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New Drug Evaluations: gepotidacin, pivmecillinam, and sulopenem etzadroxil/probenecid

Date of Review: August 2025
Generic Name: gepotidacin
Generic Name: pivmecillinam
Generic Name: sulopenem etzadroxil/probenecid

End Date of Literature Search: 06/01/2025
Brand Name (Manufacturer): Blujepa (GSK)
Brand Name (Manufacturer): Pivya (Utility therapeutics)
Brand Name (Manufacturer): Orlynvah (Iterum Therapeutics)
Dossier Received: No (applies to all 3 drugs)

Plain Language Summary:

- This review looks at the evidence for 3 new medicines used for the treatment of urinary tract infections (UTIs), caused by bacteria, which affect the bladder. Medicines used to treat infections are called antibiotics. The new antibiotics are ORLYNVAH (sulopenem/probenecid), BLUJEPA (gepotidacin) and PIVYA (pivmecillinam).
- Antibiotics are used to treat UTIs because they reduce symptoms such as painful urination (i.e. peeing), how often people must urinate, and burning associated with urinating. How well they work is measured by reducing the bacteria, also called germs, in the urine that cause UTIs. If a UTI is not treated with an antibiotic it could spread elsewhere in the body, such as the kidney.
- The antibiotic used most often to treat UTIs is nitrofurantoin.
- Some antibiotics do not work in all patients as bacteria become resistant to the effects of the antibiotic.
- The new antibiotics approved for UTIs are to be used in patients who are known to have infections caused by certain bacteria that can be identified by a lab test called a urine culture.
- A study of sulopenem/probenecid found that it worked better than ciprofloxacin, another antibiotic used for UTIs, for the treatment of UTI by reducing symptoms and bacteria in the urine in patients who had infections caused by bacteria that were resistant to ciprofloxacin.
- Two studies found that the antibiotic gepotidacin was no different than slow-release nitrofurantoin for reducing symptoms of UTI and bacteria in the urine.
- Pivmecillinam was found to be more effective than a sugar pill (placebo) for the treatment of UTI for reducing symptoms and bacteria in the urine.
- The most common adverse reactions experienced with the 3 new antibiotics used for UTIs are nausea, vomiting and diarrhea.
- Providers must request the new antibiotics for patients if other antibiotics are not an option through a process called prior authorization.

Research Questions:

1. What is the evidence for efficacy of the new drugs for uncomplicated urinary tract infection (uUTI), sulopenem/probenecid, gepotidacin, and pivmecillinam?
2. What is the evidence for the safety of the new drugs for uUTI, sulopenem/probenecid, gepotidacin, and pivmecillinam?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender, disease severity), for whom the new drugs for uUTI are more effective or associated with less harm?

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Conclusions:

- The evidence for sulopenem/probenecid, gepotidacin, and pivmecillinam are presented and reviewed in the following 6 studies.

Sulopenem/probenecid

- A double-blind, double-dummy randomized controlled trial (RCT) compared 5 days of therapy with sulopenem/probenecid to ciprofloxacin in females with uUTI.[1] For the primary endpoint of overall response of the combined clinical and microbiologic response at day 12, there is moderate quality evidence that sulopenem/probenecid was noninferior to ciprofloxacin in the modified intent to treat (mITT) population. The Food and Drug Administration (FDA) also recommended that the primary endpoint be analyzed in 2 subsets of the population; patients with baseline pathogens susceptible to ciprofloxacin and in patients who had ciprofloxacin resistant organisms at baseline. There is moderate quality evidence that sulopenem/probenecid is superior to ciprofloxacin in patients with ciprofloxacin resistant organisms for the outcome of overall response, which combined clinical (e.g., resolution of patient reported UTI symptoms and no new UTI symptoms) and microbiological response (e.g., reduction of all baseline uropathogens to less than 10^3 colony forming units (CFU)/mL in the urine). The combination of sulopenem/probenecid was not noninferior to ciprofloxacin in patients who had ciprofloxacin susceptible organism.[1] Additional study details are presented in **Table 4.**
- The most frequent adverse events associated with sulopenem/probenecid after 5 days of treatment were diarrhea, nausea, vulvovaginal mycotic infections, headache and vomiting. Sulopenem/probenecid inhibits organic anion transporters 1 and 3 (OAT1/3) and can interfere with medications using this enzyme system for metabolism.[2] See **Table 2** for a list of drug interactions.
- Sulopenem/probenecid was studied in patients with complicated UTIs and complicated intraabdominal infections and found to not be effective for these indications and should not be used in these conditions.[2]

Gepotidacin

- Gepotidacin was studied in females with uUTI in 2, methodologically similar, double-blind, double-dummy, noninferiority RCTs (EAGLE-2 and EAGLE-3).[3] Both trials compared gepotidacin to slow release nitrofurantoin for 5 days. For the primary outcome of clinical and microbiological cure, there was moderate quality evidence that gepotidacin was noninferior to nitrofurantoin in both studies for the prespecified population of nitrofurantoin susceptible organisms. In EAGLE-3, gepotidacin was superior to nitrofurantoin (treatment difference [TD] 14.6%; 95% confidence interval [CI], 6.4 to 22.8; p=0.003).[3] Additional outcome information is presented in **Table 7**.
- The most common adverse events occurring in people treated with gepotidacin are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting and vulvovaginal candiasis.[4] See **Table 5** for adverse events compared to nitrofurantoin. Gepotidacin may prolong the QT interval and also is prone to drug interactions as it is metabolized by the CYP3A4 enzyme system.[4]

Pivmecillinam

- Pivmecillinam was studied in 3 trials in women with uUTI. There is low quality evidence that pivmecillinam is not noninferior to ibuprofen for symptom relief; however, for the secondary endpoint of positive urine culture at day 14, pivmecillinam treated patients had fewer positive cultures compared to ibuprofen (risk difference [RD] -16%; 95% CI, -26% to -7%; p<0.001; absolute risk reduction [ARR] 18%/number needed to treat [NNT] 6).[5] Pivmecillinam was not superior to cephalexin based on the outcome of clinical cure (odds ratio [OR] 1.40; 95% CI, 0.4 to 4.6; P=0.58) or microbiological cure (OR 1.96; 95% CI, 0.9 to 4.3; p=0.09) (low quality evidence) (noninferiority not assessed).[6] There is low quality evidence that pivmecillinam is superior to placebo for the treatment of uUTI (ARR 52%/NNT 2).[7]
- The most common adverse events associated with pivmecillinam use in clinical trials were nausea and diarrhea (see **Table 8**).[8]
- There is no evidence available for the use of the new antibiotics for uUTI specifically in the Medicaid population or in specific subgroups.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of the evidence for the new drugs for uUTI. Nonpreferred antibiotics are subject to the non-preferred prior authorization (PA) criteria.
- Maintain sulopenem/probenecid, pivmecillinam and gepotidacin as nonpreferred.

