

Evolut Clinical Guideline 3177 for Eculizumab Products

Guideline Number: UM-ONC-1382 Evolut_CG_3177	<u>Applicable Codes</u>	
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Original Date: February 2020	Last Revised Date: September 2025 ⁵⁴	Implementation Date: September 2025 ⁵⁴

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STATEMENT

Purpose

To define and describe the accepted indications for Eculizumab Products [Soliris (eculizumab), ~~and~~ Epysqli (eculizumab-aagh), and Bkerv (eculizumab-aeeb)] usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

- The member has hemolytic paroxysmal nocturnal hemoglobinuria (PNH) and eculizumab/eculizumab biosimilar is being used to reduce hemolysis.

Atypical Hemolytic Uremic Syndrome (aHUS)

- Eculizumab/eculizumab biosimilar is being used in a member with a confirmed diagnosis of aHUS, with evidence of hemolysis (LDH above normal/Haptoglobin below normal/Schistocytes on peripheral smear), and impaired renal function (serum creatinine above normal).

CONTRAINDICATIONS/WARNINGS

- Contraindications
 - Initiation in patients with unresolved serious *Neisseria meningitidis* infection.
- US Boxed Warning
 - Serious meningococcal infection
 - Eculizumab/eculizumab biosimilar increases the risk of serious infections caused by *Neisseria meningitidis*. Life-threatening and fatal meningococcal

infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of eculizumab/eculizumab biosimilar, unless the risks of delaying therapy with eculizumab/eculizumab biosimilar outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor.
- Patients receiving eculizumab/eculizumab biosimilar are at increased risk for invasive disease caused by *N. meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.
- Because of the risk of serious meningococcal infections, eculizumab/eculizumab biosimilar is available only through the restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS, EPYSQLI REMS, or BKEMV REMS.

EXCLUSION CRITERIA

- Disease progression while on eculizumab/eculizumab biosimilar defined by a lack of response in rise of hemoglobin and continued use of blood transfusions.
- Eculizumab/eculizumab biosimilar is being used after disease progression with the same regimen or other anti-complement therapies, for example Ultomiris (ravulizumab).
- Eculizumab/eculizumab biosimilar is not indicated for the treatment of members with Shiga toxin E. coli-related hemolytic-uremic syndrome (STEC-HUS) or thrombotic thrombocytopenia purpura (TTP), defined as ADAMTS-13 activity less than 5%.
- Dosing exceeds single dose limit of eculizumab/eculizumab biosimilar 900 mg for PNH and 1,200 mg for aHUS.
- Investigational use of eculizumab/eculizumab biosimilar with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
 - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
 - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
 - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.

- Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J1299 - Injection, eculizumab, 2 mg
- Q5151 - Injection, eculizumab-aagh (epysqli), biosimilar, 2 mg
- Q5152 - Injection, eculizumab-aeeb (bkemv), biosimilar, 2 mg

Applicable Lines of Business

<input type="checkbox"/>	CHIP (Children's Health Insurance Program)
<input checked="" type="checkbox"/>	Commercial
<input checked="" type="checkbox"/>	Exchange/Marketplace
<input checked="" type="checkbox"/>	Medicaid
<input type="checkbox"/>	Medicare Advantage

POLICY HISTORY

Date	Summary
September 2025	<ul style="list-style-type: none"> Converted to new Evolent guideline template This guideline replaces UM ONC_1382 Eculizumab Products Updated verbiage in purpose statement Added new biosimilar “Bkemv (eculizumab-aeeb)” to policy Updated references
September 2024	<ul style="list-style-type: none"> Added new biosimilar “Epysqli (eculizumab-aagh)” to policy Updated references

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Clinical Guideline Review Committee

Disclaimer

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REFERENCES

- Hillmen P, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006 Sep 21;355(12):1233-43. doi: 10.1056/NEJMoa061648.
- Legendre CM, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med*. 2013 Jun 6;368(23):2169-81. doi: 10.1056/NEJMoa1208981.
- Soliris prescribing information. Alexion Pharmaceuticals, Inc. Boston, MA 2025.
- Epysqli prescribing information. Samsung Bioepis Co., Ltd. Republic of Korea 2025.
- Bkemv prescribing information. Amgen Inc. Thousand Oaks, CA 2024.

- ~~4~~.6. Clinical Pharmacology Elsevier Gold Standard 2025.
- ~~5~~.7. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2025.
- ~~6~~.8. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2025.
- ~~7~~.9. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2025.
- ~~8~~.10. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
- ~~9~~.11. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf>.
- ~~10~~.12. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>.

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6. Clinical Pharmacology Elsevier Gold Standard 2025.
7. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2025.
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10. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
11. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services:
<https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf>.
12. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA:
<http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>.