

sulopenem etzadroxil and probenecid (Orlynvah™)

Policy # 00954

Original Effective Date: 02/01/2026

Current Effective Date: 02/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member’s contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider sulopenem etzadroxil and probenecid (Orlynvah™)[‡] for the treatment of uncomplicated urinary tract infections to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for sulopenem etzadroxil and probenecid (Orlynvah) will be considered when the following criteria are met:

- Patient has a diagnosis of uncomplicated urinary tract infection caused by one of the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*; AND
- Patient is 18 years of age or older; AND
- Patient is a female with limited or no alternative oral antibacterial treatment options; AND
- Patient does not have a known blood dyscrasia or uric acid kidney stones; AND
- Patient is not on hemodialysis and has a creatinine clearance ≥ 15 mL/min; AND
- Patient will not use the requested drug with ketorolac tromethamine; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) ONE of the following alternatives to which the microorganism is susceptible: ciprofloxacin, fosfomycin, levofloxacin, nitrofurantoin, sulfamethoxazole-trimethoprim or a beta-lactam (e.g., amoxicillin-clavulanate, cefdinir, cefpodoxime) unless there is clinical evidence or patient history that suggests the alternatives will be ineffective or cause an adverse reaction to the patient.

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of sulopenem etzadroxil and probenecid (Orlynvah) without a trial and failure of ONE of the following alternatives to which the microorganism is susceptible: ciprofloxacin, fosfomycin, levofloxacin, nitrofurantoin, sulfamethoxazole-trimethoprim or a beta-lactam to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of sulopenem etzadroxil and probenecid (Orlynvah) when the patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) to be **investigational**.*

Background/Overview

Orlynvah is indicated for the treatment of uncomplicated urinary tract infections (uUTIs) caused by the designated microorganisms *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options. Orlynvah is available as film coated tablets containing 500 mg of sulopenem etzadroxil, a penem antibacterial, and 500 mg of probenecid, a renal tubular transport inhibitor. Sulopenem etzadroxil is a prodrug that is hydrolyzed to the active drug sulopenem after oral administration, which has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. Probenecid inhibits the organic anion transporters 3-mediated renal clearance of sulopenem resulting in increased plasma concentrations of sulopenem. The recommended dose of Orlynvah is one tablet (sulopenem etzadroxil 500 mg and probenecid 500 mg) taken orally twice daily with food for 5 days. Orlynvah is contraindicated in patients with known blood dyscrasias, uric acid kidney stones, or with a history of hypersensitivity to the components of Orlynvah or other beta-lactam antibacterial drugs. Concomitant use of Orlynvah and ketorolac tromethamine is also contraindicated. Orlynvah is not recommended for patients with creatinine clearance less than 15 mL/min or those receiving hemodialysis, as the pharmacokinetics of sulopenem have not been established. According to the prescribing information, Orlynvah is not indicated for the treatment of complicated urinary tract infections (cUTI), including step-down therapy following intravenous antibacterial treatment of cUTI. Additionally, Orlynvah is not indicated for the treatment of complicated intra-abdominal infections (cIAI), nor as step-down therapy after intravenous antibacterial treatment of cIAI. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Orlynvah and other antibacterial drugs, Orlynvah should be used only to treat uUTI that are proven or strongly suspected to be caused by susceptible bacteria. Culture and susceptibility information should be utilized in selecting or modifying antibacterial therapy according to the prescribing information for Orlynvah. Currently, there are no available data on sulopenem etzadroxil use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