Background:

Urinary tract infections are more common and more likely to occur in women than in men.[9] The incidence of UTI is at least one infection per year in 10-20% of adult women in the United States (US). Urinary tract infections are designated as uncomplicated or complicated based on infection location. Uncomplicated infections are confined to the bladder and occur in healthy, non-pregnant women or men.[9] A complicated UTI is a systemic infection extending beyond the bladder to the kidneys (e.g., pyelonephritis). The European Association of Urology (EAU) has recommended new nomenclature for the definitions of UTI which are localized (i.e., cystitis without any signs of systemic infection in either sex) and systemic UTI (i.e., an infection with signs and symptoms of systemic infection with or without localized symptoms that may originate from any site in the urinary tract of either sex, including pyelonephritis and prostatitis).[9] Asymptomatic bacteriuria occurs in individuals without symptoms. Asymptomatic bacteriuria is more common in the elderly and usually does not require treatment. The exception is those that are pregnant, renal transplant or undergoing a urological procedure in which treatment recommendations are similar to uUTI.[10] The focus of this review will be on the uUTIs related to the approval of 3 new antibiotics used for the treatment of uUTI. Symptoms of uUTI are: frequency, urgency, dysuria and suprapubic pain.[9] Risk factors for development of an uUTI are prior UTI, recent sexual intercourse and use of spermicides.

Patients presenting with uUTI are most often treated empirically. Most uUTIs are caused by *Escherichia coli (E. coli)*, accounting for approximately 75%-95% of infections.[11] Less common bacteria associated with uUTIs are *Proteus mirabilis (P. mirabilis), Klebsiella pneumonia* (*K. pneumonia*) and *Staphylococcus saprophyticus (S. saprophyticus)*.[11] Resistant uropathogens are more commonly seen in women 50 years and older, patients with recurrent uUTI, and patients with diabetes.[3] The most recent guidelines from the Infectious Disease Society of America (IDSA), published in 2011, recommend treatment options for women based on resistance patterns and the likely causative organisms.[11] Patient allergy, compliance, availability and cost should be considered. Empirical treatment with nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) , trimethoprim-sulfamethoxazole (TMP/SMX) (160/800 mg twice daily for 3 days), fosfomycin (3 gm single dose) or pivmecillinam (400 mg twice daily for 5 days) are all recommended as treatment options (pivmecillinam was approved in Europe prior to US approval).[11] The 2025 EAU guidelines recommend that TMP/SMX only be used empirically if resistance rates in the area of use are <20% for *E. coli*.[9] Fluoroquinolones (i.e., ofloxacin, ciprofloxacin and levofloxacin) can be considered as an option but are associated with adverse events and resistance. The Food and Drug Administration (FDA) put out a 2016 Safety Announcement advising against the use of fluoroquinolones for uUTIs who have other treatment options, due to the serious side effects associated with their use.[12] Guidance by the EAU enacted stringent regulatory actions recommending against the use of fluoroquinolones due to disabling and long-lasting adverse events associated with use.[9] The EAU guidance recommends fluoroquinolones only be used when it is inappropriate to use other antibiotics. Beta-lactam antibiotics (e.g., amoxicillin/clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil) may also be considered as an alternative, with consideration of high *E. coli* resistance rates with these medications. Resistant rates seen with TMP/SMX are approximately 25%, followed by approximately 21% being fluoroquinolone resistant. Beta-lactam antibiotics can have resistant rates up to 15% in the US.

Important outcomes in the study of uUTI are resolution of symptoms and microbiological cure to prevent the progression of the infection to pyelonephritis. The Food and Drug Administration (FDA) requires therapeutic success to be based on combined clinical success (i.e., symptom resolution) and microbiological success (i.e., reduction of qualifying uropathogens to $<10^3$ CFU/mL).[13]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Sulopenem/probenecid (ORLYMVAH)

Clinical Efficacy:
Sulopenem/probenecid is a combination tablet approved for the treatment of uUTI due to *E. coli, K. pneumoniae or P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.[2] Sulopenem/probenecid is a penem antibacterial, specifically a broad-spectrum thiopenem ß-lactam antibiotic with efficacy against multi-drug resistant bacteria.[2] Penem antibiotics differ from carbapenems because they have different chemical structures which confers a wider spectrum of action, especially against Gram-negative bacteria, associated with carbapenems. Sulopenem inhibits cell wall synthesis and is mediated through sulopenem binding to penicillin binding proteins (PBPs). Probenecid is a renal tubular transporter inhibitor, which increases sulopenem serum concentrations and extends the half-life of sulopenem. The dose is sulopenem 500 mg/probenecid 500 mg as one tablet twice daily for 5 days, with food if possible.[2] Sulopenem/probenecid is not indicated for treatment of complicated UTIs or as step-down treatment after intravenous (IV) antibacterial treatment of complicated UTI or for complicated intra-abdominal infections or as step-down treatment after IV antibacterial treatment of complicated intra-abdominal infections.

There is one published RCT that was used for the Food and Drug Administration (FDA) approval, which compared sulopenem/probenecid to ciprofloxacin .[1] Women, 18 years of age and older with a urinalysis positive for nitrite and either leukocyte esterase or microscopic evidence of white blood cells (WBC) indicating uUTI were included in the study (n=1,579). Samples were taken between 24 and 96 hours of onset of urinary symptoms. Culture and susceptibility testing was collected at each visit. Patients also had to have 2 or more signs or symptoms of uUTI (e.g., urinary frequency, urgency, dysuria, or suprapubic pain) for inclusion into the study.[1] Patients were excluded if they had fever, chills, costovertebral angle tenderness, flank pain, nausea, vomiting or fever. The modified intention to treat (mITT) population was studied. There were 785 (73.3%) women who had ciprofloxacin susceptible organisms (mITT-S) compared to those who had ciprofloxacin resistant organisms (mITT-R).[1] Those with non-susceptible organisms were more likely to have diabetes or those with a creatinine clearance <72 mL/minute. *E. coli* was the most common causative organism, present in approximately 85% patients in both the mITT-S and mITT-R groups. *K. pneumoniae* was the second most common organism (~11%) and *P. mirabilis* was the third most common (~5%).[1] In 53 (4.9%) of patients, pathogens were resistant to all 4 commonly used antibacterials (e.g., nitrofurantoin, quinolones, TMP-SMX, and ß-lactam). Thirty percent of patients had negative urine cultures but were still included in the MITT population.

The primary endpoint was overall response, which combined clinical (e.g., resolution of patient reported UTI symptoms and no new UTI symptoms) and microbiological response (e.g., reduction of all baseline uropathogens to less than 10^3 CFU/mL in the urine) on day 12.[1] The overall response was to be compared in 2 subsets by testing ciprofloxacin susceptible microbiological MITT (mMITT-S) and non-susceptible ciprofloxacin microbiological MITT (mMITT-R) patient samples from the mITT population. In the overall mITT group combined response was 65.6% in the sulopenem/probenecid group and 67.9% in the ciprofloxacin group. In the sulopenem group 28% were mITT-R and 72% were mMITT-S. In the ciprofloxacin group 25% of the samples were mITT-R and 75% were mITT-S. Superiority of sulopenem/probenecid to ciprofloxacin was based on the mMITT-R population and noninferiority was based on the comparison of sulopenem/probenecid to ciprofloxacin in the mMITT-S population.[1]

Results for the primary endpoint of clinical and microbiologic response demonstrated superiority of sulopenem/probenecid at 12 days compared to ciprofloxacin in the subset of patients in the mMITT-R group with an absolute difference of 26.6% (95% CI, 15.1 to 37.4; p-value not reported) (**Table 4**).[1] Sulopenem/probenecid was not noninferior to ciprofloxacin in the mMITT-S subset; however, sulopenem/probenecid was noninferior to ciprofloxacin in the full mMITT population.

