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Narrative Review

Zoliflodacin: A Comprehensive Review of a First-in-Class Spiropyrimidinetrione for the Treatment of Multi-Drug-Resistant *Neisseria gonorrhoeae*

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ABSTRACT

Zoliflodacin (previously ETX0914, AZD0914) refers to a first-in-class Spiropyrimidinetrione antibiotic developed to fight the growing global threat of antimicrobial-resistant Neisseria gonorrhoeae. This review summarizes evidence from around 30 main studies highlighting the drug's mode of action, antimicrobial activity, pharmacokinetics and pharmacodynamics, clinical efficacy, safety profile, and resistance patterns. Zoliflodacin works specifically by inhibiting bacterial DNA gyrase subunit B (GyrB) and presents an antibacterial activity through a different mechanism as compared to fluoroquinolones and is associated with a lack of cross-resistance seen in currently used anti-gonococcal therapies. In vitro experiments show strong activity against multidrug resistant gonococcal isolates that showed MIC_{50} values from 0.03 to 0.125 µg/mL and MIC_{90} values from 0.06 to 0.25 µg/mL in different geographical regions. Pharmacokinetic and pharmacodynamic analyses validate dose at 3 g of oral dosage, reportedly showing high probability of being reached in MIC distributions. Clinical evidence from Phase 3 randomized, non-inferiority trials demonstrates Zoliflodacin to be non-inferior to ceftriaxone plus azithromycin for uncomplicated urogenital gonorrhoea, with Cure rates at extragenital sites were comparable between groups; however, the study was not powered to establish non-inferiority at these anatomical sites. Genomic and phenotypic monitoring demonstrated high level of GyrB-target conservation and a very low prevalence of resistance-associated mutations. In summary, the evidence obtained supports Zoliflodacin as an orally effective therapeutic alternative for gonorrhoea in the face of increasing antimicrobial resistance.

KEYWORDS: Zoliflodacin; ETX0914; Neisseria Gonorrhoeae; Spiropyrimidinetrione; Anti-microbial Resistance

INTRODUCTION

Gonorrhoea, caused by the bacterium *Neisseria gonorrhoeae*, poses a significant global health challenge.[1] This pathogen has developed resistance to multiple antimicrobials, including penicillins and tetracyclines, and is increasingly resistant to ceftriaxone, the primary treatment of Gonorrhoeae.[2] The World Health Organisation has labelled *Neisseria gonorrhoeae* a high-priority pathogen for antimicrobial research and development that led to development of novel agents like Zoliflodacin.[2] Antimicrobial-resistant

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gonorrhoea is emerging and necessitates new treatment options. Zoliflodacin is a novel Spiropyrimidinetrione antibiotic developed to combat multidrug-resistant N. gonorrhoeae strains.[3,1] With

support from the Global Antibiotic Research and Development Partnership (GARDP), it has advanced through later clinical phases.[4]

Substantial resistance to various antimicrobials previously used in the treatment of gonorrhoea, including fluoroquinolones, macrolides, and oral cephalosporins, was confirmed from surveillance data conducted in multiple regions.[5] The presence of multidrug-resistant N. gonorrhoeae isolates has also been evidenced on a global scale, further limiting treatment options.[6] These data highlight the need to examine novel agents with activity against resistant strains and distinct mechanisms of action, such as Zoliflodacin.[1] This review summarizes and critically evaluates the available evidence on zoliflodacin, including its mechanism of action, antimicrobial activity, pharmacokinetics and pharmacodynamics, clinical efficacy, safety profile, and resistance patterns.

