and ~50% received non-steroidal immunosuppressive therapies (NSISTs) at stable doses
Inclusion Criteria	≥18 years of age with gMG diagnosis and confirmed positive record of autoantibodies against AChR or MuSK at screening Presence of autoantibodies against AChR or MuSK Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IVa MG-ADL total score ≥3 (with ≥3 points from non-ocular symptoms)

	On stable dose of MG therapy prior to screening that included AChE inhibitors, steroids, or NSISTs, either in combination or alone Serum IgG levels of ≥5.5 g/L
Interventions	Patients were randomized 1:1:1 to receive one of the following via subcutaneous infusion once per week for 6 weeks, followed by an observation period of up to 8 weeks: Weight-tiered doses of Rystiggo (n = 133) ≈7 mg/kg (n = 66) ≈10 mg/kg (n = 67) or Placebo (n = 67)
Endpoints	Primary: Comparison of change from baseline between treatment groups in MG-ADL total score at Day 43[a] Secondary: Change between treatment groups from baseline to Day 43 in the QMG total score[b]

[a] MG-ADL scale assesses the impact of gMG on daily functions of 8 signs or symptoms typically affected in gMG. Each item is assessed on a 4-point scale; a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. A total score ranges from 0 to 24, with the higher scores indicating more impairment.
[b] The QMG is a 13-item categorical grading system that assesses muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total possible score ranges from 0 to 39, where higher scores indicate more severe impairment.

Efficacy Endpoints	Rystiggo ≈ 7 mg/kg n = 66	Rystiggo ≈ 10 mg/kg n = 67	Placebo n = 67
Primary Endpoint: Change from Baseline in MG-ADL Total Score			
LS Mean (SE)	-3.4 (0.5)	-3.4 (0.5)	-0.8 (0.5)
Difference from placebo (95% CI)	−2.6 (−4.1, −1.2)	−2.6 (−4.0, −1.2)	–
P-value	<0.001	<0.001	–
Secondary Endpoint: Change from Baseline in QMG Total Score			
LS Mean (SE)	-5.4 (0.7)	-6.7 (0.7)	-1.9 (0.7)
Difference from placebo (95% CI)	-3.5 (-5.6, -1.6)	-4.8 (-6.8, -2.9)	–
P-value	<0.001	<0.001	–

CI = confidence interval; MG-ADL, myasthenia gravis activities of daily living scale; QMG, quantitative myasthenia gravis; LS = least square; SE = standard error.

- Adverse events that occurred in ≥10% of patients in the treatment group (n = 133): headache (44%), infections (23%), diarrhea (20%), pyrexia (17%), hypersensitivity reactions (11%), and nausea (10%).
    - In clinical trials, one patient with gMG and two patients with another neurological disease experienced a serious adverse reaction of drug-induced aseptic meningitis, which led to hospitalization and discontinuation of Rystiggo.
    - No deaths occurred.

Price Per Unit (WAC):

- $6,050 per 2 mL vial
- $72,600 per treatment cycle (based on a 70 kg patient receiving 560 mg (4 mL) once weekly for 6 weeks)
- $290,400 per year (based on four treatment cycles per year)

Therapeutic Alternatives:

FcRn Antagonists

- Rystiggo is the second FcRn antagonist FDA-approved for the treatment of gMG. It is the only treatment approved for patients who are anti-MuSK Ab+.
  - Vyvgart (IV administered) and Vyvgart Hytrulo (SC injected) are FcRn antagonist products approved only for the treatment of anti-AChR Ab+ gMG.
    - In Vyvgart's clinical trial (ADAPT), patients with anti-MusK Ab+ gMG were included and showed MG-ADL response in Cycle 1.
  - Rystiggo and Vyvgart have not been studied head-to-head, and these drugs had different primary endpoints in pivotal trials, making cross-trial comparisons difficult.

Compliment Inhibitors

- Soliris and Ultomiris are both approved for the treatment of patients with anti-AChR Ab+ gMG.
  - Both Soliris and Ultomiris have a Boxed Warning for serious meningococcal infection.
  - While FcRn antagonists are viewed as safer than complement inhibitors, given that they do not have Boxed Warnings, prescribers are aware of how to manage the risks of administering complement inhibitors and patients who are receiving complement inhibitors to good effect would not likely switch to an FcRn antagonist.
- There are no studies that have investigated use of combination therapy of FcRn antagonists and complement inhibitors for the treatment of gMG.