Sulopenem/probenecid was also studied in a non-published, phase 3, double-dummy, double-blind, multi-center RCT.[14] Details are available via the FDA Other Reviews supplemental material.[14] The trial included 2,222 adult women with uUTI. Pyelonephritis, urinary tract abnormalities, and poorly controlled diabetes were all reasons for trial exclusion. Patients received sulopenem 500 mg/probenecid 500 mg twice daily for 5 days or 2 capsules of amoxicillin 875 mg/clavulanate 125 mg for 5 days.[14] The primary outcome was the overall treatment response, the clinical (e.g., urinary frequency,/urgency, pain/burning on micturition, suprapubic pain) and microbiological (e.g., quantitative culture results and sensitivity) on the test of cure (TOC) visit on day 12 for the mITT-R and mITT-S populations. For the mMITT-S population the success rate was 61.7% in the sulopenem/probenecid group compared to 55% in the amoxicillin/clavulanate group (TD 6.7% ; 95% CI, 0.3 to 13).[14] For the mMITT-R group success occurred in 22 (52.4%) of patients in the sulopenem/probenecid group versus 17 (68%) amoxicillin/clavulanate group (TD -15.6%; 95% CI, -37.5 to 9.1).[14] Success rates were higher in the amoxicillin/clavulanate group despite being labeled as resistant.

Sulopenem/probenecid was also studied in two additional studies as stepdown treatment following complicated UTI and complicated intrabdominal infection. Sulopenem/probenecid was inferior to comparative therapies and should not be used for these conditions as described in the labeling.[2]

Clinical Safety:
The most common adverse events associated with sulopenem/probenecid were diarrhea, nausea, vulvovaginal mycotic infections, headache and vomiting.[2] Individuals with hypersensitivity, blood dyscrasias, uric acid kidney stones, or taking ketorolac should not receive sulopenem/probenecid. Sulopenem/probenecid is contraindicated in patients with a history of hypersensitivity reactions to either component. Serious adverse reactions are hypersensitivity reactions and risk of clostridium difficile-associated diarrhea, which is associated with all antibiotics.[2] Probenecid has been associated with hepatic necrosis, anaphylaxis, aplastic anemia, leukopenia and hemolytic anemia.[2] It was noted several times in the FDA review that the tablets were large and patients had difficulty swallowing them.[14] Sulopenem/probenecid inhibits OAT1/3 which can increase drug concentrations of medications that use this enzyme system for elimination (**Table 2**). Sulopenem/probenecid should be taken with food to minimize gastrointestinal adverse reactions and increase the bioavailability of sulopenem. Use of sulopenem/probenecid in pregnant women has not been evaluated.[2]

Table 1. Adverse Events with Sulopenem/probenecid Occurring in >1% of Patients[2]

Adverse Reactions	Sulopenem/probenecid N=1,932	Amoxicillin/Clavulanate N=1,107	Ciprofloxacin N=822
Diarrhea	194 (10%)	45 (4%)	21 (3%)
Nausea	80 (4%)	32 (3%)	30 (4%)
Vulvovaginal mycotic infection	46 (2%)	13 (1%)	7 (1%)
Headache	42 (2%)	17 (2%)	18 (2%)
Vomiting	29 (2%)	4 (0.4%)	11 (1%)
Abdominal Pain	22 (1%)	11 (1%)	9 (1%)

Table 2. Clinically Significant Drug Interactions with Sulopenem/probenecid[2]

Concomitant Drug /Drug Class	Effect on Drug Concentration	Recommendation
Ketorolac tromethamine	Increased ketorolac tromethamine	Contraindicated
Ketoprofen	Increased ketoprofen	Concomitant use not recommended
Indomethacin	Increased indomethacin	May increase risk of adverse reactions
Naproxen	Increased naproxen	May increase the risk of adverse reactions
Methotrexate	Increased methotrexate	Monitor frequently for adverse events if concomitant use cannot be avoided
Rifampin	Increased rifampin	Monitor for adverse reactions more frequently
Lorazepam	Increased lorazepam	Follow lorazepam prescribing dosage modifications
Oral sulfonylureas	Increased sulfonylurea	Monitor for hypoglycemia. Follow dosage recommendations.

Look-alike / Sound-alike Error Risk Potential: none identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Microbiological eradication
2) Symptom improvement
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clinical and microbiological response

Table 3. Pharmacology and Pharmacokinetic Properties for Sulopenem/probenecid.[2]

Parameter	
Mechanism of Action	Sulopenem etzadroxil is a penem antibacterial and probenecid is a renal tubular inhibitor (used as pharmacokinetic booster to increase plasma concentrations of sulopenem and extend the half-life)
Oral Bioavailability	Sulopenem: 40-64%, probenecid: unknown
Distribution and Protein Binding	Volume of Distribution - sulopenem distribution: 92-134 L, probenecid: 8.81 to 11.94 L Protein binding: sulopenem: 11%, probenecid: unknown
Elimination	Sulopenem: 50.55-77.6 L/hour, probenecid: 2.06 to 2.22 L/hour
Half-Life	Sulopenem: 1.18 – 1.28 hours, probenecid: 2.93 to 3.83 hours
Metabolism	Sulopenem: hydrolyzed by esterases to active sulopenem then metabolized by hydrolysis followed by dehydrogenation in the kidneys Probenecid: hepatic metabolism via glucuronidation

Abbreviations: L=liter

Table 4. Comparative Evidence Table for Sulopenem/probenecid.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Dunne, et al[1] DB, DD, MC, RCT	1. Sulopenem 500 mg /probenecid 500 mg orally twice daily for 5 days 2. Ciprofloxacin 250 mg orally twice daily for 3 days	Demographics: Age: 53 years White: 90% Diabetic: 15% Ciprofloxacin susceptible: 73.3% *E. coli* organism: 85% Key Inclusion Criteria: - Female - 18 years and older - uUTI diagnosis - 2 or more signs/symptoms of UTI Key Exclusion Criteria: - Acute pyelonephritis - Treatment with antibacterial within the prior 7 days for uUTI - Concurrent use of non-study medications with potential to effect outcome (e.g., NSAIDs, aspirin, acetaminophen, phenazopyridine)	mITT:‡ 1. 785 2. 794 mITT-R: 1. 147 (28%) 2. 139 (25%) mITT-S: 1. 370 (72%) 2. 415 (75%) PP: 1. 517 2. 554 Attrition: 1. 268 (34%) 2. 240 (30%)	**Primary Endpoint:** Combined clinical and microbiologic response at day 12: mMITT* Sulopenem/probenecid: 339 (65.6%) Ciprofloxacin: 376 (67.9%) AD -2.3 (95% CI, -7.9 to 3.3) Noninferiority criteria met mMITT-R† Sulopenem/probenecid: 92 (62.6%) Ciprofloxacin: 50 (36.0%) AD 26.6 (95% CI, 15.1 to 37.4) p-value not reported mMITT-S* Sulopenem/probenecid: 247 (66.8%) Ciprofloxacin: 326 (78.6%) AD -11.8 (95% CI, -18.0 to -5.6) Noninferiority criteria not met **Secondary Endpoint:** Combined clinical and microbiologic response at day 5 (end of treatment): mMITT Sulopenem/probenecid: 335 (64.8%) Ciprofloxacin: 313 (56.5%) AD 8.3 (95% CI, 2.4.0 to 14.1) p-value not reported mMITT-R Sulopenem/probenecid: 95 (64.6%) Ciprofloxacin: 42 (30.2%) AD 34.3 (95% CI, 23.1.0 to 44.8) p-value not reported mMITT-S Sulopenem/probenecid: 240 (64.6%) Ciprofloxacin: 271 (65.3%) AD -0.4 (95% CI, -7.1 to 6.2) p-value not reported	NA ARR 26.6/ NNT 4 NA NA NA NA	Drug related adverse event: Sulopenem/ probenecid: 207 (24.8%) Ciprofloxacin: 115 (13.9%) Serious adverse reaction: Sulopenem/ probenecid: 6 (0.7%) Ciprofloxacin: 2 (0.2%) Diarrhea: Sulopenem/ probenecid: 103 (12.4%) Ciprofloxacin: 21 (2.5%) Nausea: Sulopenem/ probenecid: 32 (3.8%) Ciprofloxacin: 30 (3.6%) Headache: Sulopenem/ probenecid: 18 (2.2%) Ciprofloxacin: 18 (2.2%) p-value and CI not reported	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized by a centralized interactive web randomization system. There were more patients with diabetes in the mITT-R group by a difference of 6.9%. Performance Bias: Low. Patients received matched placebos to maintain blinding. Investigators were blinded to susceptibility results until after TOC assessments. Detection Bias: Unclear. Interim analysis performed by independent data monitoring committee. Methodology for analyzing results was not described. Attrition Bias: High. High attrition rates in both groups due primarily to negative urine cultures in both groups. Reporting Bias: Low. Results reported as outlined in protocol. Other Bias: High. Manufactured funded. **Applicability**: Patient: The patient population is representative of those most likely to get UTIs and from the most causative common organism which is *E. coli.* Intervention: The dose and duration of sulopenem/probenecid is appropriate. Comparator: The dose of ciprofloxacin is the recognized dose for the treatment of female UTIs; however, the use of cipro is not recommended first-line for uUTIs due to adverse events. Outcomes: Clinical and microbiologic response are appropriate endpoints for the evaluation of antibiotic efficacy. Setting: Multicenter (142 sites) in 4 countries (specifics not provided).

