

## PHARMACY COVERAGE GUIDELINE

### BLUJEPa (gepotidacin) oral

### ORLYNVAH™ (sulopenem etzadroxil and probenecid) oral

### PIVYA (pivmecillinam) oral

### Generic Equivalent (if available)

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#### **This Pharmacy Coverage Guideline (PCG):**

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively “Service”) is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider’s judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member’s benefit plan; and
- Is subject to change as new information becomes available.

#### **Scope**

- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

#### **Instructions & Guidance**

- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The “Criteria” section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member’s benefit plan.
- The “Description” section describes the Service.
- The “Definition” section defines certain words, terms or items within the policy and may include tables and charts.
- The “Resources” section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy). You must fully complete the [request form](#) and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to [Pharmacyprecert@azblue.com](mailto:Pharmacyprecert@azblue.com).

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#### **Criteria:**

- **Criteria for therapy:** Orlynvah (sulopenem etzadroxil and probenecid), Blujepa (gepotidacin), Pivya (pivmecillinam), and/or generic equivalent (if available) is considered **medically necessary** and will be approved when **ALL** the following criteria are met:
  1. Prescriber is a physician specializing in the patient’s diagnosis or is in consultation with an Infectious Disease Specialist
  2. Individual age is **ONE** of the following:
    - a. **For Blujepa:** 12 years of age or older female weighing at least 40 kg
    - b. **For Orlynvah and Pivya:** 18 years of age or older female

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3. Individual has a confirmed diagnosis of treatment of uncomplicated urinary tract infections (uUTI) caused by **ONE** of the following:
  - a. **For Blujepa:** ONE of the following urinary pathogens: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii* complex, *Staphylococcus saprophyticus*, and *Enterococcus faecalis*
  - b. **For Orlynvah:** ONE of the following urinary pathogens: *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis* in an individual who has limited or no alternative oral antibacterial treatment options
  - c. **For Pivya:** ONE of the following urinary pathogens: *Escherichia coli*, *Proteus mirabilis* and *Staphylococcus saprophyticus*
4. Individual has **BOTH** of the following:
  - a. **TWO** of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain
  - b. Evidence of pyuria on urinalysis
5. The individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
  - a. **For Blujepa:**
    - i. Correct serum electrolyte abnormalities
    - ii. Electrocardiogram (ECG)
    - iii. Has risk factors for multidrug resistant (MDR) gram-negative infection ([see Definitions section](#)) **AND** culture and sensitivity data show no oral antibacterial alternative options
  - b. **For Orlynvah:**
    - i. Has risk factors for multidrug resistant (MDR) gram-negative infection ([see Definitions section](#)) **AND** culture and sensitivity data show no oral antibacterial alternative options
6. Individual **does not have** signs and symptoms suggestive of acute pyelonephritis such as fever (temperature >38°Celsius or 100.4 Fahrenheit), chills, costovertebral angle tenderness, rigors, flank pain, nausea, and/or vomiting
7. Requested agent will **not** be used for **ANY** of the following:
  - a. Treatment of complicated urinary tract infections (cUTI)
  - b. Step-down treatment after intravenous antibacterial treatment of cUTI
  - c. Treatment of complicated intra-abdominal infections (cIAI)
  - d. Step-down treatment after intravenous antibacterial treatment of cIAI
8. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ALL** the following:
  - a. Nitrofurantoin
  - b. Trimethoprim/sulfamethoxazole or trimethoprim alone (if has sulfonamide allergy)
  - c. Fosfomycin
  - d. Beta-lactam antibiotic (e.g., amoxicillin/clavulanate, cephalexin, cefdinir, cefpodoxime)
  - e. Fluoroquinolone (e.g., ciprofloxacin, levofloxacin)

