Gepotidacin (BLUJEPA)
National Drug Monograph
May 2026

VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AChEI, acetylcholinesterase inhibitor; AE, adverse event; cARD, calculated absolute risk difference; CDAD, *Clostridioides difficile*–associated disease; CDI, *Clostridioides difficile* infection; cRR, calculated relative risk; CTX, ceftriaxone; DB, double-blind; DD, double dummy; ESBL, extended-spectrum beta lactamase; FQ, fluoroquinolone(s); GEP, gepotidacin; GI, gastrointestinal; GPO, gram-positive organism; I, intermediate; ITT, intention-to-treat; MIC, minimum inhibitory concentration; MN, multinational; MSM, males who have sex with males; NI, noninferior(ity); NS, non-susceptible; NTF, nitrofurantoin; R, resistant; RCT, randomized clinical trial; S, susceptible; SMZ, sulfamethoxazole; SOC, standard of care; STI, sexually transmitted infection; TCN, tetracycline; TMP, trimethoprim; TOC, test of cure; Tx, treatment; uUTI, uncomplicated urinary tract infection;

FDA Approval Information

Description/Mechanism of Action

- Gepotidacin is a first-in-class triazaacenaphthylene bacterial topoisomerase inhibitor with a distinct binding site that differs from that of the fluoroquinolones. Gepotidacin inhibits topoisomerase II (DNA gyrase) and topoisomerase IV, thereby inhibiting bacterial DNA replication.
- By attaching to a different site, gepotidacin can bypass resistance mechanisms that have made fluoroquinolones less effective against certain bacterial strains. The unique binding properties give gepotidacin bactericidal efficacy against a wide spectrum of gram-positive and gram-negative organisms including those resistant to other classes of antibiotics. Furthermore, dual enzyme inhibition is believed to reduce the risk of developing resistance to gepotidacin.
- The FDA granted gepotidacin priority review.

Indications Under Review in This Document

- **Uncomplicated urogenital gonorrhea**
- **Females with uncomplicated urinary tract infections (uUTI) caused by certain susceptible pathogens**. Gepotidacin was approved for the treatment of female adult and pediatric patients 12 years of age or older weighing at least 40 kg with uUTI caused by the following susceptible bacteria:
    - *Escherichia coli*
    - *Klebsiella pneumoniae*
    - *Citrobacter freundii complex*
    - *Staphylococcus saprophyticus*
    - *Enterococcus faecalis*

  Gepotidacin shows activity against extended-spectrum-beta-lactamase (ESBL) producing isolates resistant to common oral antibiotics such as fluoroquinolones (FQ).

Dosage Forms Under Review

- Tablets containing 750 mg of gepotidacin
- Recommended dose is 2 tablets (1500 mg) taken orally with or without food twice daily for 5 days. (Taking each dose after a meal may reduce the possibility of gastrointestinal intolerance.)
    - No dose adjustment is needed if CrCl ≥ 30 mL/min
    - Not recommended if CrCl < 30 mL/min

Clinical Evidence Summary

The gepotidacin development program included one phase 3 clinical trial in uncomplicated gonorrhea (EAGLE-1) [1] and two phase 3 clinical trials in uUTI (EAGLE-2 and EAGLE-3)[2]. EAGLE-2 and EAGLE-3 supported the original FDA approval of gepotidacin for uUTI. The three phase 3 trials were conducted after two phase 2 trials showed the safety and efficacy of gepotidacin for urogenital gonorrhea[3] and acute bacterial skin and skin structure infections[4]. A Japanese RCT in uUTI (EAGLE-J) is not reviewed here. The EAGLE-1, -2, and -3 trials are summarized in Table 1.

Table 1: Summary of phase 3 clinical trials

Study	Design	Baseline Characteristics	Results
EAGLE-1	**4–8-day, phase 3, open-label, sponsor-blinded, multinational, non-inferiority (NI) RCT** **NI margin: –10.0%** **Interventions**: • Gepotidacin [GEP] 3000 mg PO q10-12 hrs x 2 doses • Standard of Care (SOC; ceftriaxone [CTX] 500 mg IM x 1 dose + azithromycin 1 g PO x 1 dose) **Eligible patients**: Age ≥ 12 y; weight > 45 kg; suspected **uncomplicated urogenital gonorrhea** (including mucopurulent discharge); positive laboratory test for *Neisseria gonorrhoeae*, or both. Participants were excluded if they had specific renal, urogenital, cardiac or hepatic medical conditions, were immunocompromised (HIV-positive allowed if CD4 ≥ 200), taking medication possibly affected by inhibition of acetylcholinesterase, or had suspected or confirmed *Chlamydia trachomatis* infection in which SOC treatment could not be withheld until the study test-of-cure (TOC).	**Micro-ITT**, **N = 406** (202 patients in GEP group and 204 in SOC group) Mean age 33 y; range 17–64 y 92% Male, 71% MSM, 20% MSW 74% White, 15% Black/African American; 17% Hispanic/Latino 55% reported STIs in previous 12 mos; 133 (88%) of 140 patients who reported gonorrhea infections over the past 12 months had 1 to 3 STIs in that period. 19% HIV-positive	**Microbiological success rates (primary outcome; GEP vs SOC):** • 92.6% (187/202) vs 91.2% (186/204) • Adjusted treatment difference (ATD): –0.1% (95% CI –5.6, 5.5) • NI met; however, superiority not met. **Subgroup Analyses**: GEP efficacy was generally maintained in the subgroup of patients with drug-resistant *N. gonorrhoeae* phenotypes and genotypes. **Microbiological success at TOC by baseline *N. gonorrhoeae* phenotype** ***N. gonorrhoeae* Isolates** / **GEP (N = 202)** / **SOC (N = 204)** Total: 187/202 (92.6%) / 186/204 (91.2%) Azithro-NS (MIC ≥ 2 µg/mL): 17/17 (100%) / 19/20 (95.0%) Cipro-R (MIC ≥ 1 µg/mL): 103/110 (93.6%) / 101/109 (92.7%) Penicillin-R (MIC ≥ 2 µg/mL): 35/36 (97.2%) / 30/33 (90.9%) TCN-R (MIC ≥ 2 µg/mL): 42/49 (85.7%) / 47/53 (88.7%) Cipro-, penicillin-, and TCN-R: 23/24 (95.8%) / 21/23 (91.3%) Azithro, azithromycin; cipro, ciprofloxacin; NS, non-susceptible; R, resistant; SOC, standard of care; TCN, tetracycline • Treatment differences for each *N. gonorrhoeae* phenotype subcategory were

