NDA 216196/S-003

**SUPPLEMENT APPROVAL**

Agios Pharmaceuticals, Inc.
Attention: María R. Trolliet, Ph.D.
Director, Regulatory Affairs
88 Sidney Street
Cambridge, MA 02139

Dear Dr. Trolliet:

Please refer to your supplemental new drug application (sNDA) dated and received November 7, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aqvesme (mitapivat) tablets.

We acknowledge receipt of your major amendment dated August 26, 2025, which extended the goal date by three months.

This Prior Approval sNDA provides for a new indication for the treatment of anemia in adults with alpha- or beta-thalassemia and for a proposed risk evaluation and mitigation strategy (REMS).

## 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.

## 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 and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

## 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 216196/S-003**." Approval of this submission by FDA is not required before the labeling is used.

## 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

[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.

## 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 assess a signal of a serious risk of changes in reproductive hormones, changes in blood lipids, bone fractures and other adverse events associated with long-term aromatase inhibition.

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.

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 changes in reproductive hormones, changes in blood lipids, bone fractures and other adverse events associated with long-term aromatase inhibition.

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

4931-1 Complete Trial AG348-C-018: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Mitapivat in Subjects with Transfusion-Dependent Alpha- Or Beta-Thalassemia (Energize-T). The final study report will include patient level data and a summary of all adverse events including changes in reproductive hormones, changes in blood lipids, bone fractures and other adverse events associated with long-term aromatase inhibition.

The timetable you submitted on November 10, 2025, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Trial Completion: | 06/2026 |
| Final Report Submission: | 01/2027 |

4931-2 Complete Trial AG348-C-017: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Mitapivat In Subjects With Non-Transfusion-Dependent Alpha- Or Beta-Thalassemia (Energize). The final study report will include patient level data and a summary of all adverse events including hepatotoxicity, changes in reproductive hormones, changes in blood lipids, bone fractures and other adverse events associated with long-term aromatase inhibition.

The timetable you submitted on November 10, 2025, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Trial Completion: | 02/2026 |
| Final Report Submission: | 09/2026 |

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 protocols to your IND 119825 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).**

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.

## RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of an approved drug outweigh the risks.

[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.

Mitapivat, under the trade name Pyruknd, was approved on February 17, 2022. As part of a review of clinical trials AG348-C-017 and AG348-C-018 conducted in patients with non-transfusion-dependent and transfusion-dependent alpha-or beta-thalassemia under NDA 216196/S-003 for Aqvesme (mitapivat), we have become aware of a serious risk of hepatocellular injury. We consider this information to be "new safety information" as defined in section 505-1(b) of the FDCA.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Aqvesme to ensure the benefits of the drug outweigh the risk of hepatocellular injury.

Your proposed REMS must include the following:

**Elements to Assure Safe Use:** Pursuant to 505-1(f)(1), we have determined that elements to assure safe use are necessary to mitigate the risk of hepatocellular injury listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate this serious risk.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring

**Implementation System:** The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on August 26, 2025, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Aqvesme into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

For each metric, provide the two previous, current and cumulative reporting periods (where applicable) unless otherwise noted.

**Implementation and Operations**

1. REMS Implementation (12-month assessment only)
    a. Date of first commercial distribution of Aqvesme
    b. Date when the Aqvesme REMS website became live and fully operational
    c. Date when the Aqvesme REMS portal became live and fully operational
    d. Date when healthcare providers could become certified
    e. Date when pharmacies could become certified
    f. Date when patients could become enrolled
    g. Date when the REMS Coordinating Center was established and fully operational
        i. Average wait times for REMS participants, stratified by time period prior to when the REMS website and portal were fully operational and time period after the REMS website and portal were fully operational
            1) Describe actions taken to mitigate burden to REMS participants
    h. Summarize any implementation issues and action taken, stratified by whether these issues impacted the REMS website and portal, the REMS Coordinating Center, or other (specify)
    i. If the REMS website and portal were not fully operational before commercial distribution began, describe actions taken to ensure REMS participants could become certified and submit Patient Enrollment Forms, Patient Status Forms, Patient Reinitiation Forms, and Liver Adverse Event Reporting Forms to the REMS
2. REMS Certification and Enrollment Statistics
    a. Healthcare Providers
        i. Number of newly certified healthcare providers
        ii. Total number of healthcare providers certified at the end of the reporting period
        iii. Number and percentage of active healthcare providers (i.e., those who have prescribed Aqvesme at least once during the reporting period) stratified by credentials, (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Advanced Practice Registered Nurse, Physician Assistant, Other), medical specialty and geographic region (as defined by US Census)
        iv. Number of healthcare providers who could not complete enrollment, include reason(s) and any action taken
    b. Pharmacies
        i. Number of newly certified pharmacies
        ii. Total number of pharmacies certified at the end of the reporting period

