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Drug Class Update with New Drug Evaluation: Type II Topoisomerase Inhibitors

Date of Review: June 2026

Date of Last Review: August 2025
Dates of Literature Search: 06/01/2025 - 02/13/2026

Generic Name: Zoliflodacin

Brand Name (Manufacturer): Nuzolvence® (Innoviva Specialty Therapeutics, Inc.)
Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To create a new preferred drug list (PDL) class for the type II topoisomerase inhibitor drugs, to evaluate new evidence published since the last review done in August of 2025 and present and evaluate the evidence for the new drug, zoliflodacin.

Plain Language Summary:
- There is a new class of antibiotics called type II toperisomerase inhibitors. There are two antibiotics in this class, gepotidacin and zoliflodacin.
- Gepotidacin is used to treat urinary tract infections, also called bladder infections, and an infection due to sexually transmitted bacteria, called gonorrhea.
- Zoliflodacin is used to treat gonorrhea infections. It is taken by mouth and is taken as one single dose.
- The Centers for Disease Control and Prevention (CDC) recommend an injectable antibiotic called ceftriaxone as the first option for treatment for gonorrhea. Ceftriaxone is injected in the muscle or administered in the vein as one-time single dose.
- Guidelines recommend the antibiotics nitrofurantoin, trimethoprim-sulfamethoxazole (TMP/SMX), fosfomycin or pivmecillinam to be tried initially for the treatment of urinary tract infections.
- Providers are asked to prescribe antibiotics that are on the preferred drug list (PDL) if it is a good choice for the patient. If a provider prescribes a non-preferred antibiotic, they must explain to the Oregon Health Authority why the patient needs that medicine before Oregon Health Plan will pay for it. This is called prior authorization. The Drug Use Research and Management (DURM) group recommends keeping gepotidacin and zoliflodacin as non-preferred so antibiotics recommended by guidelines are tried first.

Research Questions:
1. What is the evidence for efficacy for the type II topoisomerase inhibitors for uncomplicated urinary tract infection (uUTI) and uncomplicated gonorrhea infections?
2. What is the evidence for the safety of the new drugs for uUTI and uncomplicated gonorrhea infections?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender, disease severity), for whom type II topoisomerase inhibitors are more effective or associated with less harm?

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4. What is the comparative safety and efficacy of zoliflodacin for the treatment of urogenital uncomplicated gonorrhea infections?

Conclusions:

- Type II topoisomerase inhibitors are a new class of antibiotics that are oral options for patients with severe allergies to b-lactams. Gepotidacin is approved for uUTI and uncomplicated gonorrhea and zoliflodacin is approved for uncomplicated gonorrhea treatment. For the treatment of gonorrhea, the option of an oral agent versus intramuscular injection.
- Evidence identified for this review includes one high quality guideline, one randomized clinical trial (RCT), one updated indication and one new drug update.
- The European Association of Urology (EAU) updated guidance on the treatment of urological infections in 2025.[1] The type II topoisomerase inhibitors were not approved for use before guideline publication. The guidelines recommend first line treatment for uUTI with pivmecillinam, fosfomycin trometamol or nitrofurantoin.[1]
- Gepotidacin was approved for the additional indication to treat uncomplicated urogenital gonorrhea caused by *Neisseria gonorrhoeae (N. gonorrhoeae)* in adult and pediatric patients 12 years of age and older in December of 2025.[2] Approval was based on one noninferiority RCT comparing gepotidacin to ceftriaxone plus azithromycin (first line treatment recommendation at trial initiation) in which gepotidacin was found to be noninferior to the comparator regimen.[2]
- There was low quality evidence that a newly approved type II topoisomerase inhibitor, zoliflodacin, was noninferior to ceftriaxone plus azithromycin in an open-label, noninferiority RCT comparing single dose treatment for uncomplicated urogenital gonorrhea.[3] The primary outcome was microbiological cure rate at test-of-cure (TOC) day 6 (treatment difference [TD] -5.3%; 95% confidence interval [CI], 1.4 to 8.6).[3] Both treatments were well tolerated and there were no serious adverse events.