<table>
<tr><th>Study</th><th>Design</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr><td></td><td>Primary outcome: Microbiological success defined as culture-confirmed bacterial eradication of N. gonorrhoeae from the urogenital body site (urogenital for men, endocervical/vaginal discharge for women) at TOC (days 4-8) in the microbiological intention-to-treat (micro-ITT) population. The micro-ITT population consisted of all randomized patients who received at least one dose and had confirmed CTX-susceptible N. gonorrhoeae isolated from their baseline urogenital culture.</td><td></td><td>small and not significant by 95% CIs (i.e., included the value 0).

Other Microbiological Responses (GEP vs SOC)
• Rectal infection: 100% (26/26) vs 80% (12/15); ATD 20.0% (5.2, 45.5)
• Oropharyngeal 78% (14/18) vs 94% (16/17); ATD –16.3% (–41.1, 8.8)</td></tr>
<tr><td>EAGLE-2</td><td>Interim analysis of a MN DB DD NI RCT (interim analysis occurred when ≥ 60% of the maximum target sample size of 884 pts was reached) NI margin: 10%

Patients randomized in 1:1 ratio stratified by age and history of uUTI recurrence

Eligible patients: Nonpregnant females, ≥ 12 years of age, ≥ 40 kg; ≥ 2 symptoms of dysuria, frequency, urgency, or lower abdominal pain, and with evidence of urinary nitrite, pyuria, or both. Pts were excluded if they had an anatomical or physiological anomaly that predisposed them to urinary tract infections or might be a source of persistent bacterial colonization; uncontrolled diabetes, CrCl < 60 mL/min or elevated SCr, or medical condition or co-medications that could pose a safety concern.

Interventions:
GEP 1500mg PO BID x 5 d
Nitrofurantoin (NTF) 100mg PO BID x 5 d

Primary outcome: Therapeutic response (success or failure) at TOC</td><td>ITT population= 1531

mITT NTF-S population = 607 (GEP n=320; NTF n=287)

Complete mITT NTF-S population = 634 (GEP n=336; NTF n=298)

Females only
Mean age: 52.4 y
> 50 yrs old: 359/634 (57%)
White: 530/634 (84%)

Severe renal impairment (CrCl <30 mL/min): 4 (< 1%)

History of recurrent uUTI: 253/634 (40%)

E. coli was the most common qualifying uropathogen: 573/634 (90%)</td><td>Therapeutic Response:
• GEP was NI to NTF
• GEP was not superior to NTF

Therapeutic success at TOC:
GEP: 162/320 (50.6%)
NTF: 135/287 (47%)
ATD 4.3% (–3.6,12.1)

Most common reason for not having therapeutic success: Clinical failure with microbiological success (70/320 [21.9%] GEP vs 59/287 [20.6%] NTF)

Results in subgroups considered at risk of having resistant uropathogens (> 50 y old, recurrent uUTIs, diabetes) numerically favored GEP, consistent with the overall population.

Therapeutic success at TOC by baseline E. coli uropathogen, micro-ITT NTF-S population
<table>
<tr><th>Pathogen</th><th>GEP (N = 336)</th><th>NTF (N = 298)</th></tr>
<tr><td>All E. coli</td><td>156/305 (51.1%)</td><td>123/268 (45.9%)</td></tr>
<tr><td>ESBL-positive</td><td>26/50 (52.0%)</td><td>18/40 (45.0%)</td></tr>
<tr><td>FQ-resistant</td><td>46/96 (47.9%)</td><td>30/78 (38.5%)</td></tr>
<tr><td>TMP/SMZ-resistant</td><td>42/80 (52.5%)</td><td>30/67 (44.8%)</td></tr>
<tr><td>Multidrug resistant</td><td>46/90 (51.1%)</td><td>31/70 (44.3%)</td></tr>
</table>
ESBL, extended-spectrum beta-lactamase; FQ, fluoroquinolone

For all E. coli uropathogens (including ESBL-positive, FQ-resistant, TMP/SMZ-resistant, and multidrug resistant), the</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr><td></td><td>visit, defined as combined successful clinical and microbiological outcome without any additional antibiotic use for uUTI:
Clinical success: complete resolution of symptoms
Microbiological success: reduction of qualifying bacterial uropathogens from ≥ 10^5 CFU/mL at baseline to < 10^3 CFU/mL

Primary analysis population: Microbiological intention-to-treat (micro-ITT) population with NTF-susceptible isolate (NTF-S) and, because the study was stopped early, who had the opportunity to reach the TOC visit or were known to not have attained therapeutic success before the TOC visit (micro-ITT NTF-S [interim analysis set]).</td><td></td><td>calculated 95% CIs for treatment differences could not exclude no treatment difference (i.e., 95% CIs included the value 0).