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Urinary tract infections (UTIs) are generally classified as either uncomplicated (uUTI) or complicated (cUTI); however, the definitions of these classifications have been inconsistent. In 2025, Infectious Disease Society of America (IDSA) issued new treatment guidelines for cUTIs and revised the classification. According to the update, infection confined to the bladder in afebrile men or women is classified as uncomplicated. Local bladder signs and symptoms associated with a uUTI may include dysuria, urgency, frequency, and suprapubic pain. Systemic signs of illness, such as fever or bacteremia, suggest that the infection has extended beyond the bladder and is thus defined as a complicated UTI. Evidence of renal parenchymal involvement (e.g., costovertebral angle tenderness), or a prostatic abscess, would also demonstrate that the infection has extended beyond the bladder. Subsequent discovery of obstruction in the upper urinary tract, such as from a stone, would render the infection complicated. The guidelines cite that all patients diagnosed with UTI need to have signs or symptoms related to the organisms in the bladder (or spreading beyond the bladder); otherwise, the patient has asymptomatic bacteriuria (ASB) and does not need antibiotic treatment. The guidelines note that the classifications of uncomplicated and complicated UTI are intended to guide management of UTI, not diagnosis.

Therapeutic options for the treatment of uUTI depend upon the bacteria causing the infection, resistance patterns, patient medical history, and allergies. First-line oral agents commonly used for the treatment of acute uUTI include nitrofurantoin 100 mg twice daily for five days, trimethoprim-sulfamethoxazole (TMP-SMX) 160/800 mg twice daily for three days (only if local resistance rates for *E. coli* are below 20% or susceptibility is confirmed), and fosfomycin trometamol as a single 3 gram dose. Pivmecillinam may be considered where available. When these therapies cannot be used, fluoroquinolones (e.g., ofloxacin, ciprofloxacin, and levofloxacin) or beta-lactams (e.g., amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime proxetil) are second-line options. The Infectious Diseases Society of America (IDSA) archived its 2010 guidelines for the treatment of uncomplicated urinary tract infections (UTIs), as new guidelines are under development. The American Urological Association established guidelines for recurrent uUTI in women (2019). For the treatment of symptomatic UTIs in women, use of a first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) based on the local antibiogram is recommended.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Orlynvah is indicated for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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Trial 1

A total of 2222 adult women with uncomplicated urinary tract infections were randomized, and 2214 received trial medications in a randomized, double-blind clinical trial (Trial 1) comparing oral Orlynvah (sulopenem etzadroxil 500 mg and probenecid 500 mg) twice daily for 5 days to oral amoxicillin/clavulanate 875 mg/125 mg twice daily for 5 days. The microbiological modified intent-to-treat (micro-MITT) population, which included all patients who had at least one uropathogen isolated at baseline (≥ 10 colony forming unit [CFU]/mL) and received at least one dose of study drug, consisted of 990 patients. Composite response (combined microbiological response and clinical cure rates) was determined by comparing the response rate of Orlynvah to amoxicillin/clavulanate at the test of cure (TOC) visit (12 days after randomization) in the micro-MITT population as well as in two sub-populations: a) micro-MITTS (micro-MITT population with baseline pathogens susceptible to amoxicillin/clavulanate, maximum inhibitory concentration [MIC] $\leq 8/4$ $\mu\text{g/mL}$) and b) micro-MITTR (micro-MITT population with baseline pathogens non-susceptible to amoxicillin/clavulanate, MIC $\geq 16/8$ $\mu\text{g/mL}$). Clinical cure was defined as the resolution of patient reported uUTI symptoms and no new uUTI symptoms. Microbiological response was defined as a reduction of all baseline uropathogens to less than 10 CFU/mL in the urine. Orlynvah demonstrated efficacy in the micro-MITTS population. At Day 12, overall response (primary endpoint) was noted in 61.7% of patients in the Orlynvah group versus 55.0% of patients in the amoxicillin-clavulanate group in the micro-MITTS population (treatment difference of 6.7; 95% confidence interval [CI] [0.3, 13.0]; $p = 0.006$). The micro-MITTR population was small ($N = 67$) and had insufficient power to draw conclusions regarding efficacy. At Day 12, overall response (primary endpoint) was noted in 52.4% of patients the Orlynvah group versus 68.0% of patients in the amoxicillin-clavulanate group in the micro-MITTR population (treatment difference of -15.6; 95% CI [-37.5, 9.1]).