Recommendations:

- No changes to the PDL are recommended based on the review of the evidence for the use of type II topoisomerase inhibitors. Nonpreferred antibiotics are subject to the non-preferred prior authorization (PA) criteria.
- Maintain zoliflodacin as nonpreferred.
- After evaluation of costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

- Gepotidacin was evaluated in August of 2025 for the treatment of uUTI. The P&T Committee voted to keep it nonpreferred on the PDL.

Background:

Urinary tract infections (UTIs) are common infections, affecting more women than in men.[1] 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.[1] 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).[1]

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.[4] Less common bacteria associated with uUTIs are *Proteus mirabilis* (*P. mirabilis*), *Klebsiella pneumonia* (*K. pneumonia*) and *Staphylococcus saprophyticus* (*S. saprophyticus*).[4] Resistant uropathogens are more commonly seen in women 50 years and older, patients with recurrent uUTI, and patients with diabetes.[5] 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.[4] Patient allergy, compliance, availability and cost should be considered. Empirical treatment of uUTI recommended by the EAU are 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).[4] 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*.[1] Fluoroquinolones (i.e., ofloxacin, ciprofloxacin and levofloxacin) can be considered as an option but are associated with adverse events and resistance. In 2016 the Food and Drug Administration (FDA) issued a Safety Announcement advising against the use of fluoroquinolones for uUTIs in people that have other treatment options, due to the serious side effects associated with their use (i.e., tendon rupture, peripheral neuropathy and central nervous system effects).[6] 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.[1] 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 alternatives, with consideration of high *E. coli* resistance rates with these medications. Resistance 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.[1]

Type II topoisomerase inhibitors are also used to treat gonorrhea infections. Gonorrhea is a common sexually transmitted infection (STI) with an estimated US prevalence of over 600,000 cases reported in 2023.[7] Gonorrhea is diagnosed most often in adolescents and young adults equally in men and women and more commonly in Black/African American populations.[7] Antibiotic therapy is always indicated for patients diagnosed with gonorrhea, as complications and transmission to others may occur if not appropriately treated. Gonorrhea has developed resistance to many types of antibiotics (i.e., azithromycin, tetracycline and ciprofloxacin). The 2021 CDC guidance on STIs recommends ceftriaxone, 500 mg intramuscular (IM) or intravenous (IV) for those 150 kg or less and 1 g IM or IV if the patient is 150 kg or more, as first-line empiric therapy for uncomplicated gonorrhea with cefixime as a second-line option.[8] Recommendations by Canada's Drug Agency also state that ceftriaxone therapies have the most evidence for the treatment of uncomplicated gonorrhea but additional comparative evidence is needed.[9]

Type II topoisomerase inhibitors are a new class of antibiotics used for the treatment of uUTIs and gonorrhea, in which there are two approved therapies, gepotidacin and zoliflodacin. Gepotidacin is approved to treat uUTIs and uncomplicated urogenital gonorrhea in adults and pediatric patients.[10] Zoliflodacin is approved for the treatment of uncomplicated urogenital gonorrhea in adults and pediatric patients.[11]

Important outcomes in the study of uUTI are resolution of symptoms and microbiological cure to prevent the progression of the infection to pyelonephritis. The 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).[12] Microbiological cure, 7-14 days after treatment, and prevention of complications are important outcomes in treatment of gonorrhea.[13]

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness

Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, no systematic reviews met inclusion criteria due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

EAU – Urological Infections 2025
The EAU 2025 Guidelines provide updated recommendations for the use of antibiotics for urological infections.[1] Recommendations pertaining to antibiotic use will be presented. Type II topoisomerase inhibitors were not approved at the time of guideline publication and therefore were not included in the publication. Evidence is graded from 1a (Highest Quality of Evidence) to 4 (Expert Opinion). Antibiotic selection should be guided by spectrum and susceptibility patterns, efficacy, tolerability, adverse reactions, costs and availability. Strength of recommendations range from Strong to Weak and are presented in **Table 1**. Cystitis is considered localized (i.e., no systemic infection in either sex) or systemic (i.e., pyelonephritis, prostatitis, etc.).[1] Oral cephalosporins are not recommended for empiric therapy for cystitis due to risk of adverse effects on the environment (i.e., creating highly resistant organisms) and aminopenicillins are not recommended due to high resistance rates and increased selection for Extended-Spectrum Beta-Lactamase (ESBL)-producing bacteria, but both can be used in select cases (Strong recommendation).[1] Fluoroquinolones should not be used unless it is considered inappropriate to use other antibiotics.