Therapeutic success at TOC for other gram-negative organisms (GNO; Klebsiella spp, Citrobacter spp, Enterobacter cloacae complex)
GEP: 10/17 (58.8%)
NTF: 10/19 (52.6%)

Therapeutic success at TOC for gram-positive organisms (GPO; S. saprophyticus, Enterococcus spp)
GEP: 11/17 (64.7%)
NTF: 7/12 (58.3%)</td></tr>
<tr><td>EAGLE-3</td><td>Same design including primary and secondary efficacy endpoints and safety outcomes as EAGLE-2

Additional safety outcomes included EKG changes from baseline, defined as post-baseline QTc >500 ms or a change from baseline greater than 60 ms.</td><td>ITT population n=1605

mITT NTF-S population n=541 (GEP 277, NTF 264)

Complete mITT NTF-S population n= 567 (GEP 292, NTF 275)

Females only
Mean age: 50.4 y
White: 85%

Severe renal impairment: 1 (<1%)

History of recurrent uUTI: 233/567 (41%)

E. coli was the most common qualifying uropathogen: 513/567 (90%)</td><td>Therapeutic Response:
• GEP was NI to NTF
• GEP was superior to NTF

Therapeutic success at TOC:
GEP: 162/277 (58.5%)
NTF: 115/264 (43.6%)
ATD 14.6% (6.4, 22.8)

Most common reason for not having therapeutic success: Clinical failure + microbiological failure (51/277 [18.4%] GEP vs 61/264 [23.1%] NTF)

Results in subgroups considered at risk of having resistant uropathogens were consistent with the overall population, favoring GEP.

Therapeutic success at TOC by baseline E. coli uropathogen, micro-ITT NTF-S population
<table>
<tr><th>Pathogen</th><th>GEP (N = 292)</th><th>NTF (N = 275)</th></tr>
<tr><td>All E. coli†</td><td>156/261 (59.8%</td><td>111/252 (44.0%)</td></tr>
<tr><td>ESBL-positive‡</td><td>19/34 (55.9%)</td><td>7/25 (28.0%</td></tr>
<tr><td>FQ-resistant</td><td>32/65 (49.2)</td><td>20/50 (40.0%)</td></tr>
</table>
</td></tr>
</table>

Study	Design	Baseline Characteristics	Results

TMP/SMZ-resistant	45/80 (56.3%)	28/65 (43.1%)
Multidrug resistant	37/70 (52.9%)	22/57 (38.6%)

† Calculated relative risk (cRR) 1.4 (95% CI 1.14, 1.61) and calculated absolute risk difference (cARD) 15.7% (7.2, 24.3)

‡ cRR 2.0 (1.00, 4.00); cARD 27.9 (3.6, 52.1)

- GEP seemed better than NTF for *E. coli* uropathogens overall and for extended-spectrum beta-lactamase (ESBL)-positive *E. coli*, based on calculated relative risk (cRR) and calculated absolute risk difference (cARD). See table footnotes above.
- The 95% CIs for the cRRs and cARDs for TMP/SMZ-resistant and multidrug-resistant *E. coli* included the value 0.

Therapeutic success at TOC for other GNO (*Klebsiella* spp, *Citrobacter* spp, *Enterobacter cloacae* complex), pooled results
GEP: 11/21 (52.4%)
NTF: 6/18 (33.3%)

Therapeutic success at TOC for GPO (*S. saprophyticus*, *Enterococcus* spp), pooled results
GEP: 7/13 (53.9%)
NTF: 6/9 (66.7%)

ATD, adjusted treatment difference; MSM, men who have sex with men; MSW, men who have sex with women; TOC, test of cure

Efficacy Considerations in Uncomplicated Urogenital Gonorrhea

- EAGLE-1 showed that gepotidacin was noninferior and not superior to ceftriaxone + azithromycin, considered the standard of care for the study, in terms of achieving microbiological success in **CTX-susceptible *N. gonorrhoeae*** infection. The study population consisted primarily of young (mean age 33 years), non-immunocompromised males with a males-who-have-sex-with-males (MSM) sexual orientation. Non-White patients were underrepresented. It is uncertain to what extent the results are applicable to VHA.
- Gepotidacin showed no definite advantages over dual ceftriaxone + azithromycin therapy in microbiological success rates for isolates of *N. gonorrhoeae* that were not susceptible or were resistant to antibiotics (azithromycin, penicillin, ciprofloxacin, and tetracycline) considered standard in the study but are no longer considered preferred or alternate therapy for treatment of gonorrheal infection.
- For infection at other body sites, gepotidacin showed promising microbiological response benefits over ceftriaxone + azithromycin for rectal gonorrhea, but seemed less or as effective vs dual therapy for oropharyngeal gonorrhea. Results were inconclusive because of the small number of patients.
- The standard-of-care treatment in EAGLE-1 conflicts with current guidelines by the Centers for Disease Control, which recommend **ceftriaxone** monotherapy (500 mg IM for patients < 150 kg; 1 g IM for ≥ 150 kg) for treatment of uncomplicated cervical, urethral, or rectal gonococcal infection.[5] (If chlamydial

infection has not been excluded, doxycycline [100 mg PO twice daily for 7 days] should be added.) Dual ceftriaxone + azithromycin therapy is no longer recommended for gonorrheal infection. The comparative efficacy of gepotidacin vs ceftriaxone monotherapy was not evaluated and is uncertain.

