CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219491Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	219491
PDUFA Goal Date	December 15, 2025
TTT #	2025-14181, 2025-14184
Reviewer Name	Brad Moriyama, Pharm.D., BCCCP, DRM
Team Leader	Naomi Boston, Pharm.D., DRM
Acting Division Director	Laura Zendel, Pharm.D., DRM
Review Completion Date	December 10, 2025
Subject	Evaluation of Need for a REMS
[Established/Proper] Name	zoliflodacin
Trade Name	Nuzolvence
Name of Applicant	Entasis Therapeutics Inc.
Therapeutic Class	spiropyrimidinetrione bacterial type II topoisomerase inhibitor
Dosage Form(s)	oral suspension: 3 g of zoliflodacin in each unit-dose packet
Dosing Regimen	3 g administered as a single dose orally

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nuzolvence (zoliflodacin) is necessary to ensure the benefits outweigh its risks. Entasis Therapeutics Inc. submitted a New Drug Application (NDA) 219491 for zoliflodacin with the proposed indication for uncomplicated gonorrhea due to *Neisseria gonorrhoeae* in adult and pediatric patients 12 years and older, weighing at least 35 kg. During the course of the review, the Division of Anti-Infectives (DAI) revised the indication to: for the treatment of uncomplicated urogenital gonorrhea due to *N. gonorrhoeae* in adults and pediatric patients 12 years of age and older, weighing at least 35 kg. The Applicant did not submit a proposed REMS or risk management plan with this application.

The efficacy of zoliflodacin was demonstrated in the pivotal trial STI_Zoli001, in which the zoliflodacin treatment group had a microbiological cure rate of 90.9% and the ceftriaxone and azithromycin treatment group had a microbiological cure rate of 96.2%. The clinical reviewer concluded that zoliflodacin was noninferior to ceftriaxone and azithromycin for the treatment of uncomplicated urogenital gonorrhea. The serious risks associated with zoliflodacin include embryo-fetal toxicity: potential risk for pregnant females, embryo-fetal toxicity: potential risk related to males with female partners of reproductive potential, and testicular toxicity and risks to male fertility. Zoliflodacin demonstrated reproductive toxicity in nonclinical repeat-dose studies, including embryo-fetal toxicity (exencephaly) in gravid mice, reduced fertility in male rats administered zoliflodacin prior to mating, increased embryonic loss in untreated female rats mated with male rats administered zoliflodacin, and testicular toxicity (decreased spermatogenesis and degeneration) in male rats and dogs. Other serious risks include hypersensitivity reactions, *Clostridioides difficile* infection, and development of drug-resistant bacteria.

DRM and DAI agree that a REMS is not necessary to ensure the benefits of zoliflodacin outweigh its risks. The serious risks associated with zoliflodacin noted above will be communicated in the warnings and precautions section of the label and a Medication Guide. None of the risks associated with zoliflodacin rise to the level of a boxed warning. In addition, the likely prescribers will be primary care providers, obstetrics and gynecology practitioners, and infectious diseases specialists who should be knowledgeable regarding counseling for pregnancy testing in females of reproductive potential and counseling the need for contraception for males with female partners of reproductive potential. The likely prescribers should also have experience managing the other serious adverse events reported with zoliflodacin, as well as other therapies used in the treatment of sexually transmitted infections.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Nuzolvence (zoliflodacin) is necessary to ensure the benefits outweigh its risks. Entasis Therapeutics Inc. submitted a New Drug Application (NDA) 219491 for zoliflodacin with the proposed indication for uncomplicated gonorrhea due to *Neisseria gonorrhoeae* in adult and pediatric patients 12 years and older, weighing at least 35 kg.[b] This application is under review in the Division of Anti-Infectives (DAI). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Nuzolvence (zoliflodacin), a NME, is proposed for uncomplicated gonorrhea due to *N. gonorrhoeae* in adult and pediatric patients 12 years and older, weighing at least 35 kg. Zoliflodacin is a spiropyrimidinetrione inhibitor of the bacterial type II topoisomerases (DNA gyrase and topoisomerase IV), which are required for DNA synthesis. The elimination half-life in fasted and fed patients is 6.4 hours and 5.5 hours, respectively. Zoliflodacin is proposed to be supplied as an oral suspension, 3 g of zoliflodacin in each unit-dose packet. The proposed dosing regimen in adult and pediatric patients 12 years and older, weighing at least 35 kg is 3 g (one packet) administered as a single dose orally.[c] In patients weighing 35 kg to less than 50 kg, zoliflodacin is administered on an empty stomach 1 hour before or 2 hours after food. In patients weighing greater than or equal to 50 kg, zoliflodacin is administered with food. Zoliflodacin is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for zoliflodacin NDA 219491 relevant to this review:

- 04/11/2019: Fast track designation granted
- 04/16/2019: Qualified infectious disease product designation granted

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Entasis Therapeutics Inc. Nuzolvence (zoliflodacin). NDA 219491. Draft Prescribing Information with Agency Edits as of December 5, 2025.

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 04/15/2025: NDA 219491 submission for uncomplicated gonorrhea due to *N. gonorrhoeae* in adult and pediatric patients 12 years and older, weighing at least 35 kg received
- 10/16/2025: A Post Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there is currently no plan for a REMS for zoliflodacin

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Gonorrhea is a sexually transmitted infection caused by the bacterium *N. gonorrhoeae*.[d,e] It is the second most commonly reported bacterial communicable disease in the United States.[e] The reported cases of gonorrhea in the United States in 2023 was 601,319, with reported cases in women of 221,176 and in men of 378,428, respectively.[f,g] Uncomplicated gonorrhea may occur in anatomical sites including the urogenital tract, oropharynx, rectum, and eye.[h] Most women with gonorrhea do not have any symptoms.[i] In men, symptoms may include a burning sensation when urinating, a white, yellow, or green discharge from the penis, and painful or swollen testicles. Bacterial resistance is an urgent issue with *N. gonorrhoeae* infections, including the emergence of resistance to extended-spectrum

[d] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Anti-Infectives (DAI). Integrated Review: Nuzolvence (zoliflodacin), NDA 219491 Draft as of December 5, 2025.

[e] Centers for Disease Control and Prevention, 2021, Sexually Transmitted Infections Treatment Guidelines, Morbidity and Mortality Weekly Report, 70(4):1–187.

[f] Sexually Transmitted Infections Surveillance, 2024 (Provisional), STI Statistics: Centers for Disease Control and Prevention, accessed November 25, 2025, https://www.cdc.gov/sti-statistics/annual/index.html.

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[h] Entasis Therapeutics Inc. Nuzolvence (zoliflodacin). NDA 219491. Clinical Overview. April 15, 2025.

[i] Sexually Transmitted Infections, About Gonorrhea, Centers for Disease Control and Prevention, accessed December 8, 2025, https://www.cdc.gov/gonorrhea/about/index.html.

cephalosporin antibiotics.[j] Untreated *N. gonorrhoeae* infection may lead to pelvic inflammatory disease, infertility, ectopic pregnancy, and disseminated infections in both men and women.[d,j,k]

3.2. Description of Current Treatment Options

The Centers for Disease Control and Prevention (CDC) guidelines for Sexually Transmitted Infections Treatment recommend ceftriaxone 500 mg IM single dose for uncomplicated gonococcal infection of the cervix, urethra, rectum, or pharynx.[e] Alternative regimens for uncomplicated infection of the cervix, urethra, or rectum if ceftriaxone is not available include gentamicin plus azithromycin or cefixime. The CDC guidelines state to maximize adherence with recommended therapies and reduce complications and transmission, medication for gonococcal infection should be provided on-site and directly observed.

Ceftriaxone, a cephalosporin antibiotic, was approved by the FDA in 1984; it is approved for indications including uncomplicated gonorrhea (cervical/urethral and rectal) caused by *N. gonorrhoeae*, including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase producing strains of *N. gonorrhoeae*.[l] The serious risks associated with ceftriaxone in the warnings and precautions section of the label include hypersensitivity reactions, interaction with calcium-containing products, neurological adverse reactions, *Clostridium difficile*-Associated Diarrhea, hemolytic anemia, development of drug-resistant bacteria, effect on prothrombin time, gallbladder pseudolithiasis, urolithiasis and post-renal acute renal failure, and pancreatitis.