Table 1. EAU Antibiotic Recommendations for People with Urological Infections[1]

Diagnosis	Antibiotic Recommendation	Comments / Strength of Recommendation
Cystitis	Pivmecillinam 400 mg three times daily for 3-5 days	• First-line option in women / Strong
	Fosfomycin trometamol 3 g as a single dose	• First-line option in women / Strong
	Nitrofurantoin monohydrate/macrocrystal or nitrofurantoin macrocrystal prolonged release 100 mg twice daily for 5 days	• First-line option in women / Strong
	TMP/SMX 160/800 mg twice daily for 3 days or trimethoprim alone 200 mg twice daily for 5 days	• Alternative option • First choice only in areas with known resistance rates for *E.coli* of <20%
	Cephalosporins (e.g. cefadroxil 500 mg twice daily for 3 days)	• Other comparable cephalosporins can be used
	TMP/SMX or fluoroquinolone for at least 7 days	• First-line in men due to risk of prostate involvement

Cystitis in Pregnancy	Penicillins, cephalosporins, fosfomycin, nitrofurantoin, trimethoprim and sulfonamides can be considered	• Check for patient allergies • Trimethoprim should not be used in the first trimester of pregnancy and TMP/SMX is not recommended in the last trimester of pregnancy
Prevention of Recurrent Cystitis	- Nitrofurantoin 50 mg or 100 mg once daily - Fosfomycin trometamol 3 g once a week - Trimethoprim 100 mg once daily	• No evidence of statistically significant difference in efficacy between antibiotics for recurrent cystitis
	- Cephalexin 125 or 250 mg once daily - Cefaclor 250 mg once daily	• Recommended for pregnant women with cystitis
Pyelonephritis (outpatient)	- Fluoroquinolones (i.e., ciprofloxacin, levofloxacin) - Cephalosporins (i.e., cefpodoxime, ceftibuten) - TMP/SMX	• Fluoroquinolones are first-line / Strong • Only classes recommended for oral empirical therapy • If any class is used besides a fluoroquinolone, an initial intravenous dose of long-acting parenteral antimicrobial (e.g., ceftriaxone) should be used
Urethritis	Ceftriaxone and azithromycin for genitourinary urethritis	• Recommended first-line / Level 2a • Use nucleic acid amplification test (NAAT) to guide treatment
	- Ceftriaxone 1-2 gm intramuscular or intravenously as a single dose - Doxycycline 100 mg twice daily for 7 days	• For gonococcal infections
	Doxycycline 100 mg twice daily for 7 days	• For non-gonococcal infections (e.g., *Chlamydia trachomatis*)
	Azithromycin 1 gm day one and 500 mg days 2-4	• For *Mycoplasma genitalium*
	Doxycycline 100 mg twice daily for 7 days	• For *Ureaplasma urealyticum*
	Metronidazole 1.5-2 gm as a single dose	• For *Trichomonas vaginalis*
Acute Bacterial Prostatitis	Fluoroquinolone for 4-6 weeks	• First-line for empirical treatment
	Doxycycline 100 mg twice daily for 10 days	• Only for *C. trachomatis* or mycoplasma infections
	Azithromycin 500 mg once daily for up to 3 weeks	• Only for *C. trachomatis*
	Metronidazole 500 mg three times daily for 14 days	• Only for *T. vaginalis*
Chronic Bacterial Prostatitis	Fluoroquinolone	• First-line / Strong
	Doxycycline	• Only for *C. trachomatis*
	Macrolide	• If intra-cellular bacteria / Strong
	Metronidazole	• For *Trichomonas vaginalis* / Strong
Abbreviation: TMP/SMX – trimethoprim/sulfamethoxazole		

New Indications:

Gepotidacin (BLUJEPA): In December of 2025 gepotidacin was approved for the additional indication of the treatment of uncomplicated urogenital gonorrhea caused by *N. gonorrhoeae* in adult and pediatric patients 12 years of age and older and weighing at least 45 kilograms.[10] Prior to this expanded indication, gepotidacin was only approved to treat uUTI. The dose is different than the dose used for uUTI. Gepotidacin should be given as 3,000 mg (four 750 mg tablets) orally for one dose followed 12 hours later by a second dose of 3,000 mg (four 750 mg tablets).[10] Approval was based off of one, open-label, noninferiority, randomized trial comparing gepotidacin to ceftriaxone 500 mg IM in combination with a single 1 gram oral dose of azithromycin (**Table 2**).[2] Microbiological success was similar in the gepotidacin group (92.6%) and the ceftriaxone/azithromycin group (91.2%) (TD -0.1%; 95% CI, -5.6 to 5.5).[2]

New FDA Safety Alerts:

None identified.