- In the past, gonorrheal treatments with efficacy rates of greater than 95% with 95% CI lower limit of ≥ 90% were recommended as "alternative treatments" and those with treatment efficacy of 95% with a 95% CI lower limit of 95% were recommended for first-line treatments.[6,7] Gepotidacin achieved the former treatment goal for "alternative treatments," attaining a 92.6% microbiological success rate, as did ceftriaxone + azithromycin with 91.2%. Current CDC guidelines for sexually transmitted infections no longer provide a target treatment efficacy rate.[5]
- A single-dose treatment regimen is desirable for gonorrheal treatment. The single dose allows point-of-care medication administration that ensures treatment adherence. Gepotidacin has a disadvantage in that it requires two doses to be taken 10–12 hours apart, opening the possibility of suboptimal treatment due to patients failing to take the full course and potentially increasing the risk of antibiotic resistance.
- Since *Chlamydia trachomatis* infection commonly occurs with gonorrheal infections, it is important to note that *C. trachomatis* is not considered to be susceptible to gepotidacin and the efficacy of gepotidacin therapy against co-occurring *C. trachomatis* infection was not evaluated in EAGLE-1. Additional antibiotic therapy (e.g., doxycycline) will need to be added to gepotidacin to cover chlamydial infection.

Efficacy Considerations in uUTI

- Gepotidacin was evaluated in patients with uUTI/cystitis without evidence of upper urinary tract, prostate, or systemic infection.
- The results of EAGLE-2 and EAGLE-3 were inconsistent, with only EAGLE-3 showing superiority of gepotidacin over nitrofurantoin in achieving therapeutic response in females with symptomatic uUTI caused by **nitrofurantoin-susceptible isolates**, mainly *E. coli*. Patients with recurrent uUTI were included. Both trials showed noninferiority of gepotidacin to nitrofurantoin.
    - The study authors stated that two factors drove the larger difference in therapeutic success rates and gepotidacin superiority over nitrofurantoin in EAGLE-3: a higher rate of microbiological failure in the NTF group of EAGLE-3 (113/264 [42.8%]) than EAGLE-2 (93/287 [32.4%]), and a lower rate of discordance between clinical and microbiological response in EAGLE-3.
- Subgroup analyses suggested that GEP may be better than nitrofurantoin for ESBL-positive nitrofurantoin-susceptible *E. coli* uropathogens, but a lack of treatment difference could not be excluded for fluoroquinolone-resistant, TMP/SMZ-resistant, and multidrug-resistant isolates.
- Both studies involved only females. Extrapolation of results to a primarily male VHA population with uUTI is uncertain.

Safety Considerations

Safety Profile from Prescribing Information for uUTI

Boxed warnings: None
Contraindications: History of severe hypersensitivity to gepotidacin.
Warnings/Precautions:

- **QTc Prolongation**. Dose and concentration-dependent prolongation of the QTc interval has been observed with gepotidacin. Avoid gepotidacin in patients with a history of QTc prolongation or those with relevant pre-existing cardiac disease, patients taking drugs that prolong the QTc interval, strong CYP3A4 inhibitors, and in patients with severe renal impairment (eGFR <30 mL/min).
- **Acetylcholinesterase Inhibition**. Gepotidacin is a reversible acetylcholinesterase inhibitor (AChEI) in in-vitro lab studies. AEs including dysarthria, pre-syncope, muscle spasms, diarrhea, nausea, vomiting, abdominal pain, hypersalivation and hyperhidrosis, which are potentially attributed to acetylcholinesterase inhibition, have been observed in clinical trials. Increased cholinergic effects can be associated with severe AEs including atrioventricular block, bradycardia, bronchospasm, seizures/convulsions and vasovagal syncope. Gepotidacin may exaggerate the neuromuscular effects of succinylcholine-type muscle relaxation during anesthesia.
- **Hypersensitivity reactions.** These include anaphylaxis.
    - ***C. difficile* Infection (CDI).** As with virtually all systemic antibacterials, CDI has been reported in patients during or after gepotidacin therapy.
- **Adverse reactions >10%:** diarrhea 16% vs 3% for gepotidacin vs nitrofurantoin, respectively.
- **Pregnancy:** No human data. In mice and rats, decreased fetal weights and increased fetal mortality were observed.
- **Lactation**: No human data. Based on mice studies, gepotidacin is likely to be transferred into human milk.
- **Geriatric Use**: No age-related overall differences in safety or efficacy were observed between patients ≥ 65 years vs younger adults.
- **Renal Impairment**: Avoid in severe renal impairment (eGFR <30 mL/min).
- **Hepatic Impairment**: Avoid in severe hepatic impairment (Child-Pugh Class C).
- **Drug Interactions**:
    - Avoid coadministration with strong CYP3A4 inHIBitors, strong CYP3A4 inDUCers, and CYP3A4 substrates.
    - Digoxin exposure may increase. Consider monitoring digoxin serum concentrations.