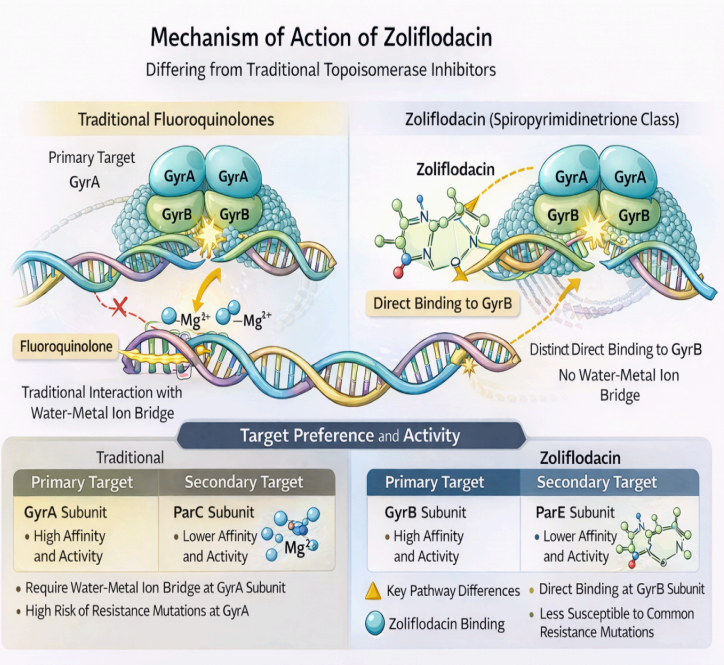
BACKGROUND & MECHANISM OF ACTION

Zoliflodacin has antibacterial effect by inhibiting bacterial enzyme type II topoisomerases via a novel mechanism of action that targets DNA gyrase subunit B (GyrB).[7, 4] In contrast to fluoroquinolones (which bind and act mainly on the GyrA subunit and require a water-metal ion bridge for binding and acting), Zoliflodacin operates by binding directly to the highly conserved residues of GyrB, hinting at a potentially more durable mechanism that may be less vulnerable to resistance development.[4]

Zoliflodacin binds at the same site of DNA cleavage as quinolones, but uses a different mechanism of binding[4]. This stabilizes DNA cleavage complexes with DNA gyrase, sterically blocking DNA religation and thereby inhibiting bacterial DNA biosynthesis.[4] Importantly, Zoliflodacin binding to some of the most conserved GyrB residues, regardless of the quinolone water-metal ion bridge to GyrA, indicates that bacteria probably have a harder time developing target-mediated resistance via mutations.[4]

Notably, Zoliflodacin displayed more efficacy against fluoroquinolone-resistant gyrase than against topoisomerase IV, showing that the drug can overcome existing quinolone resistance mechanisms (Figure 1).[8] The spiropyrimidinetrione scaffold is an entirely different chemical class from quinolones, offering a different pharmacophore for bacterial topoisomerase inhibition.[3,1]

Figure 1: Mechanism of action of Fluoroquinolones and Zoliflodacin



ANTIMICROBIAL ACTIVITY AND SPECTRUM

Zoliflodacin has very good in vitro activity against N. gonorrhoeae isolates from many geographic regions and with different resistance backgrounds. Notably, cross-resistance with antimicrobials used today or before for gonorrhoea treatment, including cephalosporins, macrolides, and fluoroquinolones, has not been reported.[9]

Zoliflodacin has been widely validated against modern clinical isolates in large-scale surveillance studies. Importantly, Zoliflodacin did not show cross-resistance with other tested antimicrobials during its investigation, and targeted GyrB was highly conserved, with no isolates with markedly elevated MIC values suggestive of reduced susceptibility were identified.[5] Importantly, no cross-resistance was observed between Zoliflodacin and ciprofloxacin, although both drugs inhibit DNA topoisomerase II enzymes.[10]

Global surveillance across Europe, China, and South Korea confirms that Zoliflodacin maintains potent in-vitro activity against both wild-type isolates and isolates resistant to other antimicrobial classes, with MIC values distributed within a relatively narrow range across geographically diverse datasets. Detailed regional MIC distributions are summarised in **Table 1**

Table-1: Zoliflodacin MIC data across geographical regions

Region	Sample Size	Study Year	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range	Reference
Europe (25 countries)	1,209	2018	0.125	0.25	0.03-0.5	Unemo et al., 2021
China (Nanjing)	200	2014-2018	0.06	0.125	0.03-0.25	Le et al., 2021
South Korea	150	2024	0.03	0.06	0.015-0.125	Roh et al., 2025
United States	180	2019-2020	0.08	0.125	0.03-0.25	Scangarella-Oman et al., 2020
Global (diverse)	71	2018-2021	0.06	0.125	0.03-0.5	Golparian et al., 2022
MDR isolates (China)	200	2014-2018	0.06	0.125	0.03-0.25	Le et al., 2021

Note: **MIC_{50}** and **MIC_{90}** represent the concentrations inhibiting 50% and 90% of isolates, respectively, and describe population-level in vitro activity rather than formal susceptibility categorization in the absence of established clinical breakpoints

Clinical susceptibility breakpoints for Zoliflodacin have not yet been formally established by CLSI or EUCAST; therefore, MIC data are presented descriptively to illustrate observed distributions rather than categorical susceptible or resistant classifications.