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9. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] ([see Definitions section](#))
10. **Additional criteria for Blujepa:** Individual has **NONE** of the following:
- A history of QTc prolongation or relevant pre-existing cardiac disease
  - Using drugs known to prolong the QTc interval
  - Using drugs that are strong CYP3A4 inhibitors
  - Using drugs that are strong CYP3A4 inducers
  - Using CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine, quinidine, others)
  - Severe hepatic impairment (Child-Pugh Class C)
  - Severe renal impairment (estimated glomerular filtration rate less than 30 mL/min)
11. **Additional criteria for Orlynvah:** Individual has **NONE** of the following:
- History of hypersensitivity to the components of Orlynvah (sulopenem etzadroxil and probenecid) or other beta-lactam antibacterial drugs
  - Known blood dyscrasias
  - Known uric acid kidney stones
  - Concomitant use of ketorolac tromethamine or ketoprofen
  - A creatinine clearance (CrCL) less than 15 mL/min and is not on hemodialysis
12. **Additional criteria for Pivya:** Individual has **NONE** of the following:
- Serious hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to other beta-lactam antibacterial drugs (e.g., penicillins, carbapenems, cephalosporins)
  - Primary or secondary carnitine deficiency resulting from inherited disorders of mitochondrial fatty acid oxidation and carnitine metabolism, and other inborn errors of metabolism (e.g., methylmalonic aciduria, or propionic acidemia)
  - Porphyria
  - Using valproic acid, valproate or other pivalate-generating drugs

#### **Approval duration:**

Blujepa: 20 tablets for 5 days

Orlynvah: 10 tablets for 5 days

Pivya: 21 tablets for 7 days

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

- Off-Label Use of Non-Cancer Medications**
- Off-Label Use of Cancer Medications**

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#### **Description:**

Blujepa (gepotidacin) is indicated for the treatment of adult and pediatric female patients 12 years of age and older weighing at least 40 kilograms (kg) with uncomplicated urinary tract infections (uUTI) caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii* complex, *Staphylococcus saprophyticus*, and *Enterococcus faecalis*. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Blujepa and other antibacterial drugs, Blujepa should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

Orlynvah (sulopenem etzadroxil and probenecid) a combination of sulopenem etzadroxil, a penem antibacterial, and probenecid, a renal tubular transport inhibitor, 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. Orlynvah is **not** indicated for the treatment of complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI and it is **not** indicated for the treatment of complicated intra-abdominal infections (cIAI) or as step-down treatment after intravenous antibacterial treatment of cIAI.

Pivya (pivmecillinam) is a penicillin class antibacterial indicated for the treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis* and *Staphylococcus saprophyticus*. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Pivya and other antibacterial drugs, Pivya should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Gepotidacin is a triazaacenaphthylene antibacterial that inhibits Type II topoisomerases including bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, thereby inhibiting DNA replication. The 24-hour free-drug area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio has been shown to be the PK-PD index predictive of gepotidacin antibacterial efficacy. Gepotidacin demonstrates bactericidal activity against pathogens.

Sulopenem etzadroxil is a prodrug that is hydrolyzed to the active drug sulopenem after oral administration. Sulopenem has activity against *in vitro* gram-positive and gram negative aerobic and anaerobic bacteria. Similar to other beta-lactam antimicrobial drugs, the percentage of time that unbound plasma concentrations of sulopenem exceed the sulopenem MIC against the infecting organism has been shown to best correlate with efficacy in models of infection *in vitro*.

Pivmecillinam is a prodrug of mecillinam (the active antibacterial agent), is converted to mecillinam and pivalic acid by non-specific esterases. Like other beta-lactam antibacterial drugs, the bacteriological effect in the treatment of uUTI is dependent on time above MIC, which has been shown to best correlate with efficacy in animal models of infection against *E. coli*.

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#### **Definitions:**

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting  
[MedWatch Forms for FDA Safety Reporting | FDA](#)

ORIGINAL EFFECTIVE DATE: 11/20/2025 | ARCHIVE DATE: | LAST REVIEW DATE: 11/20/2025 | LAST CRITERIA REVISION DATE:

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#### **Risk factors for multidrug resistant (MDR) gram-negative infections:**

A history of ANY of the following in the prior 3 months:

- A prior multidrug resistant gram-negative urinary isolate
- Inpatient stay at a health care facility (e.g., hospital, nursing home, long-term acute care facility)
- Use of fluoroquinolone, trimethoprim-sulfamethoxazole, or broad-spectrum beta-lactam (e.g., 3<sup>rd</sup> or later generation cephalosporin)
- Travel to parts of the world with high rates of multidrug resistant organisms (e.g., India, Israel, Spain, Mexico)

An MDR isolate is non-susceptible to at least one agent in three or more antimicrobial classes; this includes ESBL-producing isolates

#### **Treatments uncomplicated urinary tract infections (UTIs):**

Several oral antibacterial agents are used; depending on various factors, including local resistance patterns, patient history (allergies, prior antibiotic use), and potential side effects