Key: † Superiority comparison; * Noninferiority comparison; ‡Urine negative cultures excluded from mITT analysis
Abbreviations: AD = absolute difference; ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; DB = double-blind. DD = double-dummy; ITT = intention to treat; MC = multi-center; mITT = modified intention to treat; mITT-R = modified intention to treat in ciprofloxacin resistant organisms; mITT-S = modified intention to treat in ciprofloxacin susceptible organisms; N = number of subjects; NA = not applicable; NI = noninferiority; NNT = number needed to treat; NSAIDs = nonsteroidal anti-inflammatory drugs; PP = per protocol; RCT = randomized controlled trial; TD = treatment difference; TOC = test of cure; UTI = urinary tract infection; uUTI = uncomplicated urinary tract infection.

Gepotidacin (BLUJEPA)

Clinical Efficacy:

Gepotidacin is a triazaacenaphtheylene bacterial type II topoisomerase inhibitor.[4] Gepotidacin blocks DNA replication by the inhibition of DNA gyrase and topoisomerase IV. Gepotidacin is indicated for the treatment of uUTI infections in female adult and pediatric patients 12 years of age and older who are at least 40 kg with the following susceptible organisms: *E. coli, K. pneumoniae, C. freundii* complex, *S. saphrophyticus*, and *E. faecalis*.[4] Gepotidacin is given as two 750 mg (1500 mg) tablets twice daily for 5 days, to be taken after a meal.[4]

Gepotidacin was studied in 2 similar methodologically designed studies to determine efficacy.[3] Both studies were randomized, double-blind, double-dummy, phase 3, non-inferiority studies comparing gepotidacin 1500 mg twice daily for 5 days to nitrofurantoin 100 mg (slow release formulation) twice daily for 5 days (EAGLE-2 and EAGLE-3).[3] Patients were randomized 1:1 and stratified by age and history of recurrent uUTI. Symptoms were accessed at baseline, on-treatment (day 2-4), TOC (day 10-13) and follow-up (day 25-31) and scored from 0-3 with 0 being none and 3 being severe. Symptoms were assessed by a provider or trained medical staff.[3] Urine samples were taken at each visit and underwent culture and susceptibility testing. Patients could have one or 2 identified pathogens. Qualifying uropathogens were: gram-negative bacilli, *S. saphrophyticus* or *Enterococcus* species at concentrations of $\geq 10^5$ CFU/mL.[3] The average of age of participant was 52 years and 50 years in EAGLE-2 and EAGLE-3, respectively. There was only 1 patient under the age of 18 years randomized to gepotidacin included in EAGLE-3 and none in EAGLE-2.[3] There were 4 nitrofurantoin patients under the age of 18 enrolled between the 2 studies. The majority of patients in both studies were positive for *E. coli*.[3]

The primary endpoint was therapeutic response at TOC, which combined clinical (e.g., symptom score of 0) and microbiological response (e.g., reduction of qualifying uropathogens to less than 10^3 CFU/mL in the urine). Uropathogens had to be susceptible to nitrofurantoin to be included in the microbiological intention to treat (ITT) nitrofurantoin (NTF-S) population.[3] Both studies were stopped early due to efficacy after interim analysis. The primary analysis population included patients at the time of the interim analysis cutoff, had the opportunity to reach the TOC visit or who were known to have achieved therapeutic success before the TOC visit.

Results are for described for the microbiological ITT NTF-S unless specifically stated. Gepotidacin was non-inferior to nitrofurantoin in both studies. Gepotidacin achieved therapeutic success with 50.6% of gepotidacin patients compared to 47.0% for nitrofurantoin (TD 4.3%; 95% CI, -3.6 to 12.1) in EAGLE-2.[3] In EAGLE-3, gepotidacin was noninferior and superior to nitrofurantoin (TD 14.6%; 95% CI, 6.4 to 22.8; p=0.003). Statistical superiority for gepotidacin was most likely due to a higher microbiological failure in the nitrofurantoin group and less discordance between clinical and microbiological response in the gepotidacin group. More women used another antibiotic concurrently for uUTI in those taking nitrofurantoin (4.2%) compared to gepotidacin (1.6%) in EAGLE-2 and 6.5% for gepotidacin and 5.3% for nitrofurantoin in EAGLE-3.[3] In EAGLE-2 clinical success was the same between groups (65%) and higher in the gepotidacin group (67.9%) compared to nitrofurantoin (63.3%) in EAGLE-3. Gepotidacin resulted in a higher percentage of microbiological cure compared to nitrofurantoin in EAGLE-2, 72.5% versus 67.6% (TD 5.2%, 95% CI, -2.1 to 12.5).[3] In EAGLE-3 microbiological cure was higher with gepotidacin compare to nitrofurantoin, 72.2% versus 57.2% (TD 15.0%, 95% CI, 7.2 to 22.9). Microbiological failure was due to missing cultures or taking other antibiotic in the gepotidacin group and microbiological recurrence with

nitrofurantoin. Therapeutic success rates for those with *E. coli* was higher in gepotidacin treated patients compared to nitrofurantoin in both studies; EAGLE-2, 51.1% and 45.9% and EAGLE-3, 59.8% and 44.0%.[3]

The scoring of uUTI symptoms was subjective. There was discordance in clinical and microbiologic failure rates that can influence results but is not uncommon in trials studying antibiotics for uUTI.

Clinical Safety:
The most common adverse events associated with the use of gepotidacin are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting and vulvovaginal candidiasis.[4] See **Table 5** for specific adverse event rates.