Trial 2

A total of 1660 adult women with uUTI were randomized and received trial medications in a multinational randomized, double-blind clinical trial (Trial 2) comparing oral Orlynvah (sulopenem etzadroxil 500 mg and probenecid 500 mg) twice daily for 5 days to oral ciprofloxacin 250 mg twice daily for 3 days. The micro-MITT population, which included all patients who had at least one uropathogen isolated at baseline (≥ 10 CFU/mL), consisted of 1105 patients. Composite response (combined microbiological response and clinical cure) was determined by comparing the response rate of Orlynvah to ciprofloxacin at the TOC visit (12 days after randomization) in two primary populations: a) micro-MITTS (micro-MITT population with baseline pathogens susceptible to ciprofloxacin, MIC ≤ 1 $\mu\text{g/mL}$) and b) micro-MITTR (micro-MITT population with baseline pathogens non-susceptible to ciprofloxacin, MIC ≥ 2 $\mu\text{g/mL}$). Clinical cure was defined as the resolution of patient reported uUTI symptoms and no new uUTI symptoms. Microbiological response was defined as a reduction of all baseline uropathogens to less than 10 CFU/mL in the urine. Orlynvah demonstrated efficacy in the micro-MITTR population but did not demonstrate efficacy in the micro-MITTS population. At Day 12 (primary endpoint), composite response for the micro-MITTR population was 48.1% in the Orlynvah treated group and 32.9% in the ciprofloxacin treated group (treatment difference of 15.3; 95% CI [4.3, 25.8]; $p = 0.006$). However, for the micro-MITTS population, composite response was 60.4% for Orlynvah versus 71.8% for ciprofloxacin (treatment difference of -11.1; 95% CI [-17.9, -4.8]).

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Complicated Urinary Tract Infections - Lack of Efficacy

Orlynvah is not indicated for the treatment of complicated urinary tract infections. Trial 3 was a phase 3, multi-center, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of intravenous (IV) sulopenem followed by oral sulopenem etzadroxil and probenecid with that of IV ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate for the treatment of complicated urinary tract infections. Trial 3 did not demonstrate the efficacy of sulopenem IV followed by oral sulopenem etzadroxil and probenecid for the primary endpoint of composite response (combined clinical and microbiologic response) in the micro-MITT population at the test-of-cure visit on Day 21.

Complicated Intra-abdominal Infections - Lack of Efficacy

Orlynvah is not indicated for the treatment of complicated intra-abdominal infections. Trial 4 was a phase 3, multi-center, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem etzadroxil and probenecid with that of IV ertapenem followed by oral ciprofloxacin and metronidazole or amoxicillin/clavulanate for the treatment of complicated intra-abdominal infections. Trial 4 did not demonstrate the efficacy of IV sulopenem followed by oral sulopenem etzadroxil and probenecid for the primary endpoint of clinical response in the micro-MITT at the test-of-cure visit on Day 28.

References

1. Orlynvah [package insert]. Iterum Therapeutics US Limited. Chicago, IL. Updated March 2025.
2. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103-e120.
3. Infectious Diseases Society of America. Clinical Practice Guideline for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women. IDSA website. <https://www.idsociety.org/practice-guideline/urinary-tract-infection-in-women>. Published March 2011. Accessed November 3, 2025.
4. Infectious Disease Society of America. 2025 Guideline on Management and Treatment of Complicated Urinary Tract Infections. IDSA website. <https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections>. Published July 17, 2025. Accessed 11/3/2025.
5. Orlynvah New Drug Review. IPD Analytics. December 2024.
6. Orlynvah Drug Evaluation. Express Scripts. November 2024.
7. Anger J, Lee U, Ackerman L, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. *J Urol*. 2019;202:282-289.

Policy History

Original Effective Date: 02/01/2026

Current Effective Date: 02/01/2026

01/05/2026 Medical Policy Committee review

01/07/2026 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 01/2027

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Original Effective Date: 02/01/2026

Current Effective Date: 02/01/2026

***Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.