CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214200Orig1s000

Trade Name:	Cosela
Generic or Proper Name:	trilaciclib
Sponsor:	G1 Therapeutics, Inc.
Approval Date:	February 12, 2020
Indication:	To decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 214200

NDA APPROVAL

G1 Therapeutics, Inc.
Attention: Chandra Lovejoy
Vice President, Global Regulatory Affairs
P.O. Box 110341
Research Triangle Park, NC 27709

Dear Dr. Lovejoy:

Please refer to your new drug application (NDA) dated and received June 15, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cosela (trilaciclib) injection.

This new drug application provides for the use of Cosela (trilaciclib) injection to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer.

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), 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.

[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.

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 214200**." 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 Cosela (trilaciclib) injection shall be 24 months from the date of manufacture when stored at 20 °C to 25 °C.

ADVISORY COMMITTEE

Your application for Cosela was not referred to an FDA advisory committee because the application did not raise significant or controversial safety or efficacy issues that would have benefitted from a public advisory committee discussion.

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 this application because necessary studies are impossible or highly impracticable since the indication is for adult small cell lung cancer patients.

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 a signal

of a serious risk of worse overall survival and clinically relevant drug interaction(s) among adult patients with extensive stage-small cell lung cancer treated with trilaciclib.

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 this serious risk.

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

4018-1 Conduct a study in a sufficient number of adult patients with extensive stage-small cell lung cancer undergoing chemotherapy to evaluate the impact of trilaciclib on disease progression or survival in patients with chemotherapy-induced myelosuppression treated with a platinum/etoposide-containing regimen or topotecan-containing regimen with at least 2 years of follow-up.

The timetable you submitted on January 29, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2021
Final Protocol Submission:	03/2022
Study Completion:	03/2025
Final Report Submission:	11/2025

4018-2 Conduct an in vitro metabolism study and CYP phenotyping study at clinically relevant concentrations to appropriately determine major metabolic pathway for trilaciclib. Characterize the formation of the major circulating metabolite of trilaciclib, M8, using the purified M8 compound with a validated bioanalytical method.

The timetable you submitted on January 29, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2021
Final Protocol Submission:	06/2021
Study Completion:	09/2021
Final Report Submission:	11/2021

4018-3 Conduct an *in vitro* Drug-Drug Interaction (DDI) study to evaluate the major circulating metabolite of trilaciclib, M8, as an inhibitor for major CYP enzymes and drug transporters.

The timetable you submitted on January 29, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2021
Final Protocol Submission:	06/2021
Study Completion:	09/2021
Final Report Submission:	11/2021

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 higher drug exposure and accumulation in patients with hepatic impairment.

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

4018-4 Conduct a clinical trial to evaluate the effect of hepatic impairment on the pharmacokinetics and safety of trilaciclib**.**

The timetable you submitted on January 29, 2021, states that you will conduct this trial according to the following schedule:

Trial Completion:	07/2023
Final Report Submission:	01/2024

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 119254 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4018-5 Conduct a plasma protein binding assay study for trilaciclib with appropriate validation of plasma stability, time to equilibrium and nonspecific binding at clinically relevant concentrations.

The timetable you submitted on January 29, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2021
Final Protocol Submission:	06/2021
Study/Trial Completion:	09/2021
Final Report Submission:	11/2021

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 119254 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports 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 each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments 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.[3]

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.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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 and new biological products 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, contact Maureen DeMar, BSN, RN., Regulatory Project Manager, at 240-402-9981 or at Maureen.DeMar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

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

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