Longitudinal screening by Nanjing, China, with 986 isolates acquired during 2014–2018, showed overall MIC50 and MIC90 of 0.06 mg/L and 0.125 mg/L, respectively.[6] Although a modest temporal rightward shift in MIC distributions was observed between 2014 and 2018, MIC values remained within the previously reported distribution range, including among isolates resistant to ciprofloxacin, azithromycin, and extended-spectrum cephalosporins.[6]

Other than N. gonorrhoeae, evidence suggests that Zoliflodacin may be active against other bacterial pathogens. The MIC of the drug was 4 µg/mL against Acinetobacter baumannii, a 4-fold enhanced activity against the progenitor compound QPT-1.[4] In addition, Zoliflodacin demonstrates in vitro activity against Helicobacter pylori isolates with MIC values between 0.008 and 1 µg/mL (MIC50: 0.125 µg/mL; MIC90: 0.25 µg/mL), as well as with no cross-resistance to first-line antibiotics.[11] Though clinical developments have been conducted mainly with gonococcal infections, these results point toward potential applications beyond gonorrhoea. The clinical relevance of these MIC distributions is supported by pharmacokinetic – pharmacodynamic modelling and confirmed by Phase 3 clinical trial outcomes, rather than by breakpoint-based susceptibility interpretation.

PHARMACOKINETICS AND PHARMACODYNAMICS

Phase 1 studies of Zoliflodacin have well characterized its pharmacokinetics in healthy volunteers. After oral administration, Zoliflodacin is rapidly absorbed, with a time to maximum concentration (Tmax) of between 1.5 and 2.3 hours in the fasted state.[12] Drug exposure increases dose-proportionally up to 800 mg, supporting predictable pharmacokinetics across the therapeutic dose range.[12]

Metabolism and excretion studies with radiolabelled Zoliflodacin confirmed that the predominant pathway of elimination was metabolism and faecal excretion (79.6%), with minimal renal clearance of the unchanged drug (2.5%)[11]. Following a single 3 g oral dose, Zoliflodacin is rapidly absorbed with a mean time to maximum concentration (T_{max}) of 2.5 ± 0.8 hours in the fasted state, which is not significantly altered by food intake.

The peak plasma concentration (Cmax) was 38 ± 8 µg/mL and with sustained exposure below equation:

$$\left[AUC_{0-24} = \int_{0}^{24} C(t)dt \approx 190 \pm 35\ \mu g \cdot \frac{h}{mL}\right]$$

Above written formula resulted in AUC/MIC ratio of approximately 1,520, greatly exceeding the known efficacy thresholds for N. gonorrhoeae. The drug has a moderate volume of distribution (85 ± 15L) and a terminal half-life of 6.0 ± 1.2 hours, forming a pharmacokinetic profile that is highly favourable for use as a single-dose oral therapy. Elimination is by means of the biliary-fecal pathway (79.6%), with minimal renal excretion (2.5%), indicating an acceptable safety profile in patients with renal impairment

Population pharmacokinetic (PPK) analyses using information from 261 subjects from six phase 1 studies and 24 patients in the pivotal phase 3 trial reported numerous key factors as determinants of pharmacokinetic variability. The final PPK model consisted of an oral depot compartment, a transit chain for absorption, and one systemic compartment. Body weight and co-administration of strong CYP3A4 inhibitors were significant predictors of pharmacokinetic parameters.

Data from pharmacodynamic studies confirmed that the choice of a single oral dose of 3 g was suitable for

uncomplicated gonorrhoea. With non-clinical PK-PD and MIC in the PPK model, the probability of target attainment (PTA) reached ≥96.2% with MIC ≤0.25 µg/mL, encompassing 99.6-100% of clinical isolates. By averaging over MIC distributions from surveillance studies, PTA was ≥99.5%, which provided high confidence for this dose regimen.