Randomized Controlled Trials:

A total of 57 citations were manually reviewed from the initial literature search. After further review, 56 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Ross, et al[2] (EAGLE-1) NI, OL, Phase 3, RCT	Gepotidacin as 2 doses (3,000 mg given 10-12 hours apart) Vs. Ceftriaxone 500 mg IM and azithromycin 1g orally for one dose	Ages 12 years and older, body weight of 45 kg or more, suspected uncomplicated urogenital gonorrhea or positive lab test for *N. gonorrhoeae* or both	Microbiological success (culture-confirmed bacterial eradication at test-of-cure days 4-8)	Gepotidacin: 92.6% Ceftriaxone /azithromycin: 91.2% TD -0.1% (95% CI, -5.6 to 5.5) noninferiority margin met	- Majority of participants were male (92%) and MSM (71%). - Mean age was 33.1 years a range of 17-64 years. There was no breakdown of number of pediatric patients - Patients from the US comprised only 14% of the participants. Other sites included United Kingdom, Spain, Germany, Austria and Mexico (all areas of relatively low to moderate resistance) - Mild-moderate GI AE seen in gepotidacin group more than comparator

Abbreviations: AE = adverse events; CI = confidence interval; GI = gastrointestinal; IM = intramuscular; MSM = men who have sex with men; NI = noninferiority; OL = open label; RCT = randomized controlled trial; TD = treatment difference.

NEW DRUG EVALUATION: NUZOLVENCE (zoliflodacin)

Zoliflodacin is indicated for the treatment of uncomplicated urogenital gonorrhea due to *N. gonorrhoeae* in adults and pediatric patients who are least 12 years old and weight a least 35 pounds.[11] Zoliflodacin works by inhibiting spiropyrimidinestrione bacterial type II topoisomerase. Zoliflodacin is given as a suspension that should be mixed with water and given within 15 minutes of mixing.[11] The recommended dose is 3 g (one packet) given as a single oral dose for adult and pediatric patients. Patients that weigh 35 kg to up to 50 kg should take zoliflodacin on an empty stomach and those who weigh 50 kg or more should take zoliflodacin with food.[11] Mixing zoliflodacin with other liquids or sprinkling on foods should not be done.

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 5**.

Clinical Efficacy:

Approval of zoliflodacin is based off one open-label, noninferiority RCT (**Table 3**).[2] Patients with signs and symptoms of urogenital gonorrhea, a positive test confirming urogenital gonorrhea within the preceding 14 days or a history of unprotected sex with a partner with confirmed *N. gonorrhoeae* infection were included. Patients were randomized 2:1 to zoliflodacin 3 gm dose (n=621) or ceftriaxone 500 mg IM plus a single oral 1 gm dose of azithromycin (n=309).[3] The mean age was 30 years old with a range of 16-73 years. There were 14 patients under the age of 18 years included in the study.[3] Patients from the US represented 17% of the population. Analysis was done on the microbiological intention-to-treat urogenital population. Patients with baseline antibiotic susceptibility testing showing no preexisting resistance to both ceftriaxone and azithromycin were included in the primary endpoint analysis.[3] Sites of gonorrhea infection were from the following regions: urogenital (80%), rectal (12%) and pharyngeal (9%).[3] Baseline isolate resistance to azithromycin (6-11%), ciprofloxacin (75-86%) and tetracycline (92-100%) were similar across anatomical sites. Only one patient had a baseline isolate resistant to ceftriaxone. The primary outcome was proportion of patients with microbiological cure at the urogenital site assessed at TOC visit on day 6 (±2 days).[3] Microbiological cure was defined as negative or indeterminate *N. gonorrhoeae* culture. The noninferiority margin was less than 12% for the upper bound of the two-sided 95% CI, which is higher than the 10% noninferiority margin recommended by the FDA.[14] Participants were followed up to day 30.