None of these drugs listed above have a REMS.

4. Benefit Assessment

The pivotal trial STI_Zoli001 (NCT 03959527) supporting this application for efficacy and safety consisted of a Phase 3, randomized, open-label, active-controlled, multicenter, multinational trial which evaluated zoliflodacin in patients with suspected uncomplicated gonorrhea due to *N. gonorrhoeae*.[b,d] The primary analysis population was the microbiologic intent-to-treat (micro-ITT) urogenital population which included patients who had *N. gonorrhoeae* isolated at baseline from the urethra or cervix and who were not infected with a strain that showed resistance to both ceftriaxone and azithromycin at baseline. Patients (N=930) were randomized to zoliflodacin 3 g oral single dose (N=506 micro-ITT population) or ceftriaxone 500 mg intramuscular and azithromycin 1 g oral single dose (N=238 micro-ITT population).

[j] Allan-Blitz LT, Fifer H, and Klausner JD, 2024, Managing treatment failure in Neisseria gonorrhoeae infection: current guidelines and future directions, Lancet Infect Dis, 24(8):e532-e538.

[k] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[l] Ceftriaxone package insert. Lake Forest, IL: Hospira, Inc.; 2022 March.

The primary efficacy endpoint was microbiological cure as determined by confirmed bacterial eradication of *N. gonorrhoeae* at the urogenital body site at the test of cure visit (Day 4 to 8) and was assessed in the micro-ITT urogenital population. The zoliflodacin treatment group had a microbiological cure rate of 90.9% and the ceftriaxone and azithromycin treatment group had a microbiological cure rate of 96.2% (difference -5.3%, 95% confidence interval -8.7 to -1.4). The clinical reviewer concluded that zoliflodacin was noninferior to ceftriaxone and azithromycin for the treatment of uncomplicated urogenital gonorrhea.[m]

During the course of the review, the DAI revised the indication to: for the treatment of uncomplicated urogenital gonorrhea due to *N. gonorrhoeae* in adults and pediatric patients 12 years of age and older, weighing at least 35 kg. The indication was revised to restrict use of zoliflodacin to treatment of uncomplicated urogenital gonorrhea, as the primary endpoint of the pivotal phase 3 trial was microbiological cure as determined by culture at the urogenital site.

5. Risk Assessment & Safe-Use Conditions

The safety of zoliflodacin was evaluated in a Phase 3 clinical trial STI_Zoli001.[b,d,n] In the safety population, 619 patients received zoliflodacin and 308 patients received ceftriaxone and azithromycin. Common adverse reactions including laboratory abnormalities reported with zoliflodacin were neutropenia, headache, leukopenia, dizziness, nausea, and diarrhea.

The serious risks[o] associated with zoliflodacin include embryo-fetal toxicity: potential risk for pregnant females, embryo-fetal toxicity: potential risk related to males with female partners of reproductive potential, testicular toxicity and risks to male fertility, hypersensitivity reactions, *Clostridioides difficile* infection, and development of drug-resistant bacteria. If approved, these risks will be communicated in the warnings and precautions section of the label and a Medication Guide. The serious risks associated with zoliflodacin of embryo-fetal toxicity and testicular toxicity and risks to male fertility are summarized in the paragraphs below.

