CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215904Orig1s000

Trade Name:	Ztalmy oral suspension
Generic or Proper Name:	Ganaxolone
Sponsor:	Marinus Pharmaceuticals, Inc
Approval Date:	March 18, 2022
Indication:	For the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 215904

NDA APPROVAL

Marinus Pharmaceuticals, Inc
Attention: Kimberly McCormick, PharmD
Vice President, Head of Regulatory Affairs
5 Radnor Corporate Center
100 Matsonford Road, Suite 500
Radnor, PA 19087

Dear Dr. McCormick:

Please refer to your new drug application (NDA) dated and received July 20, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ztalmy (ganaxolone) oral suspension.

This NDA provides for the use of Ztalmy (ganaxolone) oral suspension for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older.

APPROVAL & LABELING

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

CONTROLLED SUBSTANCE SCHEDULING

FDA intends to recommend scheduling of Ztalmy under the Controlled Substances Act (CSA). The scheduling of this product in accordance with the CSA (21 U.S.C. 811) is not yet complete as of the date of this letter. Therefore, in accordance with the FDCA (21 U.S.C. 355(x)), the effective date of approval for Ztalmy shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of ganaxolone.

We note that, when the drug is scheduled by the DEA, you will need to make appropriate revisions to the Prescribing Information, Medication Guide, Instructions for Use, and carton and container labeling by submitting a supplement to your NDA. This would include the statements in the labeling detailing the scheduling of ganaxolone as the scheduled substance in Ztalmy, as required under 21 CFR 201.57(a)(2) and (c)(10)(i). Therefore, Ztalmy may be marketed only after DEA has published the notice in the Federal Register announcing the interim final scheduling of ganaxolone and you submit a supplement to your NDA to revise all applicable drug labeling to reflect the drug scheduling described in the notice. For changes to the Prescribing Information,

Medication Guide, Instructions for Use, and carton and container labeling to describe the scheduling of ganaxolone, you can submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights of Prescribing Information for Ztalmy described in 21 CFR 314.70(b)(2)(v)(C) and changes to the Medication Guide described in 21 CFR 314.70(b)(2)(v)(B).

We note that Ztalmy will be listed in the Orange Book upon the date of approval in accordance with 21 U.S.C. 355(x). With respect to the submission of patent information, as required under 21 CFR 314.53(c)(2)(ii), we note that you must submit Form FDA 3542 within 30 days after the date on which DEA has published the notice in the Federal Register announcing the interim final scheduling of ganaxolone.

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 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 February 23, 2022, 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 215904**." Approval of this submission by FDA is not required before the labeling is used.

[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.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Ztalmy (ganaxolone) oral suspension shall be 24 months from the date of manufacture when stored at 20°- 25°C.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 215904. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.

- You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

ADVISORY COMMITTEE

Your application for Ztalmy was not referred to an FDA advisory committee because the clinical trial design was acceptable, the efficacy findings were clear, and the safety profile was acceptable for use in the intended population.

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.

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 identify an unexpected serious risk of carcinogenicity resulting from exposure to ganaxolone or its major human unconjugated plasma metabolite, M2, or to identify an unexpected serious risk of toxic effects of the M2 metabolite during the juvenile period of development, or to identify an unexpected serious risk of neurotoxicity of ganaxolone's plasma metabolite, M47, or to identify an unexpected serious risk of adverse events resulting from the drug-interaction potential of the M47 metabolite.

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

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:

4218-1 A 26-week carcinogenicity study of ganaxolone in the CB6F1-Tg rasH2 transgenic mouse.

The timetable you submitted on March 6, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2023
Final Protocol Submission:	03/2023
Study Completion:	11/2023
Final Report Submission:	02/2024

4218-2 A 104-week carcinogenicity study of ganaxolone in rat.

The timetable you submitted on March 6, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2023
Final Protocol Submission:	05/2023
Study Completion:	07/2025
Final Report Submission:	10/2025

4218-3 A 2-year carcinogenicity study of the major human unconjugated plasma metabolite, M2, in rat.

The timetable you submitted on March 9, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2023
Final Protocol Submission:	05/2023
Study Completion:	07/2025
Final Report Submission:	10/2025

4218-4 A juvenile animal toxicology study of the major human unconjugated plasma metabolite, M2, in rat.

The timetable you submitted on March 9, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2023
Final Protocol Submission:	06/2023
Study Completion:	10/2023
Final Report Submission:	02/2024

4218-5 A central nervous system (CNS) distribution study of the major human plasma metabolite, M47 (sulfate-conjugated ganaxolone), in rat.

The timetable you submitted on March 9, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2023
Final Protocol Submission:	06/2023
Study Completion:	09/2023
Final Report Submission:	11/2023

4218-6 An in vitro assessment of the drug interaction potential of the M47 metabolite as a perpetrator for major drug metabolizing enzymes and transporters, in accordance with “In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry.”

The timetable you submitted on March 9, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2023
Final Protocol Submission:	06/2023
Study Completion:	09/2023
Final Report Submission:	11/2023

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.[4]

[4] 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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of toxicity resulting from increased systemic exposures of ganaxolone in patients with hepatic impairment and to determine an appropriate dose of ganaxolone in patients with hepatic impairment, or to identify an unexpected serious risk of toxicity in patients with impaired renal function and to determine an appropriate dose of ganaxolone in patients with severe renal impairment, or to identify an unexpected serious risk of QT interval prolongation.

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

4218-7 A clinical pharmacokinetic trial to determine an appropriate dose of ganaxolone to minimize toxicity in patients with varying degrees of hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on March 3, 2022, states that you will conduct this trial according to the following schedule:

Final Report Submission: 12/2022

4218-8 A clinical pharmacokinetic trial to determine an appropriate dose of ganaxolone to minimize toxicity in patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on March 3, 2022, states that you will conduct this trial according to the following schedule:

Final Report Submission: 05/2022

4218-9 A Thorough QT trial to evaluate the effect of ganaxolone on the QTc interval. Design and conduct the trial in accordance with the ICH E14 guidance entitled, "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, and its Questions and Answers (R3)."

The timetable you submitted on March 3, 2022, states that you will conduct this trial according to the following schedule:

Final Report Submission: 12/2022

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.[5]

Submit clinical protocol(s) to your IND 044020 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 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 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.

[5] 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4218-10 Provide extractable/leachable results to confirm that the container closure system does not adversely impact the drug product.

The timetable you submitted on January 25, 2022, states that you will conduct this study according to the following schedule:

Interim Reports:	04/2022 (extractables report) 06/2022 (leachable extractable correlation report)
Final Report Submission:	03/2023

Submit the postmarketing final report to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of this commitment in your annual report to this NDA. The status summary should include the expected completion and final report submission dates and any changes in plans since the last annual report. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

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.*[6]

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.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

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

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

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.

If you have any questions, email Tina Chhabra, Regulatory Project Manager, at Tina.Chhabra@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

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/

WILLIAM H Dunn
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