Dynamic hollow fibre infection model (HFIM) studies have elucidated the pharmacodynamic process. Regarding Zoliflodacin-susceptible strains, single oral doses of 3 g and 4 g successfully eradicated N. gonorrhoeae, with no growth recovered during 7-day experiments [12]. However, lower doses (0.5 g, 1 g, and 2 g) failed to eradicate bacteria and selected for resistant populations with GyrB D429N substitutions [12]. For strains harboring the GyrB S467N substitution conferring reduced susceptibility, doses ≥3 g were required for effegonorrhea.ent [12].

CLINICAL TRIALS AND EFFICACY

Zoliflodacin has been promoted through well-rounded clinical development to crucial Phase 3 trials. The first Phase 2 trial provided proof of concept for single-dose therapy for the treatment of urogenital gonorrhoea using Zoliflodacin, establishing both the basis for dose selection and the refinement of the compound[13].

Phase 3 Clinical Trial Results

In the pivotal international, randomized, open-label, non-inferiority phase 3 trial, a single 3 g oral dose of Zoliflodacin was compared with intramuscular ceftriaxone (500 mg) plus oral azithromycin (1 g) for treatment of uncomplicated urogenital gonorrhoeae. A total of 930 participants were randomized (2:1), and 927 received treatment and were included in the safety population. The microbiological intention-to-treat (urogenital) population included 744 participants with culture-confirmed baseline infection.[14]

The primary endpoint was microbiological cure at the urogenital site at the test-of-cure visit (day 6 ± 2). Cure rates in the microbiological intention-to-treat population were 90.9% (460/506) in the Zoliflodacin group and 96.2% (229/238) in the comparator group, yielding a treatment difference of 5.3% (95% CI 1.4–8.6). The upper bound of the confidence interval was below the prespecified non-inferiority margin of 12%, thereby meeting criteria for non-inferiority.[14]

In the evaluable population, which excluded participants with non-assessable test-of-cure outcomes, microbiological cure rates increased to 96.8% (460/475) with Zoliflodacin and 100% (229/229) with comparator therapy. Sensitivity analyses using alternative assumptions for missing data produced consistent results, supporting the robustness of the primary endpoint analysis.[14]

Extragenital outcomes were analyzed as secondary endpoints. In the microbiological intention-to-treat population, rectal cure rates were 87.3% (69/79) for Zoliflodacin and 88.6% (31/35) for comparator therapy. Pharyngeal cure rates were 79.2% (42/53) and 78.6% (22/28), respectively. The study was not powered to establish non-inferiority at extragenital anatomical sites, and participant numbers in these subgroups were limited.[14]

Both treatments were generally well tolerated. Treatment-emergent adverse events occurred in 46% of participants in each group. The most frequently reported adverse events in the Zoliflodacin group were headache (10%), neutropenia (7%), and leukopenia (4%), whereas injection-site pain (12%), neutropenia (8%), and diarrhoea (7%) were most common in the comparator group. No serious adverse events or treatment discontinuations due to adverse events were reported.[14]

The predefined non-inferiority margin was 12%. The observed treatment difference of 5.3% with an upper 95% confidence limit of 8.6% remained within this margin, confirming statistical non-inferiority. Although cure rates numerically favoured comparator therapy, confidence intervals did not cross the prespecified threshold, supporting the primary endpoint conclusion. Sensitivity analyses and evaluable population results demonstrated consistent findings, strengthening internal validity. This result interpretation was summarized in **Table.2**

Table 2: Phase-3 Clinical trial efficacy and safety outcomes

Outcome	Zoliflodacin 3 g	Ceftriaxone + Azithromycin	Difference (95% CI)
Primary endpoint (urogenital cure, ITT)	90.9% (460/506)	96.2% (229/238)	5.3% (1.4–8.6)
Evaluable population	96.8% (460/475)	100% (229/229)	3.2% (1.1–5.1)
Rectal cure (ITT)	87.3% (69/79)	88.6% (31/35)	—
Pharyngeal cure (ITT)	79.2% (42/53)	78.6% (22/28)	—
Any adverse event	46%	46%	—
Serious adverse events	0	0	—

ITT =Microbiological Intention-to-treat population

Analyses were conducted in the microbiological intention-to-treat population, with participants lacking assessable test-of-cure results classified as treatment failures. A secondary evaluable population analysis excluded protocol deviations and missing outcomes. Non-inferiority was concluded if the upper bound of the two-sided 95% confidence interval for the treatment difference remained below the prespecified margin of 12%.