Table 5. Adverse Events with Gepotidacin Occurring in 1% or More Patients than Nitrofurantoin[4]

Adverse Event	Gepotidacin (N=1,570)	Nitrofurantoin (N=1,558)
Diarrhea	258 (16%)	51 (3%)
Nausea	146 (9%)	64 (4%)
Adnominal pain	60 (4%)	34 (2%)
Flatulence	43 (3%)	8 (<1%)
Headache	38 (2%)	40 (3%)
Soft feces	37 (2%)	8 (<1%)
Dizziness	29 (2%)	19 (1%)
Vomiting	28 (2%)	10 (<1%)
Vulvovaginal candidiasis	20 (1%)	18 (1%)

Gepotidacin may prolong the QT interval and should be avoided in patients with a history of QT prolongation, those with relevant cardiovascular (CV) disease or taking other drugs that may prolong the QT interval.[4] Gepotidacin should not be taken with drugs that cause CYP3A4 inhibition and in those with severe hepatic (Child-Pugh Class C) or renal (estimated glomerular filtration rate [eGFR] <30 ml/min) impairment due to the risk of increased concentrations of gepotidacin.[4] Reports of dysarthria (i.e., slurred speech) have been reported with gepotidacin. Use of gepotidacin with anticholinesterase inhibitors, succinylcholine-type neuromuscular blocking agents, systemic anticholinergic medications or non-depolarizing neuromuscular blocking agents may exacerbate underlying medical conditions.[4] As with all antibiotics there is a risk of *C. difficile* infection.

Look-alike / Sound-alike Error Risk Potential: may be confused with gentamicin.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Microbiological eradication
2) Symptom improvement
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clinical and microbiological response

Table 6. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	Triazaacenaphthylene antibacterial that inhibits Type II topoisomerases including bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, thereby inhibiting DNA replication
Oral Bioavailability	45%
Distribution and Protein Binding	172.9 L 25-41%
Elimination	33.4 L/hr
Half-Life	9.3 hours
Metabolism	Oxidative metabolism mediated by CYP3A4, producing several circulating metabolites

Abbreviations: CYP = cytochrome P450 enzymes; DNA = deoxyribonucleic acid; hr = hour; L = Liters

Table 7. Comparative Evidence Table for Gepotidacin.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Wagenlehner, et al[3] EAGLE-2, DB, DD, MC, NI, Phase 3, RCT	1. Gepotidacin orally 1500 mg twice daily for 5 days 2. Nitrofurantoin slow-release formulation orally 100 mg twice daily for 5 days	Demographics: Age: 52 years White: 84% BMI: 26.9 History of recurrent UTI: 40% Total symptom score: 7.2 *E coli* organism: 90% Key Inclusion Criteria: - Female - 12 years and older - Nonpregnant - ≥ 40 kg - ≥ 2 signs/symptoms of UTI - Urinary nitrite, pyuria or both Key Exclusion Criteria: - Uncontrolled diabetes - Symptoms known to be caused by another disease process - Anatomical or physiological anomaly that might predispose patient to UTI - Complicated UTI - CrCl <60 mL/min	ITT: 1. 320 2. 287	Primary Endpoint: Combined clinical and microbiologic response at day 10 to 13 (nitrofurantoin-susceptible qualifying uropathogen): 1. Gepotidacin: 162 (50.6%) 2. Nitrofurantoin: 135 (47.0%) TD -4.3% (95% CI, -3.6 to 12.1) Noninferiority criteria met Secondary Endpoint: Clinical Success: 1. Gepotidacin: 210 (65.6%) 2. Nitrofurantoin: 187 (65.2%) TD 1.2% (95% CI, -6.3 to 8.7) Noninferiority criteria met Microbiological Success: 1. Gepotidacin: 232 (72.5%) 2. Nitrofurantoin: 194 (67.6%) TD 5.2% (95% CI, -2.1 to 12.5) Noninferiority criteria met	NA NA NA	Drug related adverse event: Gepotidacin: 197 (26%) Nitrofurantoin: 93 (12%) Diarrhea: Gepotidacin: 258 (16%) Nitrofurantoin: 51 (3%) Nausea: Gepotidacin: 146 (9%) Nitrofurantoin: 64 (4%) Serious adverse reaction: Gepotidacin: 2 (<1%) Nitrofurantoin: 3 (<1%) Adverse events leading to discontinuation: Gepotidacin: 27 (4%) Nitrofurantoin: 18 (2%) Safety population: Gepotidacin n=766 Nitrofurantoin n=760	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized 1:1 by a centralized by interactive response technology. Baseline demographics were well matched. Performance Bias: Low. Patients received matched placebos to maintain blinding. Patients, investigators and sponsor study team were blinded to treatment assignment. Detection Bias: Unclear. Scoring of symptoms was subjective and could increase risk of bias. Gastrointestinal adverse events were more common with gepotidacin and could result in unblinding. Attrition Bias: Unclear. Analysis of interim data and no data on per protocol population numbers provided for this interim set. Reporting Bias: Unclear. Results were analyzed on the interim ITT set for the primary endpoint because the trial was stopped early due to efficacy. Other Bias: High. Manufactured funded. Authors were employees, shareholders and/or advisors with GSK.

								Applicability: Patient: The patient population is representative of those most likely to get UTIs and from the most causative common organism which is *E. coli.* Intervention: The dose and duration of gepotidacin is appropriate. Comparator: Nitrofurantoin is a first-line treatment option for uUTI and is an appropriate comparator at the study dose. The dose and treatment duration were appropriate. Outcomes: Clinical and microbiologic response are appropriate endpoints for the evaluation of antibiotic efficacy. Setting: Multicenter (219 sites) in 15 countries for both studies.
2. Wagenlehner, et al[3] EAGLE 3 DB, DD, MC, NI, Phase 3, RCT	1. Gepotidacin 1500 mg twice daily for 5 days 2. Nitrofurantoin slow-release formulation 100 mg twice daily for 5 days	Demographics: Age: 50 years White: 85% BMI: 27.2 History of recurrent UTI: 41% Total symptom score: 7.4 *E coli* organism: 90% Key Inclusion Criteria: - See above Key Exclusion Criteria: - See above	ITT: 1. 277 2. 264	**Primary Endpoint:** Combined clinical and microbiologic response at day 10 to 13 (nitrofurantoin-susceptible qualifying uropathogen): 1. Gepotidacin: 162 (58.5%) 2. Nitrofurantoin: 115 (43.6%) TD -14.6% (95% CI, 6.4 to 22.8) P=0.0003 Noninferiority criteria met, and superiority was confirmed in sequential testing **Secondary Endpoint:** Clinical Success: 1. Gepotidacin: 188 (67.9%) 2. Nitrofurantoin: 167 (63.3%) TD 4.4% (95% CI, -3.5 to 12.3) Noninferiority criteria met Microbiological Success: 1. Gepotidacin: 200 (72.2%) 2. Nitrofurantoin: 151 (57.2%) TD 15.0% (95% CI, 7.2 to 22.9) Noninferiority criteria met	ARR 14.6/ NNT 7 NA NA	Drug related adverse event: Gepotidacin: 221 (27%) Nitrofurantoin: 108 (14%) Serious adverse reaction: Gepotidacin: 5 (<1%) Nitrofurantoin: 5 (<1%) Adverse events leading to discontinuation: Gepotidacin: 52 (6%) Nitrofurantoin: 12 (2%) Safety population: Gepotidacin n=804 Nitrofurantoin n=798	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: See above. Performance Bias: See above. Detection Bias: See above. Attrition Bias: See above. Reporting Bias: See above. Other Bias: See above. **Applicability**: Patient: See above. Intervention: See above. Comparator: See above. Outcomes: See above. Setting: See above.