iii. Number and percentage of active certified pharmacies (i.e., pharmacies that have dispensed Aqvesme at least once during the reporting period) by pharmacy type
iv. Number of pharmacies that could not complete enrollment, include reason(s) and any action taken

c. Patients
   i. Number of newly enrolled patients
   ii. Total number of patients enrolled at the end of the reporting period
   iii. Number and percentage of active patients (i.e., have received at least one dispense during the reporting period) stratified by geographic region (defined by US Census) and patient age
   iv. Number of patients who were in a discontinued status at any point during the reporting period
   v. Number of patients who could not complete enrollment, include reason(s) and any action taken
   vi. Number and percentage of patients who have discontinued Aqvesme treatment and the reason for discontinuation

d. Wholesalers, Distributors, and other entities that distribute
   i. Number of wholesalers, distributors and other entities authorized to distribute Aqvesme
   ii. Number of active wholesalers, distributors and other entities (i.e., have distributed Aqvesme at least once during the reporting period)

3. REMS Infrastructure and Performance

a. Aqvesme REMS Website utilization
   i. Summary report of the total number of visits to the website and types of REMS materials downloaded
   ii. Summarize any website outages or problems reported with the website and action taken

b. REMS Coordinating Center
   i. Summarize the number and types of contacts (e.g., inbound and outbound contacts), stratified by REMS participant (e.g., healthcare provider, patient)
   ii. Summary of REMS-related problems identified, root cause of the problem and corrective action taken
   iii. Summary of any contacts that would indicate patient access or healthcare delivery system burden issues with complying with REMS requirements, assessment of the root cause of the complaint, and corrective action taken

4. Aqvesme Utilization

a. Number of shipments/distributions by wholesalers, distributors, and other entities that distribute to certified pharmacies
b. Number of prescriptions dispensed by pharmacies, stratified by first-fill and refills, and stratified by prescriber specialty, and patient demographics

c. Total number of REMS Dispense Authorizations (RDAs) approved and the associated number of dispenses with each approved RDA, stratified by whether patients have completed their total liver monitoring period* (*Total liver monitoring period includes a minimum of 24 weeks or may be longer with treatment interruption. During the total liver monitoring period, liver monitoring is required to be conducted and documented every 4 weeks before each prescription is dispensed while receiving Aqvesme.)
d. Total number of RDAs that encountered rejections, stratified by initial and refill prescriptions. Include reasons for rejected RDAs.
e. Total number of RDA reversals completed during the reporting period, stratified by the reasons for these reversals

5. REMS Compliance

a. Audits
   i. Provide a copy of the current REMS Audit Plan
   ii. Provide a report of audit findings for each REMS participant (i.e., certified pharmacies, wholesalers, distributors, and other entities that distribute, and the REMS Coordinating Center) including but not limited to:
      1) The number of audits required, and the number of audits conducted for each group of REMS participants
      2) If all required audits were not conducted, indicate reason and corrective action(s) taken
      3) The number and type of deficiencies (e.g., training not documented) noted for each group of audited participants
      4) For those with deficiencies noted, provide a summary of critical, major and minor observations identified during audits and corrective actions (e.g., re-education, required corrective and preventive action (CAPA plan)) taken to address any noncompliance. Include whether any deficiencies required CAPA plans and if they were satisfactorily completed during the reporting period. For those that required a CAPA:
         a) Include the number that successfully completed the CAPA plan within the timeline specified in the audit plan
         b) For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
      5) Number of participants with verified existence of documented processes and procedures for complying with the REMS requirements

b. REMS Noncompliance
   i. Provide a copy of the current REMS Noncompliance Plan which addresses the criteria for noncompliance for each type of REMS participant, actions taken to address noncompliance for each event, and under what circumstances a participant would be decertified from the REMS
   ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence. For each instance of noncompliance, including but not limited to metrics 5biii-x, report the following information:

1) The unique ID(s) of the participant(s) associated with the noncompliance event or deviation to enable tracking over time, and whether the site has been decertified for noncompliance previously
2) Severity categorization (e.g., critical, major, minor)
3) The source of the noncompliance data (e.g., REMS Coordinating Center, spontaneous reports, audit findings, dispensing data, etc.)
4) If the noncompliance event was recurring per individual REMS participant
5) The results of root cause analysis
6) What action(s) were taken (e.g., CAPA) in response and whether any follow up is planned

iii. Number and percentage of Aqvesme prescriptions dispensed that were written by noncertified or decertified prescribers out of all prescriptions dispensed, stratified by prescriber certification status
iv. Number of noncertified or decertified pharmacies that dispensed Aqvesme to patients. Include the number of dispenses per pharmacy.
v. Number and percentage of prescriptions dispensed by noncertified or decertified pharmacies out of all prescriptions dispensed, stratified by pharmacy certification status
vi. Number and percentage of prescriptions dispensed without an RDA out of all dispensed prescriptions, stratified by dispenses for patients with their total liver monitoring period in progress, and dispenses for patients who have completed their total liver monitoring period
vii. Number of wholesalers, distributors, and other entities that distribute that sent shipments to noncertified or decertified pharmacies
    1) Number and percentage of shipments sent to noncertified or decertified pharmacies out of all shipments, stratified by pharmacy certification status
viii. Number of prescribers and pharmacies that have had their certification deactivated, including the reasons for such action
ix. Number and percentage of prescriptions dispensed for greater than 28-day supply out of all prescriptions dispensed for patients with their total liver monitoring period in progress, and a breakdown of reasons for the dispensing (prescriber noncompliance, other)
x. Number and percentage of pharmacies that distributed, transferred, loaned, or sold Aqvesme stratified by pharmacy certification status
xi. Unintended system interruptions and corrective actions taken
xii. Other barriers or delays in dispensing and corrective actions taken

6. An assessment of whether Aqvesme was dispensed with an RDA when it was not appropriate based on the patient status, stratified by the reason for that status (e.g., Liver Adverse Event Reporting Form was submitted, Patient Status Form was not submitted for more than 8 weeks). Provide the root cause analysis and corrective actions taken by the REMS to prevent future occurrences of noncompliant dispensing.

**Safe Use Behaviors**

7. Percentage of patients with documentation of completion of all required liver test monitoring out of all patients who were anticipated to have completed liver test monitoring prior to each dispense for their total monitoring period, during the reporting period
    a. Numerator: Patients with documentation of completion of all required liver test monitoring prior to each dispense for their total liver monitoring period during the reporting period
    b. Denominator: Patients who were anticipated to have completed their total liver test monitoring period during the reporting period. To include patients with and without documentation of all required liver test monitoring prior to each dispense.
    c. Include any reported noncompliance that would inform on this assessment (e.g., Aqvesme dispensed without an RDA, Patient Status Form incomplete)
    d. If less than 99%, provide the reason(s) and actions taken to remediate
    e. Provide a secondary analysis evaluating the extent to which patients are compliant with every 4-week liver monitoring and report an assessment of the typical liver monitoring schedule. Include in your analysis the mean, median, and range of days between liver test monitoring dates according to the dates of liver test monitoring on the Patient Status Forms.
8. Patient Enrollment Forms
    a. Provide an assessment of whether all patients who initiated treatment had their pre-treatment liver tests completed per the REMS requirements. The assessment should include, but not be limited to, the following:
        i. Number and percentage of patients who had a Patient Enrollment Form submitted prior to initial dispensing out of all patients who were dispensed a new prescription for Aqvesme
        ii. Number and percentage of patients whose prescriber documented on the Patient Enrollment Form that they had assessed the patient's pre-treatment liver tests prior to being enrolled in the REMS. If <100% provide the reason and actions taken to remediate.
9. Patient Status Forms (for patients with their total liver monitoring period in progress)
    a. Number of Patient Status Forms expected, and the number of Patient Status Forms received
    b. Number and percentage of Patient Status Forms submitted where the prescriber documented the patient was authorized to receive Aqvesme out of all Patient Status Forms received by the REMS
    c. Number and percentage of patients with their total liver monitoring period in progress who had a Patient Status Form submitted prior to every dispense out of all patients who were dispensed a refill prescription for Aqvesme