Microbiological TOC rates in the microbiological intent to treat (ITT) population were 90.9% in the zoliflodacin group and 96.2% in the comparator group (TD 5.3%; 95% CI, 1.4 to 8.6) groups, which met the noninferiority margin.[3] Secondary analysis of the per protocol population found 96% of patients taking zoliflodacin cured and 99.5% of the comparator group cured (TD 3.5%; 95% 1.0 to 5.8).[3] Efficacy of zoliflodacin at other sites besides urogenital were not powered to determine efficacy; however, cure rates were similar between rectal and pharyngeal sites.

Limitations to the study include the open-label design in which providers and patients were not blinded to treatment. The use of an objective primary outcome, such as microbiological cure, helps to minimize bias; however, other outcomes such as adverse events may be subject to bias. Most of the patients were male from areas with high prevalence of gonorrhea infections which may reduce the external validity to other populations.

Clinical Safety:

The most common adverse events with zoliflodacin use, occurring in 2% or more of the study population, were headache, neutropenia, leukopenia, dizziness, nausea and diarrhea.[11] Most adverse events were mild to moderate and there were no serious adverse events. Animal studies have demonstrated embryo-fetal

toxicity and zoliflodacin use should be avoided during pregnancy.[11] Potential embryo-fetal toxicity related to males with female partners of reproductive potential has been identified and contraception should be advised for at least 3 months after administration of zoliflodacin.[11] Zoliflodacin has also been associated with a potential to cause testicular toxicity and impair male fertility based on animal studies.[11] Plasma concentrations of zoliflodacin may be reduced when used with other moderate or strong CYP3A4 inducers so concomitant use is not recommended.

Zoliflodacin has not been studied beyond a single dose and patients were only followed for 30 days after use. Additional safety studies are needed on repeated dosing and long-term use.

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) Microbiological cure

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Luckey, et al [3] NI, OL, Phase 3, RCT	1. Zoliflodacin 3 g orally as a single dose 2. Ceftriaxone 500 mg IM plus azithromycin 1 g orally as a single dose	Demographics: Mean age: 29.7 years Younger than 18 years: 14 (2%) Male: 88% African American: 55% White: 12% HIV positive: 22% US participants: 158 (17%) Key Inclusion Criteria: - 12 years of age and older - Signs and symptoms of urethral or endocervical gonorrhea - Positive lab test confirming urogenital gonorrhea in the preceding 14 days or history of unprotected	ITT: 1. 621 2. 309 Microbiological ITT: 1. 506 2. 238 PP: 1. 434 2. 218 Attrition: 1. 50 (9%) 2. 24 (11%)	Primary Endpoint: Proportion of patients with microbiological cure on day 6* in the microbiological ITT population: 1.460 (90.9%) 2.229 (96.2%) TD 5.3% (95% CI, 1.4 to 8.6) non-inferiority margin set at 12% or less and was met Secondary Endpoints: Proportion of patients with microbiological cure on day 6 in the per protocol population*: 1. 434 (96%) 2. 218 (99.5%) TD 3.5% (95% CI, 1.0 to 5.8)	NA	Headache: 1. 61 (10%) 2. 14 (5%) Neutropenia: 1. 42 (7%) 2. 24 (8%) Leukopenia: 1. 24 (4%) 2. 7 (2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Computer-generated random numbers and treatment allocation via a web-based randomization system. Randomized 2:1. Baseline characteristics were similar between groups. Performance Bias: (high) Treatment assignment was known to participant and clinical trial site personnel. Detection Bias: (low) Microbiology staff was blinded to treatment allocation. Attrition Bias: (low) Low amount of attrition and similar between groups. Per protocol population is preferred for non-inferiority trials. Reporting Bias: (low) The study was conducted as outlined in the methods. Other Bias: (unclear) The study was funded by several ministries of health and public health organizations. Many of the authors had conflicts of interest with industry. **Applicability**:

		sexual contact in the preceding 14 days with a partner with confirmed *N. gonorrhoeae* Key Exclusion Criteria: - Systemic or intravaginal antibiotic with activity against *N. gonorrhoeae* - Pregnant - Breastfeeding						Patient: Study results are most applicable to male participants who are diagnosed with urogenital gonorrhea and from areas of high gonorrhea activity and less commonly from the US. Patients were not resistant to ceftriaxone or azithromycin at baseline. Intervention: The combination of ceftriaxone and azithromycin was formerly a recommended treatment of choice but has fallen out of favor due to rising azithromycin resistance. Comparator: Dose of zoliflodacin was based off phase 2 trials. Outcomes: Microbiological cure is an appropriate primary outcome. Setting: Seventeen outpatient clinics in Belgium, the Netherlands, South Africa, Thailand, and the US.
Key: *Determined by eradication of Neisseria gonorrhoeae via urethral or endocervical cure at test-of-cure date (day 6 ± 2) Abbreviations: ARR = absolute risk reduction; CI = confidence interval; g = grams; HIV = human immunodeficiency virus; IM = intramuscular; ITT = intention to treat; mg = milligrams; N = number of subjects; NA = not applicable; NI = non-inferiority; NNT = number needed to treat; OL = open-label; PP = per protocol; RCT = randomized controlled trial; TD = treatment difference; US = United States								

References:

1. Bonkat G, Kranz J, Cai T, et al. EAU Guidelines on Urological Infections. European Association of Urology. March 2025. Available at:https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urological-infections-2025_2025-05-24-110339_pxmf.pdf. Accessed June 2, 2025.

2. Ross J, Wilson J, Workowski K, et al. Oral gepotidacin for the treatment of uncomplicated urogenital gonorrhoea (EAGLE-1): a phase 3 randomised, open-label, non-inferiority, multicentre study. Lancet. 2025;405(10489):1608-1620.

3. Luckey A, Balasegaram M, Barbee L, et al. Zoliflodacin versus ceftriaxone plus azithromycin for treatment of uncomplicated urogenital gonorrhoea: an international, randomised, controlled, open-label, phase 3, non-inferiority clinical trial. Lancet. 2026;407(10524):147-160.

4. Gupta K, Hooton T,, Naber K, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Disease Society of America and the European Society for Microbiolgoy and Infectious Disease. Clinical Infectious Diseases. 2011;52(5);e103-e120.

5. Wagenlehner F, Perry CR, Hooton TM, et al. Oral gepotidacin versus nitrofurantoin in patients with uncomplicated urinary tract infection (EAGLE-2 and EAGLE-3): two randomised, controlled, double-blind, double-dummy, phase 3, non-inferiority trials. *Lancet*. 2024;403(10428):741-755. doi:10.1016/S0140-6736(23)02196-7

6. Food and Drug Administration. FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. Drug Safety Communication. May 2016. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-advises-restricting-fluoroquinolone-antibiotic-use-certain. Accessed June 16, 2025.

7. Bash M, Connelly M. Epidemiology and pathogenesis of Neisseria gonorrhoeae infection. UpToDate by subscription. January 2026. Accessed February 10, 2026.

8. Centers for Disease Control and Prevention. Sexually Transmitted Infections Treatment Guidelines, 2021. Morbidity and Mortality Weekly Report. 2021;70(4).

9. Health Technology Review. The efficacy and safety of treatment options for uncomplicated gonococcal infection. Canada's Drug Agency. August 2024. Available at: https://www.cda-amc.ca/efficacy-and-safety-treatment-options-uncomplicated-gonococcal-infections. Accessed February 13, 2026.

10. Blujepa (gepotidacin) [prescribing information]. Durham NC; GlaxoSmithKline. December 2025.

11. Nuzolvence (zoliflodacin)[prescribing information]. Waltham, MA. La Jolla Pharmaceutical Company. December 2025.

12. US Food and Drug Administration. Uncomplicated Urinary Tract Infections: Developing Drugs for the Treatment Guidance for Industry-2019. Available at:https://www.fda.gov/media/129531/download. Accessed May 15, 2025.

13. Lazarus, J. Asymptomatic Bacteria in Adults. UpToDate. May 2025. Available at:https://www-uptodate-com.liboff.ohsu.edu/contents/asymptomatic-bacteriuria-in-adults?search=asymptomatic%20bacteriuria&source=search_result&selectedTitle=1~62&usage_type=default&display_rank=1. Accessed June 15, 2025.