Safety Results from Clinical Trials

- Adverse events (AEs) and drug-related AEs were more common on gepotidacin than either ceftriaxone + azithromycin in uncomplicated gonorrhea or nitrofurantoin in uUTI. The majority of AEs experienced by patients in the gepotidacin cohort were related to the gastrointestinal (GI) tract.
- AEs potentially related to AChEI were reported more frequently with gepotidacin than either ceftriaxone + azithromycin in uncomplicated gonorrhea or nitrofurantoin in uUTI, and mainly consisted of hyperhidrosis, syncope, and dysarthria.
- GI intolerance was the most common AE.
- Additionally, there were no clinically significant changes from baseline in vital signs or QTc in EAGLE-3.
- Safety results are summarized in Table 2.

Table 2: Summary of safety results from clinical trials

Study	Results
EAGLE-1	**GEP (N = 309) vs ceftriaxone + azithromycin (N = 313)** • Any Adverse Event: 230 (74%) vs 104 (33%) • Grade 3/Severe or 4/Life-threatening AE: 0 vs 0 • Most common AE: diarrhea (147 [48%] vs 22 [7%]) • Majority of AEs in GEP cohort were deemed mild or moderate. • Drug-related AE, Total|Led to Tx Discontinuation: 210 (68%)|3 (<1%) vs 44 (14%)|NA • Drug-related Serious AE: 0 vs 0 • Adverse events of special interest ○ *Clostridioides difficile*-associated disease [CDAD]: 0 vs 0 ○ Cardiovascular: 1 (< 1%) vs 1 (< 1%) ○ GI: 206 (67%) vs 49 (16%) ○ AE potentially related to acetylcholinesterase inhibition (AChEI): 197 (64%) vs 34 (11%)
EAGLE-2	GEP (N = 766) vs NTF (N = 760) • Any AE: 266 (35%) vs 165 (22%) • Drug-related AE, Total|Leading to Tx Discontinuation: 197 (26%)|25 (3%) vs 93 (12%)|13 (2%) • Serious AE: 2 (<1%) vs 3 (<1%) • Most common AE: diarrhea (14% vs 4%); nausea (11% vs 4%) • CDAD: GEP 5/766 (<1%) vs NTF 0 (0%) • AE potentially related to AChEI: 169/766 (22%) vs 60/760 (8%)
EAGLE-3	GEP (N = 804) vs NTF (N = 798) • Any AE: 285 (35%) vs NTF 200 (25%) • Drug-related AE, Total|Leading to Tx Discontinuation: 221 (27%)|46 (6%) vs 108 (14%)|7 (<1%) • Serious AE: 5 (<1%) vs 5 (<1%) • Most common AE: diarrhea (18% vs 3%), nausea (8% vs 4%) • CDAD: 3/804 (<1%) vs 0 (0%) • AE potentially related to AChEI: 178/804 (22%) vs 64/798 (8%)

Safety Considerations in Uncomplicated Gonorrhea

- One of the established advantages of ceftriaxone or ceftriaxone + azithromycin therapy is good tolerability with few AEs. Gepotidacin may have a disadvantage vs ceftriaxone + azithromycin because of a high rate of GI AEs (67% vs 16%, respectively) including diarrhea (48% vs 7%, respectively) and nausea, and AChEI AEs (64% vs 11%, respectively). Although there was a low rate of discontinuations due to AEs (<1% for gepotidacin), it remains to be seen whether treatment discontinuation will be a problem in real-world experience. Early treatment discontinuation would not be an issue with single-dose therapy.

Safety Considerations in uUTI

- There are three potential reasons for development of diarrhea during gepotidacin therapy:
  - **CDI**: Can occur up to 2 months after completing antibiotic therapy; potentially serious or life-threatening.
  - **AChEI**: Diarrhea may occur with other reactions due to AChEI such as dysarthria, presyncope, muscle spasms, nausea, vomiting, abdominal pain, hypersalivation, and hyperhidrosis. Severe AChEI may manifest as atrioventricular block, bradycardia, bronchospasm, seizures, and vasovagal syncope.
  - **GI AE**: Diarrhea was the most common GI AE.

Other Considerations

FDA Review (uUTI)[8]	**Clinical MIC Breakpoint Recommendations** | Pathogen | MIC (mcg/mL) S | I | R | Disk Diffusion (mm) S | I | R | | Enterobacterales* | ≤ 16 | 32 | ≥ 64 | ≥ 12 | 8–11 | ≤ 7 | | *S. saprophyticus* | ≤ 0.25 | — | — | ≥ 23 | — | — | | *E. faecalis* | ≤ 4 | — | — | ≥ 14 | — | — | Disk diffusion refers to zone diameter in mm. I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible * Clinical efficacy was shown for *E. coli*, *K. pneumoniae*, and *C. freundii complex*
ICER Review	None
NICE Review (STI)	Not pertinent to gepotidacin
UpToDate[16,17]	Recommends reserving gepotidacin for females with uUTI due to resistant uropathogens or allergies to standard agents, ideally with infectious diseases consultation, and makes no recommendation for use in males.