Abbreviations: ARR = absolute risk reduction; BMI = body max index; CI = confidence interval; CrCl = creatinine clearance; DB = double-blind. DD = double-dummy; ITT = intention to treat; kg = kilogram; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = noninferiority; NNT = number needed to treat; PP = per protocol; RCT = randomized controlled trial; TD = treatment difference; UTI = urinary tract infection.

Pivmecillinam (PIVYA)

Clinical Efficacy:

Pivmecillinam is a penicillin antibacterial used for the treatment of uUTI in female patients 18 years old and older caused by susceptible isolates of *E. coli, P. mirabilis and S. saprophyticus.*[8] Pivmecillinam is given as a single 185 mg tablet by mouth 3 times a day for 3-7 days as clinically indicated.

Pivmecillinam was studied in 3, phase 3, clinical trials for evidence for FDA approval. The first trial was a dosing study in Sweden.[7] The second trial compared pivmecillinam to cephalexin and the third trial was a trial comparing pivmecillinam to ibuprofen.[5,6]

In a 2007 study, pivmecillinam was compared to placebo in adult women (n=1162) with symptoms of uUTI in a multi-center, randomized, double-blind study in Sweden.[7] Women took pivmecillinam 185 mg (package insert states 185 mg and published study states 200 mg) three times daily for 7 days, 185 mg twice daily for 7 days (not approved regimen) or 370 mg twice daily for 3 days (not an approved regimen) or placebo three times a day for 7 days.[7] The primary outcome was to compare 4 different treatment regimens based on symptoms and bacterial counts after 8-10 days and at 1 month follow-up (days 35-49). Clinical and microbiological cure was similar between the all the doses (**Table 10**). Overall, the combined clinical and microbiological endpoint was achieved in 62% of patients in the combined pivmecillinam group compared to 10% of placebo treated patients (TD 52%; 95% CI, 41 to 62).[8] At one month the percentage of clinical cure was similar between pivmecillinam and placebo (87-88%). Microbiological cure was higher at the one month follow up in the pivmecillinam groups compared to placebo.[7] The seven day regimens were found to be more effective than the 3 day regimen. Few details were provided on study methodology which prevented strong conclusions. The study was considered low quality. One patient in each group developed pyelonephritis.

The second trial compared the use of pivmecillinam 185 mg (package insert states 185 mg and published study states 200 mg) three times daily for 3 days compared to cephalexin 250 mg four times daily for 7 days in a multi-center, double-blind, superiority RCT in the U.S.[6] Women 18 years with uUTI were included. Patients were seen at entry day, day 10 and day 14. The composite endpoint was clinical and microbiological cure. Symptoms were monitored and recorded by investigators. Clinical cure was based no symptoms that persisted during treatment or post treatment. Microbiological cure was a negative urine culture on day 10 for presenting pathogen.[6] Microbiological cure and clinical cure was not significantly different between pivmecillinam compared to cephalexin.[6] The composite endpoint was achieved in 72% of those treated with pivmecillinam compared to 76% of patients treated with cephalexin (TD -4%; 95% CI, -16 to 7; p>0.05).[8]

In a third trial, pivmecillinam 185 mg three times daily was compared to ibuprofen 600 mg daily three times daily.[5] Both regimens were given for 3 days. Ibuprofen was chosen as a comparator to see if symptomatic uUTI treatment could reduce antibiotic use since uUTIs are often self-limiting. The trial was a double-blind, double dummy, noninferiority trial. Patients were asked to record symptoms daily, including if they felt cured, in a provided diary that had been validated. Adverse events and information on adherence were also requested. Patients were contacted on day 14 and 28 to ask about symptoms and if the patient felt they were cured. A baseline urine dipstick (leukocytes, protein, nitrates and blood) was obtained and again at 2 weeks. Results of the dipstick testing were not used for inclusion but included for additional analysis. The main outcome was proportion of patients who felt cured by day 4, as recorded in their diary.[5] Missing cure data was obtained by telephone follow-up. A key secondary outcome was the proportion of patients with a positive second urine culture at 14 days for primary pathogen.

Pivmecillinam was found to be associated with a higher number of patients who felt cured by day 4 of treatment compared to those randomized to ibuprofen (RD 35%; 95% CI, 27% to 43%; noninferiority not met).[5] There were fewer patients in the pivmecillinam group that experienced a positive bacterial culture at 14 days compared to ibuprofen (RD -16%; 95% CI, -26% to -7%; p<0.001; ARR 18%/NNT 6).

Limitations to the evidence are efficacy evidence based on subjective patient reported symptoms. Resistance to *E. coli* was not studied or reported. The number of previous uUTIs at baseline was not reported. Methodology was not well described for the first 2 trials resulting in an unclear risk of bias for many domains.

Clinical Safety:
The most common adverse reactions with pivmecillinam are nausea and diarrhea.[8] Contraindications to treatment are history of serious hypersensitivity reactions to pivmecillinam or other beta-lactam antibacterial drugs, primary or secondary carnitine deficiency , or acute porphyria. Serious adverse events were rare in clinical trials. See **Table 8** for specific adverse event rates.

Table 8. Adverse Reactions in Patients Receiving Pivmecillinam Compared to Placebo Occurring in ≥1% of Patients[8]

Adverse Event	Pivmecillinam (N=282)	Placebo (N=288)
Nausea	12 (4.3%)	6 (2.1%)
Diarrhea	6 (2.1%)	2 (0.7%)
Vulvovaginal candidiasis	5 (1.8%)	0
Genital pruritus	5 (1.8%)	4 (1.4%)
Headache	4 (1.4%)	1 (0.3%)

Look-alike / Sound-alike Error Risk Potential: none identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Microbiological eradication
2) Symptom improvement
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clinical and microbiological response

Table 9. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	A pro-drug containing pivaloxyloxymethylester of the amidinopenicillanic acid, mecillinam. Pivmecillinam is hydrolyzed to mecillinam to the active antibacterial agent. Mecillinam is a beta-lactam antibacterial drug. Majority of activity is against gram-negative bacteria by interfering with the biosynthesis of the bacterial cell wall. There is high specificity against the penicillin-binding protein-2 (PBP-2) in the gram-negative cell wall.
Oral Bioavailability	25-35%
Distribution and Protein Binding	51 L <25%
Elimination	Renal: 580 mL/min
Half-Life	61 minutes
Metabolism	Pivmecillinam converted to mecillinam and pivalic acid by non-specific esterases. Mecillinam undergoes minimal metabolism.