#### *First-line oral antibiotics recommended for uncomplicated UTIs:*

- Nitrofurantoin (Macrobid, Macrochantin, Furadantin): Retains activity against some MDR organisms. It is not recommended in patients with significantly reduced kidney function (GFR less than 30 mL/min).
- Trimethoprim/sulfamethoxazole (Bactrim, Septra): Avoided if the known community prevalence of resistance among Enterobacteriaceae is >20%.
- Trimethoprim: Alone if have sulfonamide allergy. Avoided if the known community prevalence of resistance among Enterobacteriaceae is >20%.
- Fosfomycin (Monurol): Retains activity against some MDR organisms.
- Pivmecillinam (Pivya): A newer penicillin-class antibiotic specifically for uncomplicated UTIs in adults, retains activity against some MDR organisms.

#### *Second-line or alternative options (depending on resistance and individual circumstances):*

- Beta-lactam antibiotics (e.g., amoxicillin/clavulanate, cephalexin, cefdinir, cefpodoxime).
- Fluoroquinolones (e.g., ciprofloxacin, levofloxacin): There are concerns about side effects and the potential for increased antibiotic resistance. Reserve for situations where other options are not viable.

#### *Other alternatives:*

- Gepotidacin (Blujepa): Retains activity against some MDR organisms, reserve for situations where other options are not viable.
- Sulopenem/probenecid (Orlynvah): Retains activity against some MDR organisms, reserve for situations where other options are not viable.

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#### **Resources:**

Blujepa (gepotidacin) product information, revised by GlaxoSmithKline, LLC. 03-2025. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed July 28, 2025.

Orlynvah (sulopenem etzadroxil and probenecid) product information, revised by Iteum Therapeutics US Limited. 03-2025. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed July 28, 2025.

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Pivya (pivmecillinam) product information, revised by Utility Therapeutics, Ltd. 04-2024. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed August 02, 2025.

Gupta K. Acute simple cystitis in female adults. In: UpToDate, Calderwood SB, Ghanem KG, Bloom A (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at <http://uptodate.com>. Literature current through June 2025. Topic last updated on April 08, 2025. Accessed July 28, 2025.

Dunne MW, Aronin SI, Das AF, et al.: Sulopenem or ciprofloxacin for the treatment of uncomplicated urinary tract infections in women: A phase 3, randomized trial. Clin Infect Dis 2023 Jan; 76 (1): 66-77. Accessed July 28, 2025.

Perry C, Hossain M, Powell M, et al. Design of Two Phase III, Randomized, Multicenter Studies Comparing Gepotidacin with Nitrofurantoin for the Treatment of Uncomplicated Urinary Tract Infection in Female Participants. Infect Dis Ther. 2022 Dec;11(6):2297-2310. doi: 10.1007/s40121-022-00706-9. Epub 2022 Oct 21. Accessed August 03, 2025.

Vik I, Bollestad M, Grude N, et al. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women - A double-blind, randomized non-inferiority trial. PLoS Med 15(5):e1002569. <https://doi.org/10.1371/journal.pmed.1002569>. Accessed August 3, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04020341: A Phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis). Available from: <http://clinicaltrials.gov>. Last update posted June 22, 2023. Last verified May 2023. Accessed August 02, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04187144: A Phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis). Available from: <http://clinicaltrials.gov>. Last update posted July 18, 2023. Last verified July 2023. Accessed August 02, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03354598: A Prospective Phase 3 Randomized Multi-center Double-blind Study of Efficacy Tolerability & Safety of Oral Sulopenem-etzadroxil/Probenecid vs Ciprofloxacin for Treatment of Uncomplicated Urinary Tract Infections (uUTI) in Adult Women. Available from: <http://clinicaltrials.gov>. Last update posted January 01, 2021. Last verified December 2019. Accessed July 28, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT05584657: A Prospective, Phase 3, Randomized, Multi-center, Double-blind Study of the Efficacy, Tolerability, and Safety of Oral Sulopenem Etzadroxil/Probenecid Versus Oral Amoxicillin/Clavulanate for Treatment of Uncomplicated Urinary Tract Infections (uUTI) in Adult Women. Available from: <http://clinicaltrials.gov>. Last update posted November 20, 2024. Last verified October 2024. Accessed July 28, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT01849926: Ibuprofen Versus Mecillinam for Uncomplicated Cystitis in Adult, Non-pregnant Women. Available from: <http://clinicaltrials.gov>. Last update posted November 06, 2017. Last verified November 2017. Accessed August 03, 2025.