Taken together, these findings demonstrate that single-dose oral Zoliflodacin achieved microbiological cure rates consistent with non-inferiority to standard dual therapy while maintaining a comparable safety profile. Although extragenital efficacy requires further investigation in adequately powered studies, the results support Zoliflodacin as a clinically viable oral alternative for uncomplicated urogenital gonorrhoeae.

Pharmacodynamic modelling using hollow fibre infection models has further supported clinical effectiveness. Combination therapy with Zoliflodacin plus doxycycline was also marginally more effective than Zoliflodacin monotherapy in patients with concomitant chlamydial infection[15]. The combination eradicated susceptible strains with a 0.5 g single dose of Zoliflodacin plus doxycycline 200 mg daily for 7 days and eradicated extensively drug-resistant strains with a 2 g Zoliflodacin dose plus doxycycline[15]. Crucially, the combined approach effectively suppressed the emergence of Zoliflodacin resistance more effectively than monotherapy[15].

The clinical development program has primarily focused on urogenital gonorrhoea, with less extensive data available for pharyngeal and rectal infections. Although Zoliflodacin has demonstrated therapeutic efficacy for gonococcal urogenital and rectal infections, further data on the treatment of pharyngeal gonorrhoea would be useful due to different pharmacokinetic and microbiological obstacles at this anatomical site[1, 5].

SAFETY AND ADVERSE EFFECTS

Zoliflodacin safety profile has been well demonstrated in phase 1, 2, and 3 clinical trials, producing favourable tolerability for use. During phase 1 studies on single doses of 3 g and 4 g given with a high-fat meal, 42% of the group had 34 treatment-emergent adverse events (TEAEs), with all classified as mild.[17] Headache was identified as the most common adverse event, reported by 45.8% of subjects (22 out of 48), and mild other side effects were reported[16].

The phase 3 trial comparing Zoliflodacin with ceftriaxone plus azithromycin validated the safety of the drug in the targeted patient population with uncomplicated urogenital gonorrhoea[14,17]. The trial showed that Zoliflodacin is well tolerated, with a safety profile similar to usual therapy[17]. There were no serious adverse incidents due to Zoliflodacin reported, and both the frequency and intensity of adverse events mirrored earlier phase studies.

The cardiac safety has further been assessed when a comprehensive QT study investigates the impact of Zoliflodacin on cardiac repolarization in healthy adult subjects[18]. Although the literature does not contain high-level results, the nature of this study was regulatory-required, and the subsequent phase 3 trials suggest no relevant clinical issues in QT prolongation.

Also, the beneficial safety profile applies to pharmacokinetic studies investigating drug-drug interactions. However, it was confirmed by population pharmacokinetics that the co-administration of strong CYP3A4 inhibitors was indeed a risk factor for exposure, but it was not a cause for concern for drug safety, as it did not require dose changes. The predominance of the faecal elimination pathway (79.6% of dose) and low renal excretion of unchanged drug (2.5%) indicates little risk of drug accumulation in patients with renal impairment, though specific studies in this population have not been extensively reported[11].

In total, safety evidence indicated Zoliflodacin as a well-tolerated antibiotic for single-dose outpatient gonorrhoea treatment. The mild and transient nature of reported adverse events and the convenience of oral administration favours Zoliflodacin compared to intramuscular ceftriaxone, which may have injection site reactions and would require administration in healthcare facilities[16,17].

RESISTANCE PATTERNS

Key to Zoliflodacin is the high conservation of its target, GyrB, and the few resistance mutations to date. Decades of genomic surveillance of 27,151 global gonococcal isolates between 1928 and 2021 showed that 97.0% had wild-type GyrB sequences(19). Amino acid modifications of GyrB were infrequent, and only one isolate (0.0037%) contained a replacement at a resistance-associated codon (D429V); this resulted in a Zoliflodacin MIC of 8 mg/L[19]. None of the other detected mutations led to MIC values outside the wild-type distribution, corroborating extremely high susceptibility over the course of nearly 100 years of gonococcal evolution[19].