Abbreviations: L = Liters; mL = milliliters

Table 10. Comparative Evidence Table for Pivmecillinam.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Ferry, et al[7] DB, MC, PC, RCT, Phase 3	1. Pivmecillinam 200 mg orally three times daily for 7 days† 2. Pivmecillinam 200 mg orally two times daily for 7 days† 3. Pivmecillinam 400 mg orally two times daily for 3 days 4. Placebo	Demographics: Mean age: 43 years Mean symptom duration: 10 days Mean baseline symptom score: 5.3 points *E. coli* as baseline pathogen: 62.1% Key Inclusion Criteria: - Females - 18 years and older - Clinical symptoms of lower UTI (terminology used in 2007) - Symptom score of 2 or greater Key Exclusion Criteria: - Antibiotic therapy in the last month	ITT: 1. 281 2. 289 3. 285 4. 288 PP: 1. 172 2. 187 3. 164 4. 94 Attrition: 1. 109 (39%) 2. 94 (33%) 3. 121 (42%) 4. 194 (67%)	Primary Endpoint (m-ITT population): Clinical Cure day 8-10: 1. 62 (29%) 2. 64 (29%) 3. 55 (25%) 4. 25 (11%) P<0.001 for all pivmecillinam groups compared to placebo Microbiological Cure day 8-10: 1. 93 (43%) 2. 94 (43%) 3. 38 (25%) 4. 34 (15%) P<0.001 for all pivmecillinam groups compared to placebo Composite Response Rate at day 8-10: Combined pivmecillinam groups: 85 (62%)	ARR 52%/	Adverse reactions: 1. 48 (17%) 2. 35 (12%) 3. 40 (14%) 4. 35 (12%) p-value not reported Gastrointestinal: Pivmecillinam (pooled doses reported): 5-8% Placebo: 4% p-value not reported Severe adverse events were not reported.	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Not described. Performance Bias: Low. Stated that it was a double-blind, double-dummy trial design. Detection Bias: High. There was no detail on how symptoms were tracked and recorded. Attrition Bias: High. Attrition was high in all groups. Study duration went out to 49 days follow-up contributing to high attrition rates. Reporting Bias: High. There was insufficient reporting of study details to assess. Other Bias: High. Manufacture funded. **Applicability**: Patient: Patients had a lower incidence of pathogens caused by *E. coli* than seen in the community. Intervention: It is the appropriate dose of pivmecillinam. Comparator: An active comparison would be more appropriate in quantifying efficacy. Outcomes: Microbiological cure and clinical cure are appropriate outcomes. Reporting of resistance patters would be helpful. Setting: Eighteen primary healthcare centers in Sweden.

		- Participation in a study within the last 3 months - Penicillin allergy - Genital infection - Signs of upper UTI - Diabetes - Pregnancy		Placebo: 14 (10%) TD 52% (95% CI, 41 to 62)	NNT 2			
2. Menday, et al[6] DB, DD, MC, NI, RCT	1. Pivmecillinam 200 mg orally three times daily for 3 days† 2. Cephalexin 250 mg four times daily for 7 days	Demographics: Females: 98% Age: 32 years *E coli* as baseline pathogen: 92% Key Inclusion Criteria: - Females and males - 18 years and older - Uncomplicated UTI - No more than 2 symptomatic episodes within the last year - No history of obstructive uropathy Key Exclusion Criteria: - Pregnant - Febrile - Allergy to study drugs - Signs of upper UTI	ITT: 1. 219 2. 221 PP: 1. 107 2. 109 Attrition: 1. 112 (51%) 2. 112 (51%)	Primary Endpoint: Clinical cure: Pivmecillinam: 102 (95.3%) Cephalexin: 102 (93.6%) OR 1.40 (95% CI, 0.4 to 4.6) P=0.58 Microbiological cure: Pivmecillinam: 96 (89.7%) Cephalexin: 89 (81.7%) OR 1.96 (95% CI, 0.9 to 4.3) P=0.09	NA NA	Adverse event: Pivmecillinam: 13 (5.9%) Cephalexin: 16 (7.2%) Gastrointestinal: Pivmecillinam: 11 (5%) Cephalexin: 5 (2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Not described. Performance Bias: Low. Medications were packaged with a double dummy design and patients and investigators were blinded to treatment. Detection Bias: Unclear. Limited detail on symptom and outcome assessment. Attrition Bias: High. Attrition was high in both groups primarily due to not having adequate bacteria in the urine and inadequate cultures. Reporting Bias: High. There was a lack of detail on study methodology. Other Bias: High. Manufacture funded. **Applicability**: Patient: Patients were representative of those presenting with uUTI. Intervention: It is the appropriate dose of pivmecillinam. Comparator: Cephalexin is not a first line treatment and is considered an alternate therapy. Outcomes: The combined outcome of microbiological and clinical response is recommended by the FDA. Setting: Twenty-eight centers in the United States.
3. Vik, et al[5] DB, MC, NI, RCT	1. Pivmecillinam 185 mg orally three times daily for 3 days 2. Ibuprofen 600 mg three times daily for 3 days	Demographics: Age: 29 years Dysuria: 96% Urinary urgency: 98% Urinary frequency: 99% *E coli* as baseline pathogen: 80% History of 0-2 UTIs in last 12 months: 92% Key Inclusion Criteria: - Females - 18-60 years	ITT: 1. 181 2. 178 PP: 1. 150 2. 154 Attrition: 1. 31 (17%) 2. 24 (13%)	Primary Endpoint: Proportion of patients who felt cured (i.e. no symptoms) by day 4: Pivmecillinam: 131 (73.6%) Ibuprofen: 70 (38.7%) RD 35% (95% CI, 27% to 43%) Noninferiority criteria not met Secondary Endpoint: Positive Urine Culture at day 14:	NA	Adverse event: Pivmecillinam: 38 (21%) Ibuprofen: 32 (18%) Serious adverse reaction: Pivmecillinam: 1 (<1%) Ibuprofen: 6 (3%)		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized in a 1:1 ratio by computer-generated randomization list. Performance Bias: Low. The medications were formulated to be identical in appearance, weight, and taste. Providers and patients were blinded to drug assignment. Detection Bias: Unclear. Patients recorded symptoms in diary. Subjective outcome reporting may increase the risk of bias. Attrition Bias: High. Attrition was high in both groups primarily due to dropouts and lost to follow-up. Reporting Bias: Unclear. The primary outcome was done on the ITT population which can bias results in noninferiority

		- Clinical symptoms of uUTI* Key Exclusion Criteria: - Pregnant - Symptoms more than 7 days - Allergy to study drugs - Signs of upper UTI - Diabetes - Kidney disease -Immunosuppressants or blood thinners - Previous pyelonephritis		Pivmecillinam: 16 (10%) Ibuprofen: 43 (28%) RD -16% (95% CI, -26% to -7%; p<0.001) Patients without symptoms by day 4: Pivmecillinam: 112 (73%) Ibuprofen: 60 (40%) RD -33% (95% CI, -22% to -43%)	ARR 18%/ NNT 6 ARR 33%/ NNT 3	Gastrointestinal adverse reactions: Pivmecillinam: 27 (15%) Ibuprofen: 20 (11%)		studies. Analysis of the per protocol population is recommended. This was a secondary endpoint and results were similar. Other Bias: High. Manufacture funded. **Applicability**: Patient: Patients had a lower incidence of pathogens caused by *E. coli* than seen in the community. There is no data on resistance patterns so it is unknown if pivmecillinam would be effective in this population. Intervention: It is the appropriate dose of pivmecillinam. Comparator: Ibuprofen has no antibacterial properties and is not standard of care for the treatment of symptomatic uUTI. Comparative efficacy to another antibiotic would be more appropriate in assessing efficacy. Outcomes: The combined outcome of microbiological and clinical response is recommended by the FDA. Setting: Centers in Norway (2 sites), Denmark (7 sites), Sweden (7 sites) from accident and emergency outpatient clinics (AEOCs).
Key: * Dysuria with either increased urinary frequency or urinary urgency or both; † Package insert states 185 mg and published study states 200 mg Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; DB = double-blind. DD = double-dummy; FDA = Food and Drug Administration; ITT = intention to treat; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = noninferiority; NNT = number needed to treat; OR = odds ratio; PP = per protocol; RCT = randomized controlled trial; RD = risk difference; UTI = urinary tract infection.								