Other Therapeutic Options

Alternative treatments are listed by indication in Table 3 and Table 4 below.

Table 3: Treatment Alternatives for Uncomplicated Gonorrhea

Drug	VANF	PBM Clinical Guidance	FDA Indication	Other Considerations
First-line Antibiotic				
Ceftriaxone x 1 dose • 500 mg IM for weight < 150 kg • 1 g for weight ≥ 150 kg	Yes	None	Treatment of uncomplicated cervical, urethral, rectal, and pharyngeal infection caused by *N. gonorrhoeae*, including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase-producing strains of *N. gonorrhoeae*.	Weight-based dosing. PKs and ability to maintain drug concentrations > MIC are better characterized than with other cephalosporins. Add doxycycline (100 mg PO BID x 7 d) if chlamydial infection is not excluded.
Alternative Cephalosporin				
Cefixime 800 mg PO x 1 dose	Yes	None	Treatment of uncomplicated cervical/urethral gonorrhea due to *N. gonorrhoeae* (penicillinase- and nonpenicillinase-producing)	CDC-recommended if ceftriaxone is not available. Add doxycycline (100 mg PO BID x 7 d) if chlamydial infection is not excluded.
Alternative Antibiotics				
Gentamicin 240 mg IM x 1 dose + Azithromycin 2 g PO x 1 dose	Yes Yes	None None	Off label Treatment of urethritis and cervicitis due to *C. trachomatis* or *N. gonorrhoeae.*	Dual therapy is CDC-recommended if cephalosporin allergy.

Source: 9

Table 4: Treatment Alternatives for Symptomatic Uncomplicated UTI

Drug	VANF	PBM Guidance for uUTI	FDA Indication Related to UTI	Other Considerations
First-line Empiric Oral Antibiotics				
Nitrofurantoin monohydrate/ macrocrystals	Yes	None	Treatment of acute uncomplicated cystitis caused by susceptible strains of *Escherichia coli* or *Staphylococcus saprophyticus* in adults and pediatric patients ≥12 years of age. Chronic suppression of recurrent UTI.	Useful option for documented or suspected multidrug-resistant uropathogens. Low risk of selection for resistance.[17] Contraindicated if CrCl <60 mL/min according to labeling. Evidence for this CrCl cutoff is lacking.[10] Beers criteria recommend avoiding nitrofurantoin in patients with CrCl <30 mL/min.[11] Use of nitrofurantoin in patients with CrCl 30–60 mL/min for short-term treatment of uncomplicated acute cystitis has been reported to be safe and effective, although evidence is limited.[12,13,14,15] Risks of non–dose-related peripheral neuropathy and pulmonary toxicity.
Trimethoprim/ sulfamethoxazole (TMP/SMZ)	Yes	None	Treatment of UTI due to *E. coli*, *Klebsiella* and *Enterobacter* spp, *Morganella morganii*, *Proteus mirabilis*, and *Proteus vulgaris*	Avoid empiric TMP/SMZ if regional prevalence of resistance is known to be > 20%.[17] Requires dosage adjustment for kidney impairment.
Alternative Oral Antibiotics				
Beta-lactams				
Amoxicillin/ clavulanate	Yes	None	Treatment of UTI caused by beta-lactamase–producing strains of *E. coli*, *Klebsiella* spp, and *Enterobacter* spp	
Cefpodoxime	Yes	None	Treatment of acute uncomplicated cystitis caused by *E. coli*, *K. pneumoniae*, *P. mirabilis*, or *S. saprophyticus*.	
Cefadroxil	Yes	None	Treatment of UTIs caused by *E. coli*, *P. mirabilis*, and *Klebsiella* species.	
Cephalexin	Yes	None	Treatment of genitourinary tract infections, including acute prostatitis, caused by *E. coli*, *P. mirabilis*, and *K. pneumoniae*.	Achieves lower bladder urine drug concentrations vs other oral cephalosporins.
Cefdinir	Yes	None	Off-label for acute uUTI	
Fluoroquinolones				
Ciprofloxacin, oral	Yes	None	Treatment of the following infections when caused by susceptible bacteria: UTI; acute uncomplicated cystitis in females	Consider if beta-lactams are medically inadvisable (e.g., severe allergy); reserve for more serious infections than uUTI, and base use on regional resistance rates. Associated with serious tendinopathy/tendon rupture and peripheral and central neurologic effects.
Levofloxacin, oral	Yes	None	Treatment of UTI (uncomplicated or complicated)	
Ofloxacin	No	None	Treatment of uUTI, complicated UTIs, prostatitis	

Drug	VANF	PBM Guidance for uUTI	FDA Indication Related to UTI	Other Considerations
Other Oral Antibiotics				
Sulopenem etzadroxil/ probenecid	No	None	Treatment of uUTI caused by *E. coli, K. pneumoniae,* or *P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.	First oral penem in fixed combination with probenecid. Contraindicated in patients with known blood dyscrasias or known uric acid kidney stones, and patients on ketorolac tromethamine. Not recommended if CrCl <15 mL/min, patient is on hemodialysis, or for use with ketoprofen. In patients with a history of gout, treatment should be given to reduce the risk of uric acid kidney stones (e.g., increased fluid intake, urine alkalinization) and to treat gout.
Fosfomycin	Yes, PA-F	CFU*	Treatment of uUTI in women due to susceptible strains of *E. coli* and *E. faecalis.* If persistence or reappearance of bacteriuria occurs after treatment, other agents should be selected.	Single-dose regimen. Considered a first-line alternative in UpToDate.[16] Not evaluated in males with uUTI. Use selectively per PBM criteria.
Pivmecillinam (PIVYA)	No	TBD	Treatment of females ≥ 18 years of age with uUTI caused by susceptible isolates of *E. coli, Proteus mirabilis,* and *S. saprophyticus.*	Penicillin with extended gram-negative spectrum. Low risk of selection for resistance.
Gepotidacin	TBD	TBD	Treatment of female adult and pediatric patients 12 years of age or older weighing at least 40 kg with uUTI caused by the following susceptible bacteria: • *E. coli* • *K. pneumoniae* • *C. freundii complex* • *S. saprophyticus* • *E. faecalis*	Use for uUTI in males is off label (not studied).