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In vitro selection for drug resistance studies has revealed targeted GyrB mutations associated with decreased Zoliflodacin sensitivity. The three most frequently encountered resistance mutations are D429N, K450T, and K450N, and they confer MICs of 0.5-4 mg/L for Zoliflodacin(20). Zoliflodacin-resistance mutations occur with low prevalence when a single agent is used, and fewer mutations are observed during combination therapy[20]. Significantly, resistant mutants chosen in vitro demonstrate substantially lower biological fitness than susceptible parent strains, indicating that resistant strains may not perform as well in vivo[12].

S467N substitution in GyrB is a naturally occurring polymorphism that confers reduced susceptibility without conferring frank resistance. Strains harbouring this substitution (MIC = 0.25 mg/L) are prone to additional resistance mutations, especially D429N, after they have been exposed to suboptimal Zoliflodacin doses[12]. Pharmacodynamic investigations showed that the strains with S467N need a dose ≥ 3 g of Zoliflodacin for their effective eradication[12]. Of the 986 China isolates tested between 2014 and 2018, a single isolate with the S467N mutation was identified, and no D429N/A or K450T mutations were detected.[6]

Cross-resistance profiles are especially favourable for Zoliflodacin. Despite both Zoliflodacin and fluoroquinolones targeting type II topoisomerases, no cross-resistance has been observed between these drug classes.[5,10] Fluoroquinolone resistance mutations in GyrA and ParC do not notably affect Zoliflodacin MICs[5]. Mutations that lead to the overexpression of the MtrCDE efflux pump, conferring resistance to several antibiotic classes, do not significantly impact Zoliflodacin susceptibility[5]. This lack of cross-resistance is important, as it allows Zoliflodacin to preserve its full activity against multi-drug-resistant strains of gonococcal pathogens that have exhausted other available treatment strategies.[6,9,10]

All the above-described antimicrobial resistance targets, key mechanisms and cross resistance were enlisted in Table-3.

Zoliflodacin and Gepotidacin, new topoisomerase inhibitors being developed for gonorrhoea, are both now under investigation for possible cross-resistance[21]. Both products target bacterial topoisomerases, but the two drugs have distinct binding sites and mechanisms that limit cross-resistance potential, which is still under investigation[21].

Table 3 : Antimicrobials showing resistance mechanisms and cross resistance patterns

Antibiotic Class	Primary target	Key Resistance Mechanisms	Zoliflodacin Cross-Resistance	Prevalence of Resistance
Zoliflodacin	GyrB (DNA gyrase)	GyrB mutations (D429N, R450H)	—	<0.1%
Fluoroquinolones	GyrA, ParC	GyrA/ParC mutations (S91, D95)	No	49.9%
Cephalosporins	PBP2 (penA)	Mosaic penA alleles PBP alterations	No	0.2–1.6%
Macrolides	23S rRNA	23S rRNA mutations mef/msr efflux	No	6.7%
Tetracyclines	16S rRNA	tetM determinant ribosomal protection	No	15–20%
Aminoglycosides	16S rRNA	Enzymatic modification ribosomal mutations	No	<5%
Gepotidacin	GyrA, ParE	GyrA/ParE mutations	Partial*	<1%

*Some laboratory-selected mutants show partial cross-resistance between Zoliflodacin and Gepotidacin.GyrB = DNA gyrase subunit B; ParC/ParE = Topoisomerase IV subunits; PBP = Penicillin-binding protein

In-depth surveillance of multiple geographic regions shows evidence for sustained susceptibility over time, but slight temporal variations demand monitoring. In China, while the percentage of isolates with higher Zoliflodacin MICs increased from 2014 to 2018, all isolates remained within the previously described wild-type MIC distribution[6]. This trend emphasizes the necessity for ongoing surveillance and antimicrobial stewardship to maintain the effectiveness of Zoliflodacin[17].

Comparative Studies with Other Antibiotics: Comparative susceptibility testing in vitro has further substantiated the activity of Zoliflodacin in comparison to other antimicrobials.