Drug	FDA-Approved Indication	ROA, Administration Time	Monitoring Time	Dosing Frequency	Estimated Annual WAC
FcRn Antagonists					
Vyvgart (efgartigimod alfa-fcab)	Adults with AChR Ab+ gMG	IV, 1 hour	1 hour	Once weekly for 4 weeks per cycle	$242,760
Vyvgart Hytrulo (efgartigimod alfa & hyaluronidase-qvfc)	Adults with AChR Ab+ gMG	SC injection, 30–90 seconds	30 minutes	Once weekly for 4 weeks per cycle	$315,460
Rystiggo (rozanolixizumab-noli)	Adults with AChR Ab+ or MuSK Ab+ gMG	SC infusion, ~12 mins for a patient weighing 80 kg	15 minutes	Once weekly for 6 weeks per cycle	$290,400
Compliment Inhibitors					
Soliris (eculizumab)	Adults with AChR Ab+ gMG	IV, 35 minutes	1 hour	Once every 2 weeks	$678,392
Ultomiris (ravulizumab-cwvz)	Adults with AChR Ab+ gMG	IV, dose-dependent	1 hour	Once every 8 weeks	$457,886

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with neurologist or other specialist in the treated disease state **AND**
- Participant aged ≥ 18 years **AND**
- Participant has documented diagnosis of generalized myasthenia gravis **AND**

	• Documented disease classification as Myasthenia Gravis Foundation of America (MGFA) Class II, III, or IV **AND**
	• Documented positive anti-AChR or anti-MuSK antibody test **AND**
	• Documented baseline MG-ADL total score of ≥3 (with ≥3 from non-ocular symptoms) **AND**
	• Adequate therapeutic trial of 2 conventional agents (AChE inhibitors, steroids, or NSISTs) (90/120 days)
	• Initial approval period: 3 months
	
	<u>Continuation of Therapy:</u>
	• Subsequent cycles to be administered if:
	  ○ MG-ADL total score is ≥3 (with ≥3 from non-ocular symptoms) **OR**
	  ○ Participant was a MG-ADL responder initially, but no longer has a clinically meaningful improvement (defined as < 2-point improvement in total MG-ADL score) **AND**
	• Treatment has a sustained effect for at least 4 weeks after the end of the previous treatment cycle **AND**
	• Minimum time between treatment cycles should be no less than 63 days from the start of previous treatment cycle and the start of the next treatment cycle
	• Continuation approval period: 6 months
	
	<u>Denial Criteria:</u>
	• Therapy will be denied if all approval criteria are not met
	• Participant is currently pregnant
	• Dose exceeds 840 mg (6 mL) per infusion
	• Therapy exceeds 30 infusions per year
	
	<u>Default Approval Period:</u>
	• 3 months

Implication to State Medicaid Program:	**LOE: 2037**
	
	Pipeline drugs:
	• Vyvgart Hytrulo PFS (Manufacturer: argenx)
	  ○ Anti-AChR Ab+ adults with gMG
	  ○ SC, self-administered - more convenient for patients.
	  ○ Cost estimated to be in a similar range as Vyvgart; however, may be higher given the convenience advantage.
	  ○ Approval and launch timeline is unknown
	• Batoclimab (Manufacturer: Immunovant)
	  ○ Adults with gMG
	  ○ SC, likely HCP administered
	  ○ Phase 3 development, weekly induction followed by biweekly maintenance.
	  ○ Data not yet available. Approval may not occur until 2025.
	• Nipocalimab (Manufacturer: Janssen)
	  ○ Adults with gMG
	  ○ IV infusion, HCP administered
	  ○ Phase 3 development, every-other-week administration.
	  ○ Trial planned for children 2 to less than 18 years of age.
	  ○ Data not yet available. Approval may not occur until 2025.
	
	Additional Information:
	• Currently, MO HealthNet has 231 documented participants with a primary diagnosis of Myasthenia Gravis for the calendar year 2022.
	• Claims information for Vyvgart 1/01/2022 to 12/31/2022

Drug	Claims	Spend	Avg Spend per Claim
Vyvgart 400 mg/20 mL vial	40	$537,027	$13,425
Vyvgart Hytrulo	-	-	-

References:

- Rystiggo [package insert]. Smyrna, GA: UCB, Inc.; June 2023.
- IPD analytics. New drug review. Rystiggo (rozanolixizumab-noli). August 2023.
- Bird SJ. Overview of the treatment of myasthenia gravis. UpToDate. https://www.uptodate.com/contents/overview-of-the-treatment-of-myasthenia-gravis. Updated August 2023. Accessed August 11, 2023.
- Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. Neurology. 2021;96(3):114-122. doi:10.1212/WNL.0000000000011124