NDA 215151

NDA APPROVAL

Phathom Pharmaceuticals, Inc.
Attention: Esha Desai, MS, RAC
Director, Regulatory Affairs
2150 East Lake Cook Road, Suite 800
Buffalo Grove, IL 60089

Dear Ms. Desai:

Please refer to your new drug application (NDA) dated and received March 11, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Voquezna (vonoprazan) tablets.

We acknowledge receipt of your amendment dated May 19, 2023, which constituted a complete response to our February 7, 2023, action letter.

This NDA provides for the use of Voquezna (vonoprazan) tablets:

- for healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
- to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
- in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults.
- in combination with amoxicillin for the treatment of *H. pylori* infection in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter with minor editorial revisions listed below and reflected in the enclosed labeling.

- Added page numbers to the Patient Package Insert

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, Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL 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 carton and container labeling submitted on May 19, 2023, 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 215151**." 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 Voquezna (vonoprazan) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F).

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 identify an unexpected serious risk of congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes , including assessing risks of adverse effects on the developing neonate.

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:

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

4367-1 Conduct a prospective, registry based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to vonoprazan-containing products during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on October 23, 2023, states that you will conduct these trials according to the following schedule:

Final Protocol Submission:	12/2023
Interim Report:	07/2024
	07/2025
	07/2026
	07/2027
	07/2028
	07/2029
	07/2030
	07/2031
	07/2032
	07/2033
	07/2034
	07/2035
Study Completion:	07/2035
Final Report Submission:	04/2036

4367-2 An additional pregnancy study that uses a different design from the Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to vonoprazan-containing products during pregnancy compared to an unexposed control population.

The timetable you submitted on October 23, 2023, states that you will conduct these trials according to the following schedule:

Draft Protocol Submission:	12/2023
Final Protocol Submission:	07/2024
Interim Report:	07/2025

	07/2026
	07/2027
	07/2028
	07/2029
	07/2030
	07/2031
Study Completion:	07/2031
Final Report Submission:	04/2032

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.

Submit clinical protocols to your IND 079212 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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 protocols 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.

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 the indications 1) in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* (*H. pylori*) infection and 2) in combination with amoxicillin for the treatment of *H. pylori* infection because necessary studies are impossible or highly impracticable as the prevalence of *H. pylori* infection that requires treatment is low in the pediatric population.

We are also waiving the pediatric study requirement for the indications of 1) healing of erosive esophagitis and relief of heartburn associated with erosive esophagitis and 2) to maintain healing of erosive esophagitis and relief of heartburn associated with erosive esophagitis in ages birth to less than 1 month because necessary studies are impossible or highly impracticable. The number of pediatric patients with erosive esophagitis in this age group is limited.

We are deferring submission of your pediatric studies for ages 1 month to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

4367-3 Complete the ongoing randomized, parallel-group, multiple-dose, 14-day dose-ranging study to evaluate the pharmacokinetics and safety of Voquezna (vonoprazan) in pediatric patients 12 to <18 years of age with gastroesophageal reflux disease with or without erosive esophagitis.

Final Report Submission: 02/2024

4367-4 Conduct a randomized, parallel-group, multiple-dose, 14-day, dose ranging study to evaluate the pharmacokinetics and safety of Voquezna (vonoprazan) in pediatric patients ≥ 6 to <12 years of age with gastroesophageal reflux disease with or without erosive esophagitis.

Trial Completion: 01/2025
Final Report Submission: 07/2025

4367-5 Conduct a randomized, parallel-group, multiple-dose, 14-day, dose ranging study to evaluate the pharmacokinetics and safety of Voquezna

(vonoprazan) in pediatric patients ≥1 month to <1 year of age with erosive esophagitis and pediatric patients ≥1 year to <6 years of age with gastroesophageal reflux disease with or without erosive esophagitis.

Final Protocol Submission:	01/2025
Trial Completion:	12/2026
Final Report Submission:	06/2027

4367-6 Conduct a trial to evaluate the efficacy and safety of Voquezna (vonoprazan) for the healing of endoscopically confirmed erosive esophagitis and relief of heartburn symptoms and the maintenance of healed erosive esophagitis and relief of heartburn symptoms in pediatric patients ≥1 month to <18 years of age with endoscopically confirmed erosive esophagitis. The trial will include two study periods: an 8-week healing phase and a randomized, blinded, placebo-controlled 24-week maintenance phase.

Final Protocol Submission:	08/2024
Trial Completion:	08/2030
Final Report Submission:	02/2031

4367-7 Develop an age-appropriate formulation for pediatric patients 1 month to <6 months of age.

Final Report Submission:	01/2025

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 the protocols to your IND 079212, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[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.

PROMOTIONAL MATERIALS

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

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Juli Tomaino, MD, MS
Deputy Division Director
Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[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

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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/

JULI A TOMAINO
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