14. Center for Drug Evaluation and Research. Integrated Review - Nuzolvence. Application number: 219491Orig1s000. Food and Drug Administration. November 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2026/219491Orig1s000IntegratedR.pdf. Accessed February 19, 2026.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
gepotidacin mesylate	BLUJEPA	TABLET	N
zoliflodacin	NUZOLVENCE	ORAL SUSP	

Appendix 2: Abstracts of Comparative Clinical Trials

Oral gepotidacin for the treatment of uncomplicated urogenital gonorrhoea (EAGLE-1): a phase 3 randomised, open-label, non-inferiority, multicentre study
Jonathan D C Ross, Janet Wilson, Kimberly A Workowski, et al

Background: Gepotidacin, a first-in-class, bactericidal, triazaacenaphthylene antibacterial that inhibits bacterial DNA replication, was shown to be efficacious and well tolerated in the treatment of uncomplicated urinary tract infections. We evaluated the efficacy and safety of gepotidacin for the treatment of uncomplicated urogenital gonorrhoea.
Methods: EAGLE-1 (NCT04010539) was a phase 3, open-label, sponsor-blinded, multicentre, non-inferiority study evaluating oral gepotidacin (two 3000 mg doses administered 10-12 h apart) compared with 500 mg intramuscular ceftriaxone plus 1 g oral azithromycin for the treatment of gonorrhoea. Eligible participants were aged 12 years and older, had a bodyweight over 45 kg, and had suspected uncomplicated urogenital gonorrhoea (including mucopurulent discharge), a positive laboratory test for Neisseria gonorrhoeae, or both. Participants were randomly allocated in a 1:1 ratio to each treatment group, stratified by sex (original urogenital anatomy at birth) and sexual orientation (men who have sex with men [MSM], men who have sex with women [MSW], and female) in combination, and age group (age <18 years, ≥18 to 65 years, or >65 years). The primary efficacy endpoint was microbiological success, defined as culture-confirmed bacterial eradication of N gonorrhoeae from the urogenital body site at test-of-cure (days 4-8). The non-inferiority margin was prespecified at -10%. The primary outcome was assessed in the microbiological intention-to-treat (micro-ITT) population, all participants randomly allocated to a study treatment who received at least one dose of their study treatment and had confirmed ceftriaxone-susceptible N gonorrhoeae isolated from the baseline culture of their urogenital specimen. The safety population comprised all participants who received one or more doses of any study treatment.
Findings: Between Oct 21, 2019, and Oct 10, 2023, 628 participants were randomly allocated (314 allocated to each treatment group). Overall, 39 (6%) of 628 participants discontinued the study prematurely (20 in the gepotidacin group and 19 in the ceftriaxone plus azithromycin group), with the primary reason being lost to follow-up. The micro-ITT population included 406 participants (202 in the gepotidacin group and 204 in the ceftriaxone plus azithromycin group). Most participants in the micro-ITT population were male (372 [92%] vs 34 [8%] female), and there was a higher percentage of participants who were MSM (290 [71%]) compared with participants who were MSW (82 [20%]). Participants were predominantly White (299 [74%]) or Black or African American (61 [15%]), with 70 (17%) identifying as Hispanic or Latino. Results of the primary analysis of microbiological response at test-of-cure demonstrated microbiological success rates of 92·6% (187 of 202 [95% CI 88·0 to 95·8]) in the gepotidacin group and 91·2% (186 of 204 [86·4 to 94·7]) in the ceftriaxone plus azithromycin group (adjusted treatment difference -0·1% [95% CI -5·6 to 5·5]). Gepotidacin was non-inferior to ceftriaxone plus azithromycin. No bacterial persistence of urogenital N gonorrhoeae was observed at test-of-cure for either group. The gepotidacin group had higher rates of adverse events and drug-related adverse events, mainly due to gastrointestinal adverse events, and almost all were mild or moderate. No treatment-related severe or serious adverse events occurred in either group.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 13, 2026
Search Strategy:

#	Searches	Results
1	gepotidacin.mp.	123
2	zolifodacin.mp.	1
3	1 or 2	124
4	limit 3 to yr="2024 -Current"	57

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUZOLVENCE safely and effectively. See full prescribing information for NUZOLVENCE.