Sources: 16,17 There were no American clinical practice guidelines for uUTI that were current (published within the past 5 years). A 2019 guideline on management of recurrent uUTI in women recommended nitrofurantoin, TMP/SMZ, or fosfomycin (given for the shortest duration possible, generally not more than 7 days) as first-line therapy depending on local antibiograms.[18]

* Fosfomycin criteria related to uUTI require cystitis with *E. coli* or *Enterococcus spp.* not susceptible to other appropriate oral agents (e.g., nitrofurantoin, beta-lactams, TMP/SMZ) in urine culture, or severe allergy or contraindication to other appropriate oral agents.

Projected Place in Therapy

Evidence Summary	• In patients with **uncomplicated urogenital gonorrheal infection due to ceftriaxone-susceptible *N. gonorrhoeae* (EAGLE-1)**, gepotidacin achieved a microbiological success rate of 92.6% and was noninferior to, but not superior to, ceftriaxone + azithromycin. The comparative efficacy of gepotidacin to current standard-of-care therapy, ceftriaxone monotherapy, is uncertain. In a subgroup of patients with ciprofloxacin-resistant *N. gonorrhoeae* isolates, gepotidacin produced a microbiological success rate comparable to that of ceftriaxone + azithromycin, suggesting that gepotidacin may not

	have a benefit over dual therapy specifically in patients with fluoroquinolone-resistant, ceftriaxone-susceptible isolates. The efficacy of gepotidacin in ceftriaxone-resistant *N. gonorrhoeae* is uncertain. A potential advantage of gepotidacin is a lower risk of microbial resistance; however, this remains to be proven. Disadvantages of gepotidacin relative to single-dose, provider-administered IM ceftriaxone monotherapy include potential patient nonadherence with the requirement to take two oral doses and frequent, mild–moderate GI AEs. Determination of the real-world treatment success with gepotidacin requires further study. • In females with uUTI due to **nitrofurantoin-susceptible pathogens**, mainly *E. coli* (EAGLE-2, EAGLE-3), gepotidacin was consistently noninferior to nitrofurantoin but inconsistently superior to nitrofurantoin across trials in achieving combined clinical and microbiological success without need for additional antibiotics. Results of exploratory analyses of small subgroups by baseline *E. coli* uropathogen favored gepotidacin for ESBL-positive isolates in EAGLE-3 only but were generally inconclusive.
Potential Place in Therapy in VHA	• For **uncomplicated gonorrheal infection**, gepotidacin may be considered in consultation with an infectious disease specialist for third-line therapy in patients who have an inadequate response, documented non-susceptibility, or medical inadvisability to first-line therapy with ceftriaxone AND second-line therapy with gentamicin + azithromycin. In patients unable to take IM injections of ceftriaxone, oral cefixime may be used before considering gepotidacin. • For **uncomplicated urinary tract infection due to susceptible *E. coli, K. pneumoniae, C. freundii complex, S. saprophyticus, or E. faecalis***, gepotidacin may be considered in consultation with an infectious disease specialist for off-label use in males and on-label use in females who have an inadequate response, documented non-susceptibility, or medical inadvisability to all preferred oral antibiotics (nitrofurantoin and TMP/SMZ) and alternative oral beta-lactam antibiotics (amoxicillin/clavulanate and a cephalosporin) and fluoroquinolones (low-dose, 3-day course). Uncomplicated urinary tract infection refers to **simple cystitis without evidence of infection beyond the bladder)** in males or females, and without prostatitis in males.

Original: May 2026
Prepared by: Jack Sorensen, Pharmacy Resident, and Ian Pace and Francine Goodman, National PBM Clinical Pharmacy Program Managers
Contact: Francine Goodman, National PBM Clinical Pharmacy Program Managers, VA Pharmacy Benefits Management Services – Formulary Management (12PBM)

References

[1] Ross JDC, Wilson J, Workowski KA, Taylor SN, Lewis DA, Gatsi S, Flight W, Scangarella-Oman NE, Jakielaszek C, Lythgoe D, Powell M, Janmohamed S, Absalon J, Perry C. Oral gepotidacin for the treatment of uncomplicated urogenital gonorrhoea (EAGLE-1): a phase 3 randomised, open-label, non-inferiority, multicentre study. Lancet. 2025 May 3;405(10489):1608-1620. doi: 10.1016/S0140-6736(25)00628-2. Epub 2025 Apr 14. PMID: 40245902.