d. Number of patients who had a Patient Status Form submitted where their prescriber documented that they were not authorized to receive Aqvesme, stratified by the reasons why (e.g., clinically significant increases in liver tests or symptoms suggestive of hepatocellular injury, non-hepatic adverse effects, cost, treatment burden, etc.)
e. Number and percentage of patients who experienced treatment interruption due to incomplete liver test monitoring as documented by their prescriber on the Patient Status Form(s) out of all patients with their total liver monitoring period in progress. Include reason(s) why the monitoring was not completed and any follow-up actions taken by the REMS.
    i. Include the mean, median, and range length of the treatment interruption due to incomplete liver test monitoring
f. Assessment of compliance with ensuring that each new Patient Status Form has a new date reflecting that updated liver test monitoring was completed on a prospective basis before a Patient Status Form was considered to be complete and appropriate for dispensing
    i. Number and percentage of Patient Status Forms that were populated with updated liver test monitoring dates out of all Patient Status Forms submitted. If <100%, provide the reason and actions taken to remediate.
g. Number and percentage of patients who had a Patient Status Form submitted where their prescriber documented that they permanently discontinued Aqvesme. Stratify by suspected hepatocellular injury and non-hepatocellular injury reasons for discontinuation.
h. For patients who permanently discontinued Aqvesme prior to the completion of their total liver monitoring period, provide an assessment of whether they had documentation of liver test monitoring prior to each dispense for their duration of treatment

10. Liver Adverse Event Reporting Forms

a. Number of Liver Adverse Event Reporting Forms expected based on prescriber's documentation on the Patient Status Form that their patient experienced clinically significant increases in liver tests or symptoms suggestive of hepatocellular injury, and the number of Liver Adverse Event Reporting Forms received. Include reasons why any Liver Adverse Event Reporting Forms were not submitted, if known.
b. Number and percentage of patients who had a Liver Adverse Event Reporting Form submitted out of those patients where the prescriber documented on the Patient Status Form that the patient had clinically significant increases in liver tests or symptoms suggestive of hepatocellular injury
c. Of the patients who had a Liver Adverse Event Reporting Form submitted, provide the following:
    i. Number and percentage of patients whose enrollment status was changed to discontinued as required. If < 100% provide the reason and actions taken to remediate.
    ii. Number and percentage of patients who reinitiated Aqvesme

1) Mean, median, and range of time (in days) that Aqvesme was withheld due to suspected Aqvesme-related liver injury

iii. Mean, median, and range of time (in days) between the onset date of new or worsening symptoms and the date the patient sought medical care, stratified by symptom type

11. Patient Reinitiation Forms

a. Number of Patient Reinitiation Forms submitted
b. Number of patients who had a Patient Reinitiation Form submitted
c. Provide an assessment of whether patients in the following two categories were monitored appropriately per the REMS requirements (i.e., received liver test monitoring prior to each dispense for their total liver monitoring period)
   i. Patients who reinitiated treatment after suspected Aqvesme-related liver injury was not ruled out, but peak ALT was <10×baseline without elevation of bilirubin above baseline
   ii. Patients who reinitiated treatment after a treatment interruption more than 8 weeks

