NDA 219491

NDA APPROVAL

Entasis Therapeutics, Inc.
Attention: Marie Minassian
Senior Director, Regulatory Operations
930 Winter Street, Suite 1500
Waltham, MA 02451

Dear Marie Minassian:

Please refer to your new drug application (NDA) received April 15, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nuzolvence (zoliflodacin) for oral suspension.

This NDA provides for the use of Nuzolvence (zoliflodacin) for oral suspension 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of the Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 219491**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Nuzolvence (zoliflodacin) for oral suspension shall be 36 months from the date of manufacture when stored in the original packaging at room temperature 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F). [See USP Controlled Room Temperature.]

ADVISORY COMMITTEE

Your application for Nuzolvence was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of Nuzolvence (zoliflodacin) in the treatment of uncomplicated urogenital gonorrhea.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 12 years of age because necessary studies are impossible or highly impracticable as uncomplicated urogenital gonorrhea does not commonly occur in pediatric patients less than 12 years of age.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We note that you have fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of a serious risk of adverse maternal, fetal, neonatal, and infant outcomes resulting from the use of zoliflodacin during pregnancy, to identify an unexpected serious risk of the potential presence of zoliflodacin in human breast milk resulting in effects on the breastfed infant, to assess a signal of a serious risk of the development of drug resistance to zoliflodacin, and to assess a signal of a serious risk of reduced fertility and testicular toxicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4942-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Nuzolvence (zoliflodacin) during pregnancy to assess risk of maternal complications and adverse effects on the developing fetus, neonate, and infant during the first year of life.

The minimum number of patients will be specified in the protocol.

The timetable you submitted on November 26, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2026
Final Protocol Submission:	01/2027
Interim Report Submission:	10/2030
Study Completion:	07/2036
Final Report Submission:	01/2037

4942-2 Perform a lactation study (milk only or mother-infant pair study) in lactating women who have received Nuzolvence (zoliflodacin) to measure concentrations of zoliflodacin in breast milk using a validated assay.

Assess the effects on the breastfed infant, if available, based on the study population.

The timetable you submitted on November 26, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2026
Final Protocol Submission:	10/2026
Study Completion:	12/2027
Final Report Submission:	06/2028

4942-3 Conduct a U.S. surveillance study over a five-year period after the introduction of Nuzolvence (zoliflodacin) to the market to determine if resistance or decreased susceptibility to Nuzolvence is occurring in the target population of bacteria that are in the approved Nuzolvence label.

The timetable you submitted on November 26, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2026
Final Protocol Submission:	12/2026
Interim Report #1 Submission:	10/2028
Interim Report #2 Submission:	10/2029
Interim Report #3 Submission:	10/2030
Interim Report #4 Submission:	10/2031
Interim Report #5 Submission:	10/2032
Study Completion:	10/2032
Final Report Submission:	06/2033

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of reduced fertility and testicular toxicity.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4942-4 Conduct a clinical trial to evaluate the effect of Nuzolvence (zoliflodacin) on human testicular function.

The timetable you submitted on November 26, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2026
Final Protocol Submission:	06/2026
Study Completion:	12/2027
Final Report Submission:	06/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 118958 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o), REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[7] https://www.uspnf.com/

If you have any questions, contact Joseph Nguyen, PharmD, Regulatory Project Manager, at Joseph.Nguyen@fda.hhs.gov or call (301) 348-3937.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling

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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