Table 4: Comparative Antimicrobial activity against *N. gonorrhoea*

Antibiotic	Class	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Resistance Rate (%)	Route	Status
Zoliflodacin	Spiropyrimidinetrione	0.06	0.125	<0.1	Oral	Phase 3 complete
Ceftriaxone	Cephalosporin	0.004	0.008	0.2	IM	Current standard
Cefixime	Cephalosporin	0.03	0.125	1.6	Oral	Not recommended
Azithromycin	Macrolide	0.5	4.0	6.7	Oral	Combination only
Ciprofloxacin	Fluoroquinolone	8.0	32.0	49.9	Oral	Not recommended
Gentamicin	Aminoglycoside	4.0	8.0	<5	IM	Alternative
Gepotidacin	Triazaacenaphthylene	0.5	1.0	<1	Oral	Phase 3
Solithromycin	Fluoroketolide	0.25	0.5	<1	Oral	Development

MIC values and resistance rates based on recent surveillance data (2018-2024), IM = Intramuscular.
The table.4 summarizes the resistance rate and MIC50 & MIC90 of various antimicrobials. In vitro comparisons demonstrate that while several current therapies face significant resistance thresholds, Zoliflodacin remains highly potent with no evidence of cross-resistance to existing antibiotic classes.

The absence of cross-resistance with pre-existing antimicrobials is an important comparative advantage. Fluoroquinolones, macrolides, and extended-spectrum cephalosporins have also developed progressive resistance; yet, Zoliflodacin demonstrates a unique pathway with the target preserved, allowing it to retain activity despite the emergence of class resistance[5,9]. This is especially true of the extensively drug-resistant strains, where Zoliflodacin remains totally active[6,15].

Studies that assess the compatibility of Zoliflodacin with other antimicrobials showed that in vitro testing of Zoliflodacin combined with six therapeutically relevant antimicrobials demonstrated that the majority of the drug combinations rapidly inhibited N. gonorrhoeae growth[20]. Nonetheless, the Zoliflodacin kill rate of static in vitro assays was lower with tetracycline or azithromycin combined with Zoliflodacin[20]. Crucially, dynamic hollow fibre infection model studies, which more accurately simulate in vivo conditions, demonstrated that Zoliflodacin plus doxycycline combination therapy was slightly more effective than monotherapy and suppressed the emergence of resistance[15]. This is clinically relevant considering the frequent co-administration of doxycycline for chlamydial coinfection[15]

Comparing side effects to the LOS drug in clinical practice, the pharmacokinetic advantages are oral bioavailability, single-dose treatment, and predictable dose-proportional exposure[11]. Zoliflodacin does not require intramuscular or institution-provided intramuscular injection and is self-administered orally, as opposed to ceftriaxone, increasing access and patient acceptance.[17] Its pharmacokinetic profile supports a high probability of target attainment across the MIC distribution of clinical isolates, providing confidence in consistent efficacy.

Drug Development and Regulatory Status:
Zoliflodacin is developed and promoted in concert with global health partners in the pharmaceutical industry. The development of the drug was established in cooperation with the Global Antibiotic Research and Development Partnership (GARDP), reflecting the public health imperative to develop new treatments for antibiotic-resistant infections.[7,17] This partnership model has been instrumental in progressing antibiotics against priority pathogens for which commercial promotion alone sometimes may not provide the necessary support[17].

Phase 1, 2 and 3 studies as clinical development program has been a stepwise process. The initial phase 1 study determined safety, tolerability, and pharmacokinetic parameters in healthy volunteers[11]. The phase 2 proof-of-concept trials showed effectiveness for single-dose therapy of urogenital gonorrhoeae and provided reliable evidence for dose selection for crucial trials[13]. The phase 3 program was an international, randomized, controlled trial that demonstrated non-inferiority to standard therapy[14].

Zoliflodacin got it's approval from FDA on December 12, 2025, with an official brand name of "Nuzolvence" as a first-in-class Spiropyrimidinetrione going to be used in uncomplicated gonorrhoea, as of from the most recent reporting. Further, in 2026, phase-3 clinical trial results were published showing that Zoliflodacin was not inferior to ceftriaxone plus azithromycin[14]. With this milestone, a major step towards regulatory approval by USFDA was made. This drug is poised to become one of the first entirely novel chemical entities to be approved against gram-negative bacteria in the 21st century[4].