[2] Scangarella-Oman NE, Butler DL, Breton J, Brown D, Kasapidis C, Millns H, Huang C, Perry CR, Sheets AJ, Dennison J, Janmohamed S. Efficacy and *in vitro* activity of gepotidacin against bacterial uropathogens, including drug-resistant phenotypes, in females with uncomplicated urinary tract infections: results from two global, pivotal, phase 3 trials (EAGLE-2 and EAGLE-3). Antimicrob Agents Chemother. 2025 Oct;69(10):e0164024. doi: 10.1128/aac.01640-24. Epub 2025 Sep 9. PMID: 40924001; PMCID: PMC12486842.

[3] Taylor SN, Morris DH, Avery AK, Workowski KA, Batteiger BE, Tiffany CA, Perry CR, Raychaudhuri A, Scangarella-Oman NE, Hossain M, Dumont EF. Gepotidacin for the Treatment of Uncomplicated Urogenital Gonorrhea: A Phase 2, Randomized, Dose-Ranging, Single-Oral Dose Evaluation. Clin Infect Dis. 2018 Aug 1;67(4):504-512. doi: 10.1093/cid/ciy145. PMID: 29617982; PMCID: PMC6070052.

[4] O'Riordan W, Tiffany C, Scangarella-Oman N, Perry C, Hossain M, Ashton T, Dumont E. Efficacy, Safety, and Tolerability of Gepotidacin (GSK2140944) in the Treatment of Patients with Suspected or Confirmed Gram-Positive Acute Bacterial Skin and Skin Structure Infections. Antimicrob Agents Chemother. 2017 May 24;61(6):e02095-16. doi: 10.1128/AAC.02095-16. PMID: 28373199; PMCID: PMC5444153.

[5] Centers for Disease Control and Prevention (September 21, 2022). *Sexually Transmitted Infections Treatment Guidelines, 2021*. Available at: https://www.cdc.gov/std/treatment-guidelines/gonorrhea-adults.htm. Accessed: October 7, 2025.

[6] Workowski KA, Berman SM, Douglas JM Jr. Emerging antimicrobial resistance in Neisseria gonorrhoeae: urgent need to strengthen prevention strategies. Ann Intern Med. 2008 Apr 15;148(8):606-13. doi: 10.7326/0003-4819-148-8-200804150-00005. Erratum in: Ann Intern Med.2008 Jun 3;148(11): 888. PMID: 18413622.

[7] Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. Clin Infect Dis. 2007 Apr 1;44 Suppl 3:S84-101. doi: 10.1086/511422. PMID: 17342672.

[8] FDA Center for Drug Evaluation and Research. Integrated Review of Gepotidacin (BLUJEPA). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/218230Orig1s000IntegratedR.pdf . Accessed: October 7, 2025.

[9] St. Cyr S, Barbee L, Workowski KA, et al. Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1911–1916. DOI: http://dx.doi.org/10.15585/mmwr.mm6950a6

[10] Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. Ann Pharmacother. 2013 Jan;47(1):106-11. doi: 10.1345/aph.1R352. Epub 2013 Jan 22. PMID: 23341159.

[11] 2023 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023 Jul;71(7):2052-2081. doi: 10.1111/jgs.18372. Epub 2023 May 4. PMID: 37139824; PMCID: PMC12478568.

[12] Chung C, Bouwmeester C. Nitrofurantoin Use in Frail, Community-Dwelling, Older Adults with Renal Impairment. Sr Care Pharm. 2019 May 1;34(5):303-307. PMID: 31054588.

[13] Cunha BA, Cunha CB, Lam B, Giuga J, Chin J, Zafonte VF, Gerson S. Nitrofurantoin safety and effectiveness in treating acute uncomplicated cystitis (AUC) in hospitalized adults with renal insufficiency: antibiotic stewardship implications. Eur J Clin Microbiol Infect Dis. 2017 Jul;36(7):1213-1216. doi: 10.1007/s10096-017-2911-1. Epub 2017 Feb 2. PMID: 28155015.

[14] Santos JM, Batech M, Pelter MA, Deamer RL. Evaluation of the Risk of Nitrofurantoin Lung Injury and Its Efficacy in Diminished Kidney Function in Older Adults in a Large Integrated Healthcare System: A Matched Cohort Study. J Am Geriatr Soc. 2016 Apr;64(4):798-805. doi: 10.1111/jgs.14072. PMID: 27100576.

[15] Santos JM, Batech M, Pelter MA, Deamer RL. Evaluation of the Risk of Nitrofurantoin Lung Injury and Its Efficacy in Diminished Kidney Function in Older Adults in a Large Integrated Healthcare System: A Matched Cohort Study. J Am Geriatr Soc. 2016 Apr;64(4):798-805. doi: 10.1111/jgs.14072. PMID: 27100576.

[16] Gupta K. Acute simple cystitis in male adults. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on October 8, 2025).

[17] Gupta K. Acute simple cystitis in female adults. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on October 8, 2025).

[18] Anger J, Lee U, Ackerman AL, Chou R, Chughtai B, Clemens JQ, Hickling D, Kapoor A, Kenton KS, Kaufman MR, Rondanina MA, Stapleton A, Stothers L, Chai TC. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. J Urol. 2019 Aug;202(2):282-289. doi: 10.1097/JU.0000000000000296. Epub 2019 Jul 8. Update in: J Urol. 2022 Oct;208(4):754-756. doi: 10.1097/JU.0000000000002888. PMID: 31042112.