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[m] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[n] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[o] A Serious Adverse Event (SAE) is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Embryo-fetal toxicity: potential risk for pregnant females

Zoliflodacin may cause fetal harm based on animal studies. Zoliflodacin has been reported to cause fetal malformations (exencephaly) and increased embryo-fetal loss in reproductive and developmental toxicity studies at AUC exposures 1.6-fold (mice) and 8.5-fold (rats) the maximum recommended human dose (MRHD) to pregnant rodents during organogenesis. No clinical data is available with zoliflodacin in pregnancy in humans. A Division of Pediatric and Maternal Health (DPMH) consult recommended addition of a warnings and precautions for embryo-fetal toxicity to labeling, but did not recommend a contraindication for pregnancy since the causal relationship between exposure to zoliflodacin during pregnancy and exencephaly is not well established and the risk to humans is theoretical.[p] DPMH recommended addition of pregnancy testing to the proposed label due to the concerning animal findings of exencephaly. However, a contraception was not recommended as zoliflodacin will only be administered as a single oral dose and has a relatively short half-life. The proposed label states to advise pregnant females about the potential risk to the fetus with maternal exposure to zoliflodacin and to avoid use of zoliflodacin during pregnancy. The proposed label recommends obtaining a pregnancy test prior to initiation of treatment in females of reproductive potential**.**

Embryo-fetal toxicity: potential risk related to males with female partners of reproductive potential

The risk of early pregnancy loss may be increased in female partners of males treated with zoliflodacin based on an animal study. Reduced number of live embryos and increased number of embryonic losses were observed in untreated female rats mated with male rats administered zoliflodacin at exposures approximately 3.9-times the clinical exposure at the MRHD for 4 weeks. The risk may be related to the testicular toxicity or a direct effect causing decreased sperm quality, however, no direct data on sperm from clinical or nonclinical studies is available.[d] A Division of Urology, Obstetrics and Gynecology (DUOG) consult recommended warnings in product labeling to convey the potential risks to male reproduction. DUOG recommended to advise males with female partners of reproductive potential to use effective contraception for at least 3 months (time it takes for sperm to regenerate) after single-dose administration of zoliflodacin.[p,q]

Testicular toxicity and risks to male fertility

Zoliflodacin may cause testicular toxicity and impair male fertility based on animal studies. Minimal to moderate decreased spermatogenesis and testicular histopathological changes were observed in rats and dogs administered zoliflodacin for durations of 2 days to 4 weeks at AUC exposures 3- to 11-times the MRHD. In rats, loss of male fertility was no longer observed 4 weeks after the last dose, but testicular histopathological changes in rats and dogs were only partially reversible after 2 to 3 months. A DUOG consult indicated that zoliflodacin is a testicular toxin in rats and dogs and recommended a

[p] Ceresa C, Dinatale M, Yao LP. Division of Pediatrics and Maternal Health. Internal Consult for Nuzolvence (zoliflodacin), NDA 219491. Pregnancy and Lactation Labeling Formatting and Recommendations. October 6, 2025.

[q] Dannis M, Hirsch MS, Gassman A. Division of Urology, Obstetrics and Gynecology (DUOG). Internal Consult for Nuzolvence (zoliflodacin), NDA 219491. September 26, 2025

warnings in product labeling to convey the potential risks to male reproduction.[q] However, DUOG indicated that testing of male reproductive function in humans has not been done and the impact of zoliflodacin on human male reproduction is currently unknown. The proposed label states an evaluation of spermatogenesis has not been conducted in humans. Advise males that zoliflodacin may cause testicular toxicity and impair male fertility.

The clinical reviewer concluded while the available data indicate that zoliflodacin's safety profile is acceptable for its intended use as a single dose treatment, the potential safety risks related to the nonclinical signals will be described in zoliflodacin's labeling. There were no serious risks associated with zoliflodacin that rise to the level of a boxed warning. DAI is recommending post-marketing requirements (PMRs) including a descriptive pregnancy safety study to evaluate pregnancy outcomes in females exposed to zoliflodacin during pregnancy and a human testicular function study to evaluate the impact of zoliflodacin administration on sperm count and viability.