NUZOLVENCE® (zoliflodacin) for oral suspension
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
NUZOLVENCE is a spiropyrimidinetrione bacterial type II topoisomerase inhibitor indicated for the treatment of uncomplicated urogenital gonorrhea due to *Neisseria gonorrhoeae* in adults and pediatric patients 12 years of age and older, weighing at least 35 kg. (1.1)

Usage to Reduce Development of Drug-Resistant Bacteria
To reduce the development of drug-resistant bacteria and maintain the effectiveness of NUZOLVENCE and other antibacterial drugs, NUZOLVENCE 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----------
- Pregnancy Testing: Obtain a pregnancy test in females of reproductive potential prior to initiating NUZOLVENCE. (2.1)
- NUZOLVENCE must be mixed with water before administering. (2.2)
- Do **not** mix NUZOLVENCE with other liquids or sprinkle on food. (2.2)
- Administer the entire dose within 15 minutes of mixing. If the dose is not administered within 15 minutes of mixing, a new dose of NUZOLVENCE must be prepared. (2.2, 2.4)
- Adults and pediatric patients 12 years of age and older, weighing at least 35 kg: Recommended dose is 3 g (one packet) administered as a single dose orally. (2.3)
- Patients weighing 35 kg to less than 50 kg: Administer NUZOLVENCE on an empty stomach, 1 hour before or 2 hours after food. (2.3)
- Patients weighing greater than or equal to 50 kg: Administer NUZOLVENCE with food. (2.3)
- See full prescribing information for complete details on preparation and administration of NUZOLVENCE. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For oral suspension: 3 g of zoliflodacin in each unit-dose packet of NUZOLVENCE. (3)

----------CONTRAINDICATIONS----------
- Known history of hypersensitivity to NUZOLVENCE. (4)
- Concomitant use with moderate or strong CYP3A4 inducers because this is predicted to result in decreased plasma concentrations of zoliflodacin and may reduce NUZOLVENCE efficacy. (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------
- Embryo-Fetal Toxicity: Potential Risk for Pregnant Females: May cause fetal harm when administered during pregnancy based on data from animal studies. Advise pregnant females about the potential risk to the fetus with maternal exposure to NUZOLVENCE. Avoid use of NUZOLVENCE during pregnancy. (5.1, 8.1, 8.3)
- Embryo-Fetal Toxicity: Potential Risk Related to Males with Female Partners of Reproductive Potential: Advise males with female partners of reproductive potential to use effective contraception for at least 3 months after administration of NUZOLVENCE. (5.2, 8.3, 13.1)
- Testicular Toxicity and Risks to Male Fertility: May cause testicular toxicity and impair male fertility based on data from animal studies. An assessment of spermatogenesis has not been conducted in humans. Advise males of the potential risk. (5.3, 8.3, 13.1)
- Hypersensitivity Reactions: Hypersensitivity reactions, including rash and pruritus, have been reported in patients receiving NUZOLVENCE. Discontinue NUZOLVENCE and institute appropriate supportive measures, if an allergic reaction occurs. (5.4)
- *Clostridioides difficile* Infection: Evaluate if diarrhea occurs. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions including laboratory abnormalities (incidence ≥2%) with NUZOLVENCE are neutropenia, headache, leukopenia, dizziness, nausea, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Entasis Therapeutics, Inc. at 1-800-651-3861 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2025

Appendix 5. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Spiropyrimidinetrione bacterial type II topoisomerase inhibitor
Oral Bioavailability	High-fat meal increases AUC by 40%
Distribution and Protein Binding	Fasted: 177 L / Fed: 98.7 L Protein binding 83%
Elimination	Fecal
Half-Life	Fasted: 19.1 L / Fed 12.5 L
Metabolism	CYP-mediated (mostly CYP 3A4/5 enzymes, with lesser contributions from CYP1A2, CYP2C9, CYP2C8 and CYP2C19) and non-CYP mediated pathways

Abbreviations: AUC = area under the curve; CYP = cytochrome; L = liter

Appendix 6: Key Inclusion Criteria

Population	Patients with uncomplicated urinary tract infection or uncomplicated gonorrhea
Intervention	Type II topoisomerase inhibitors
Comparator	Placebo or active comparison
Outcomes	Microbiological cure and symptom improvement
Setting	Outpatient