**Health Outcomes and/or Surrogates of Health Outcomes**

12. Hepatocellular injury events

a. Using the U.S. cases of hepatocellular injury from your recent periodic safety reports (e.g., PADER), provide the following:
   i. Number of reported U.S. suspected hepatocellular injury events and outcome of event, for the three recent periodic safety reporting periods (if applicable) and cumulatively
   ii. Provide an analysis of whether REMS requirements for liver test monitoring per US Prescribing Information were followed during the 24-week monitoring period
   iii. Include a reference list of case identifiers (e.g., manufacturer control numbers) for all cases included in the analysis above
b. Provide an assessment of the impact of the REMS liver test monitoring schedule and requirements in mitigating the risk of hepatocellular injury

**Knowledge**

13. Knowledge Assessments (for certification)

a. Pharmacy Knowledge Assessment (for certification) of educational materials regarding the risks and safe-use conditions of Aqvesme
   i. Total number of pharmacy knowledge assessments administered
   ii. Number of pharmacies with a passing rate (100% correct responses) divided by the total number of certified pharmacies who initiated the certification process during the reporting period
   iii. Mean, median, and range of attempts to complete the knowledge assessment
   iv. A summary of the most frequently missed questions

v. A summary of potential comprehension or perception issues identified with the knowledge assessment

b. Prescriber Knowledge Assessment (for certification) of educational materials regarding the risks and safe-use conditions of Aqvesme
   i. Total number of prescriber knowledge assessments administered
   ii. Number of prescribers with a passing rate (100% correct responses) divided by the total number of certified prescribers during the reporting period
   iii. Mean, median and range of attempts to complete the knowledge assessment
   iv. A summary of the most frequently missed questions
   v. A summary of potential comprehension or perception issues identified with the knowledge assessment

**Overall Assessment of REMS**

14. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

    If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan
    to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

    i. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 216196 REMS ASSESSMENT METHODOLOGY**
**(**insert concise description of content in bold capital letters, e.g.,
**ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a

proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rational to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 216196 REMS ASSESSMENT METHODOLOGY**

**(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 216196 REMS ASSESSMENT**

***or***

**NEW SUPPLEMENT FOR NDA 216196/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 216196/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA/ 216196/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX**

***or***

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 216196/ S-000**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISION FOR NDA 216196**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

## SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

## 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]

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

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this

[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

supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

## PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

## REPORTING REQUIREMENTS

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

## REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for Aqvesme you submit all serious cases of hepatotoxicity – whether domestic or foreign – as though they were 15-day “Alert reports” (which are described under 21 CFR 314.80(c)(1)) through the 5th year following the date of this letter.

We request that you investigate all serious cases of hepatotoxicity (domestic and foreign) as if they were subject to 21 CFR 314.80(c)(1)(ii) to obtain data elements included in the bulleted list below.

We also request that you provide a narrative summary including analysis of hepatotoxicity reported with Aqvesme as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)] annually through the 5th year following the date of this letter.

Your analysis should include interval and cumulative data relative to the date of this letter with stratification of the analysis by US and non-US reports. Include the number of cases with total bilirubin >5 mg/dL, hospitalizations for liver injury, INR >1.5, hepatic decompensation (e.g., ascites, hepatic encephalopathy, variceal bleeding), liver transplantation and death. Furthermore, provide a line listing that includes the following information for each case:

- Aqvesme dose
- Duration of therapy
- Indication (including all labeled and off-label use)
- Temporal association
- De-challenge/re-challenge
- Associated signs and symptoms
- Hepatic enzymes and liver function tests
- Concomitant medications [list all, including prescription and over-the-counter medications (indications, dosage), herbal, and illicit substances]
- Medical history
- Underlying risk factors
- Hospitalizations, diagnostic test results (including labs and imaging), and treatment given for the event
- Outcome at the time of the report
- Assessment of causality

If you have any questions, contact May Zuwannin, Regulatory Project Manager, at 301-796-7775 or May.Zuwannin@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Tanya Wroblewski, MD
Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information (Aqvesme)
  - Prescribing Information (Pyrukynd)
  - Medication Guide (Aqvesme)
  - Patient Package Insert (Pyrukynd)
- Carton and Container Labeling
- REMS

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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.**

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/s/

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TANYA M WROBLEWSKI
12/23/2025 04:44:14 PM