6. Expected Postmarket Use

Sexually transmitted diseases are diagnosed at various health care settings including primary care clinics, physician offices, emergency departments, family planning clinics, community health centers, and sexually transmitted diseases clinics.[r] The likely prescribers include primary care providers, such as internal medicine practitioners including nurse practitioners and physician assistants, family physicians, obstetrics and gynecology practitioners, and infectious diseases specialists. If approved, zoliflodacin will likely be prescribed in the outpatient setting and dispensed by outpatient pharmacies or provided on-site in a health care setting for self-administration. The likely prescribing population should be knowledgeable regarding pregnancy testing in females of reproductive potential and contraception for males with female partners of reproductive potential. The likely prescribers should also have experience managing the other serious adverse events reported with zoliflodacin. Labeling which includes a Medication Guide and instructions for use is sufficient to ensure the safe-use conditions described in Section 5 for mitigating the risks associated with zoliflodacin.

7. Discussion of the Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of zoliflodacin outweigh the risks.

The efficacy of zoliflodacin was demonstrated in the STI_Zoli001 study, in which the zoliflodacin treatment group had a microbiological cure rate of 90.9% and the ceftriaxone and azithromycin

[r] Centers for Disease Control and Prevention, 2020, Recommendations for Providing Quality Sexually Transmitted Diseases Clinical Services, Morbidity and Mortality Weekly Report, 68(5):1–20.

treatment group had a microbiological cure rate of 96.2%. The serious risks associated with zoliflodacin of embryo-fetal toxicity: potential risk for pregnant females, embryo-fetal toxicity: potential risk related to males with female partners of reproductive potential, testicular toxicity and risks to male fertility, hypersensitivity reactions, *C. difficile* infection, and development of drug-resistant bacteria will be communicated in the warnings and precautions section of the label and a Medication Guide. Zoliflodacin demonstrated reproductive toxicity in nonclinical repeat-dose studies, including embryo-fetal toxicity (exencephaly) in gravid mice, reduced fertility in male rats administered zoliflodacin prior to mating, increased embryonic loss in untreated female rats mated with male rats administered zoliflodacin, and testicular toxicity (decreased spermatogenesis and degeneration) in male rats and dogs.[d] However, there are no clinical data regarding zoliflodacin exposure during pregnancy and the risk to humans remains theoretical based on nonclinical data. In addition, there is no human data on the effects of fertility from zoliflodacin use and the impact of zoliflodacin on human male reproduction is currently unknown.[p,q] None of the risks associated with zoliflodacin rise to the level of a boxed warning. The clinical reviewer concluded while the available data indicate that zoliflodacin's safety profile is acceptable for its intended use as a single dose treatment, the potential safety risks related to the nonclinical signals will be discussed in zoliflodacin's labeling. The proposed label recommends obtaining a pregnancy test prior to initiation of treatment in females of reproductive potential, to advise males with female partners of reproductive potential to use effective contraception for at least 3 months after administration of zoliflodacin, and to advise males that zoliflodacin may cause testicular toxicity and impair male fertility.

In evaluating the necessity of a REMS for the safe use of this product, DRM determined that a REMS will be unfeasible to mitigate the risk of embryo-fetal toxicity and testicular toxicity. Pregnancy testing and counseling regarding contraceptive use for males and females will be likely done by healthcare providers at the point of zoliflodacin prescribing. Zoliflodacin is administered as a single oral dose. In this scenario, education and counseling on pregnancy prevention is the primary source of mitigating potential embryo-fetal toxicity, which is already commonly practiced amongst the likely prescribers for zoliflodacin. In addition, commonly used resources are available that include information on pregnancy prevention, risks, and monitoring (e.g., UpToDate) for patients with sexually transmitted infections. The likely prescribers will be primary care providers (internal medicine practitioners including nurse practitioners and physician assistants, family physicians), obstetrics and gynecology practitioners and infectious diseases specialists who should be knowledgeable regarding pregnancy testing in females of reproductive potential and contraception for males with female partners of reproductive potential. The likely prescribers should also have experience managing the other serious adverse events reported with zoliflodacin, as well as other therapies used in the treatment of sexually transmitted infections.

DAI is recommending PMRs including a descriptive pregnancy safety study to evaluate pregnancy outcomes in females exposed to zoliflodacin during pregnancy and a human testicular function study to evaluate the impact of zoliflodacin administration on sperm count and viability.

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for zoliflodacin beyond routine pharmacovigilance and labeling.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for zoliflodacin to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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