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BLUJEPA safely and effectively. See full prescribing information for BLUJEPA.

BLUJEPA (gepotidacin) tablets, for oral use
Initial U.S. Approval: 2025

INDICATIONS AND USAGE

BLUJEPA is a triazaacenaphthylene bacterial type II topoisomerase inhibitor indicated for the treatment of female adult and pediatric 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*. (1.1)

Usage to Reduce Development of Drug-Resistant Bacteria
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. (1.2)

DOSAGE AND ADMINISTRATION

- The recommended dosage of BLUJEPA is 1,500 mg (two 750 mg tablets) taken orally, twice daily (approximately 12 hours apart), for 5 days. (2.1)
- Administer BLUJEPA tablets after a meal to reduce the possibility of gastrointestinal intolerance. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 750 mg of gepotidacin. (3)

CONTRAINDICATIONS

A history of severe hypersensitivity to BLUJEPA. (4)

WARNINGS AND PRECAUTIONS

- QTc Prolongation: Avoid use of BLUJEPA in patients with a history of QTc prolongation, or with relevant pre-existing cardiac disease, and in patients receiving drugs that prolong the QTc interval. Due to an increase in BLUJEPA exposure, avoid concomitant administration of BLUJEPA with strong CYP3A4 inhibitors and in patients with severe hepatic impairment (Child-Pugh Class C) and in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min). (5.1)
- Acetylcholinesterase inhibition: Dysarthria and other adverse reactions have been reported in patients receiving BLUJEPA. Monitor patients with underlying medical conditions that may be exacerbated by acetylcholinesterase inhibition and patients receiving succinylcholine-type neuromuscular blocking agents, systemic anticholinergic medications, or non-depolarizing neuromuscular blocking agents. (5.2)
- Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving BLUJEPA. If an allergic reaction to BLUJEPA occurs, discontinue the drug and institute appropriate supportive measures. (5.3)
- *Clostridioides difficile* Infection (CDI): CDI has been reported with nearly all systemic antibacterial agents, including BLUJEPA. Evaluate patients who develop diarrhea. (5.4)

ADVERSE REACTIONS

The most common adverse reactions occurring in ≥1% of patients are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting, and vulvovaginal candidiasis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 Inhibitors: Avoid coadministration of BLUJEPA with strong CYP3A4 inhibitors. (7.1)
- CYP3A4 Inducers: Avoid coadministration of BLUJEPA with strong CYP3A4 inducers (7.1)
- CYP3A4 Substrates: Avoid coadministration of BLUJEPA with drugs that are extensively metabolized by CYP3A4 and have a narrow therapeutic window. (7.2)
- Digoxin: Due to an increase in digoxin exposures, consider monitoring digoxin serum concentration, as appropriate, with concomitant administration of BLUJEPA. (7.2)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Avoid use of BLUJEPA in patients with severe renal impairment with eGFR <30 mL/min, including those receiving dialysis. (8.6)
- Hepatic Impairment: Avoid use of BLUJEPA in patients with severe hepatic impairment (Child-Pugh Class C). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2025

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PIVYA™ safely and effectively. See full prescribing information for PIVYA.

PIVYA (pivmecillinam) tablets, for oral use
Initial U.S. Approval: 2024

INDICATIONS AND USAGE

PIVYA 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*. (1.1)

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. (1.2)

DOSAGE AND ADMINISTRATION

- The recommended dosage of PIVYA is one 185 mg tablet orally 3 times a day for 3 to 7 days as clinically indicated. (2.1)
- Administer PIVYA with or without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 185 mg pivmecillinam. (3)

CONTRAINDICATIONS

- Serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to PIVYA or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins). (4.1)
- 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). (4.2)
- Acute porphyria. (4.3)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Serious hypersensitivity reactions including anaphylaxis have been reported in patients treated with PIVYA. If hypersensitivity reactions occur, discontinue treatment with PIVYA and institute appropriate therapy. (5.1)
- Severe Cutaneous Adverse Reactions (SCAR): Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with PIVYA. Monitor patients closely and discontinue PIVYA at the first signs or symptoms of SCAR or other signs of hypersensitivity. (5.2)
- Carnitine Depletion: Clinically significant hypocarnitinemia has been observed in patients at risk for reductions in serum carnitine. In patients with significant renal impairment or decreased muscle mass and those patients requiring long term antimicrobial treatment, consider alternative antibacterial therapies. PIVYA is not recommended when prolonged antibacterial treatment is necessary. Avoid concurrent treatment with valproic acid, valproate or other pivalate-generating drugs due to increased risk of carnitine depletion. (5.3)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): This has been reported for nearly all systemic antibacterial agents, including PIVYA. Evaluate if diarrhea occurs (5.5)
- Interference with Newborn Screening Test: Treatment of a pregnant individual with PIVYA prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening. Prompt follow-up of a positive newborn screening result for isovaleric acidemia is recommended. (5.7)

ADVERSE REACTIONS

The most common adverse reactions observed in ≥2% of the patients receiving PIVYA in clinical trials are nausea and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UTILITY therapeutics Ltd at 1-888-353-3180 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2024

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORLYNVAH™ safely and effectively. See full prescribing information for ORLYNVAH™.

ORLYNVAH™ (sulopenem etzadroxil and probenecid) tablets, for oral use

Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------

ORLYNVAH 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. (1.1)

Limitations of Use

ORLYNVAH is not indicated for the treatment of:

- Complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI. (1.1, 14.2)
- Complicated intra-abdominal infections (cIAI) or as step-down treatment after intravenous antibacterial treatment of cIAI. (1.1, 14.3)

Usage to Reduce Development of Drug-Resistant Bacteria

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. (1.2, 5.5)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of ORLYNVAH is one tablet orally twice daily for 5 days. (2.1)
- Administration of ORLYNVAH with food is recommended. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

- ORLYNVAH Tablets: 500 mg sulopenem etzadroxil and 500 mg probenecid. (3)

----------CONTRAINDICATIONS----------

- Patients with a history of hypersensitivity to the components of ORLYNVAH (sulopenem etzadroxil and probenecid) or other beta-lactam antibacterial drugs. (4)
- Patients with known blood dyscrasias. (4)
- Patients with known uric acid kidney stones. (4)
- Concomitant use of ORLYNVAH and ketorolac tromethamine is contraindicated. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions: Hypersensitivity reactions have been reported in patients treated with ORLYNVAH. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, have been reported with beta-lactam antibacterial drugs. Severe allergic reactions and anaphylaxis have been reported with the use of probenecid (a component of ORLYNVAH). If an allergic reaction to ORLYNVAH occurs, discontinue the drug and institute appropriate therapy. (5.1)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): This has been reported with nearly all systemicantibacterial agents. Evaluate if diarrhea occurs. (5.2)
- Exacerbation of Gout: When prescribing ORLYNVAH to patients with a known history of gout, ensure appropriate therapy of gout is instituted. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥2%) in patients treated with ORLYNVAH were diarrhea, nausea, vulvovaginal mycotic infection, headache, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Iterum Therapeutics. at 1-866-414-SULO or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Ketoprofen: Concomitant use is not recommended (7.1)
- See full prescribing information for additional clinically significant drug interactions with ORLYNVAH (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2025