CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
1Q18 January – February

BRAND NAME
Soliris®

GENERIC NAME
Eculizumab

MANUFACTURER
Alexion Pharmaceuticals, Inc.

DATE OF APPROVAL
October 23, 2017

PRODUCT LAUNCH DATE
Currently commercially available

REVIEW TYPE
☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
New/Revised Indication(s)
Treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody-positive

Current Indication(s)
- Treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
- Treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy

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OFF LABEL USES
Not applicable

CLINICAL EFFICACY
Background
Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs. Myasthenia gravis affects both men and women and occurs across all racial and ethnic groups. It most commonly impacts young adult women (under 40) and older men (over 60), but it can occur at any age, including childhood.[1] In approximately 85% of patients, autoantibodies directed against the postsynaptic nicotinic AchR can be detected in the serum and confirm the diagnosis, but in general, do not precisely predict the degree of weakness or response to therapy.[2]

<table>
<tr><th></th><th>Howard JF Jr, et al. REGAIN Study [3]</th></tr>
<tr><td>Study Design</td><td>Multicenter, double-blind, randomized, parallel-group, placebo-controlled, phase 3 study</td></tr>
<tr><td>N</td><td>125</td></tr>
<tr><td>Drug Regimen</td><td>Randomized 1:1 to either intravenous eculizumab or intravenous matched placebo for 26 weeks.</td></tr>
<tr><td>Primary Outcome(s)</td><td>Change from baseline in Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) total score at week 26 for eculizumab as compared to placebo</td></tr>
<tr><td>Secondary Outcome(s)</td><td>Change from baseline in the Quantitative Myasthenia Gravis (QMG) total score at week 26
Overall safety and tolerability of eculizumab at end of study (week 26), adverse events, vital signs, laboratory assessments, physical exams, and electrocardiograms (ECGs)</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Efficacy Endpoints</th><th>Soliris-LS Mean (n=62) (SEM)</th><th>Placebo-LS Mean (n=63) (SEM)</th><th>Soliris change relative to placebo – LS Mean Difference (95% CI)</th><th>p-values</th></tr>
<tr><td>MG-ADL</td><td>-4.2 (0.49)</td><td>-2.3 (0.48)</td><td>-1.9
(-3.3, -0.6)</td><td>(0.006a;
0.014b)</td></tr>
<tr><td>QMG</td><td>-4.6 (0.60)</td><td>-1.6 (0.59)</td><td>-3.0
(-4.6, -1.3)</td><td>(0.001a;
0.005 b)</td></tr>
</table>
SEM= standard error of the mean;
Soliris-LSMean = least square mean for the treatment group;
Placebo-LSMean = least square mean for the placebo group;
</td></tr>
</table>

	LSMean-Difference (95% CI) = Difference in least square mean with 95% confidence interval; P-values (testing the null hypothesis that there is no difference between the two treatment arms a: in least square means at Week 26 using a repeated measure analysis; b: in ranks at Week 26 using a worst rank analysis). The change in the MG-ADL score was not statistically significant between eculizumab and placebo, as measured by the worst-rank analysis. Eculizumab was well tolerated.
# Withdrew due to Lack of Efficacy	Not reported
# Withdrew due to Adverse Effects	Not reported

CONTRAINDICATIONS
- Patients with unresolved serious Neisseria meningitidis infection
- Patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection

BLACK BOX WARNINGS
Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early.

DRUG INTERACTIONS
Not applicable

ADVERSE REACTIONS
- Headache
- Nasopharyngitis
- Diarrhea
- Arthralgia
- Upper respiratory tract infection
- Nausea
- Abdominal pain
- Peripheral edema
- Pyrexia
- Herpes simplex virus infections
- Contusions
- Musculoskeletal pain

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DOSAGE AND ADMINISTRATION
900 mg IV infusion weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter.

PRODUCT AVAILABILITY
Injection: 300 mg single-dose vials each containing 30 mL of 10 mg/mL sterile, colorless, preservative-free eculizumab solution

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Cholinesterase Inhibitors		
pyridostigmine (Mestinon®, Regonol®)	Oral immediate release: 600 mg daily in divided doses (range, 60-1500 mg PO daily in divided doses) Oral sustained release: 180-540 mg PO once daily or twice daily IV or IM: 2 mg every 2-3 hours	Considered as first line therapy for initial treatment
neostigmine (Bloxiverz®)	Oral: 15 mg PO 3 times per day. The daily dosage should be gradually increased at intervals of 1 or more days. The usual maintenance dosage is 15-375 mg/day (average 150 mg) IM or SC: 0.5 mg based on response to therapy	
Corticosteroids		
betamethasone	Oral: 0.6 to 7.2 mg PO per day	
dexamethasone	Oral: 0.75 to 9 mg/day PO	
methylprednisolone	Oral: 12 to 20 mg PO per day; increase as needed by 4 mg every 2 to 3 days until there is marked clinical improvement or to a maximum of 40 mg/day	
prednisone	Oral: 15 mg/day to 20 mg/day; increase by 5 mg every 2 to 3 days as needed. Maximum: 60 mg/day	
Immunosuppressants		
azathioprine (Imuran®)	Oral: 50 mg PO once daily for 1 week, then increase gradually to 2 to 3 mg/kg/day	
mycophenolate mofetil (Cellcept®)	Oral: Dosage not established. 1 gram twice daily has been used with adjunctive corticosteroids or other	Off-label use; data from randomized, controlled trials do not support use

	non-steroidal immunosuppressive medications.	
cyclosporine (Sandimmune®)	Oral: initial dose of cyclosporine (nonmodified), 5 mg/kg/day PO in 2 divided doses	Off-label use
Rituxan® (rituximab)	IV: 375 mg/m^2 IV once a week for 4 weeks; an additional 375 mg/m^2 dose may be given every 1 to 3 months afterwards	Off-label use

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be maintained for the following reason(s):
  - ☒ Opportunity exists to obtain clinically significant medical or laboratory information necessary to determine appropriate use of the medication.
    - i) Soliris is only approved in gMG patients who are anti-AchR antibody-positive.
    - ii) Soliris only has proven efficacy as a 2nd/3rd line therapy in the pivotal trial for approval.
    - iii) Recommended utilization management tool(s): (check all that apply)
      - (1) ☒ Prior authorization
      - (2) ☐ Quantity limits
      - (3) ☐ Provider newsletter
      - (4) ☐ Hard block (plan exclusion)
      - (5) ☐ Messaging
      - (6) ☐ Electronic step therapy
      - (7) ☐ Clinical program
    - iv) Soliris currently requires PA; recommend to maintain PA status.

Product Comparison

- It would be clinically appropriate to require a trial of cholinesterase inhibitors and/or immunosuppressive therapies prior to Soliris.

REFERENCES

[1]Nih.gov Myasthenia Gravis Fact Sheet
[2]Meriggioli M and Sander SB. Muscle autoantibodies in myasthenia gravis: beyond diagnosis? Expert Review of Clinical Immunology 2014; 8(5): 427-438.
[3]Howard JF Jr, 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, randomised, doubleblind, placebo-controlled, multicentre study. Lancet Neurol 2017; 16(12):976-986.0.

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