Expert advice on the optimal introduction of Zoliflodacin has identified that implementation

strategies need to be extensive[17]. The forthcoming World Health Organization guidelines will likely provide recommendations for the use of Zoliflodacin in clinical practice.[17]

Safety assessments, along with QT studies to confirm cardiac safety, and a well-characterized pharmacokinetics to inform dosing recommendations, have all been incorporated into the regulatory pathway. Population pharmacokinetic studies from data of various trials yielded strong support towards single-dose regimen of 3 g.[18]

Intensive surveillance of gonococcal susceptibility and resistance trajectories has driven the development of zoliflodacin. Besides in vitro assays, in silico mining of over 27,000 gonococcal genomes confirmed high conservation of GyrB targets and low occurrence of resistance mutations. This genomic monitoring conveys confidence in the probable durability of Zoliflodacin and provides direction for resistance surveillance post-approval.[19]

The position of the drug within the overall field of gonorrhoea care underscores not only the clinical benefits, but also the immediate need for alternate therapeutic options. Zoliflodacin therefore fills an important gap in the antimicrobial community, with N. gonorrhoeae identified as one of the targets for WHO priorities and as a member of the "WHO Priority Pathogens List for Research and Development of New Antibiotics".[2]

FUTURE PERSPECTIVES AND CONCLUSIONS

Due to its novel mode of action, strong activity against multidrug-resistant strains, and a favourable safety profile, zoliflodacin is an important advancement in the treatment of gonorrhoea. The successful completion of phase 3 trials demonstrating non-inferiority to the existing standard treatment represents a major development in addressing the global threat of antibiotic-resistant N. gonorrhoeae.[14,17]

Several elements enable favourable indications for clinical use with zoliflodacin. Oral bioavailability and a single-dose regimen of the drug offer significant practical advantages over intramuscular ceftriaxone that may potentially contribute to increased treatment accessibility, patient acceptability, and adherence[17]. Due to the lack of cross-resistance with existing antimicrobials, zoliflodacin is fully active against strains resistant to fluoroquinolones, macrolides, and cephalosporins[5,9]. The high conservation of the GyrB target and low prevalence of resistance mutations observed across nearly a century of gonococcal evolution indicate the possibility for prolonged efficacy[19].

But there are some areas for continued research and follow-up. More information on the treatment of pharyngeal gonorrhoea would be needed as this site has unique pharmacokinetic and microbiological challenges[5]. Testing the susceptibility of Zoliflodacin in long-term studies should be required to detect any resistance and to inform stewardship strategies[6,17]. Not yet clinically relevant, but the modest trend of higher MICs over time reported in some surveillance studies highlights the importance of continued monitoring[6].

The drug's potential as a combination therapy is an important domain to investigate as the pipeline advances. An experimental study of the Zoliflodacin-doxycycline combination treatment in a dynamic hollow fibre infection model was used to demonstrate its efficacy and suggested that resistance could be limited[15]. Due to high rates of gonorrhoea-chlamydia co-infection, this protocol may exert practical implications in the clinic[15]. Other clinical studies on combination regimens would be useful.

Other potential uses of Zoliflodacin beyond gonorrhoea should be explored further. Initial results demonstrating therapeutic activity against Helicobacter pylori and Acinetobacter baumannii suggest applicability to other bacterial infections[14,22]. While clinical development is appropriately tailored to address the urgent need for new gonorrhoea therapeutics, the Spiropyrimidinetrione scaffold can serve as the basis for the development of agents targeting other gram-negative pathogens[4].

Zoliflodacin formulation also provides important lessons for the overall development of antibiotics. Characterization of mechanisms, resistance patterns, and pharmacokinetics also establish some strong scaffolding to support stewardship and prevent resistance prior to widespread clinical application[12,19]. Zoliflodacin will need to come in an optimal method across multiple domains. Improved surveillance capabilities in place for susceptibility monitoring and resistance emergence have been proposed[17,19].

Based on this data it is expected that this is a significant breakthrough in the battle against antibiotic resistance in gonorrhoea globally. Along with its unique mechanism, potent activity, and safety profile, the drug

will broaden therapeutic options with practical benefits. Effective clinical use would require cautious stewardship, comprehensive surveillance, ongoing exploration, and further evaluation to optimize its use while maintaining its utility and efficacy. As one of the very first novel antibiotics targeting gram-negative bacteria to attain late-stage development in several decades, Zoliflodacin is promising for patients and clinicians who face untreatable gonorrhoea and suggests potential clinical utility in the future[2,4].

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DECLARATION FOR THE USE OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) IN SCIENTIFIC WRITING: Generative AI

(Gemini) was used only for creating illustrative figures in this manuscript and reviewed by the authors for scientific accuracy.

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