CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

219908Orig1s000

Trade Name:	**REVTORPYK for injection, for intravenous infusion**
Generic or Proper Name:	**(gedatolisib)**
Sponsor:	**Celcuity Inc.**
Approval Date:	**July 14, 2026**
Indication:	**This NDA provides for the use of Revtorpyk (gedatolisib) Injection in combination with fulvestrant, with or without palbociclib, for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer without a detectable PIK3CA mutation detected following progression on or after treatment with at least one line of endocrine therapy in the metastatic setting.**

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APPROVAL LETTER

NDA 219908

NDA APPROVAL

Celcuity Inc.
Attention: Sunni Miller
Vice President, Regulatory Affairs
2800 Campus Drive, Suite 140
Minneapolis, MN 55441

Dear Sunni Miller:

Please refer to your new drug application (NDA) received November 17, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Revtorpyk (gedatolisib) Injection.

This NDA provides for the use of Revtorpyk (gedatolisib) Injection in combination with fulvestrant, with or without palbociclib, for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer without a detectable *PIK3CA* mutation detected following progression on or after treatment with at least one line of endocrine therapy in the metastatic setting.

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 (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 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 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 219908."** 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 Revtorpyk (gedatolisib) for injection shall be 24-months from the date of manufacture when stored at controlled room temperature: 20°–25°C (68°–77° F) with excursions permitted between 15°C–30°C (59°F–86°F).

ADVISORY COMMITTEE

Your application for Revtorpyk was not referred to an FDA advisory committee because outside expertise was not necessary. There were no controversial issues that would benefit from 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 breast cancer occurs very rarely in children.

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 known serious risks of severe adverse events leading to dosage reduction and interruption, including severe stomatitis/mucosal inflammation, and to identify an

unexpected serious risk of increased drug toxicity in patients with moderate-to-severe hepatic impairment and when gedatolisib is used concomitantly with with P-gp and BCRP inhibitors.

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 these serious risks.

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

5031-1 Conduct a multicenter, randomized clinical trial to further characterize known serious risks with gedatolisib including severe stomatitis/mucosal inflammation and severe adverse events leading to dosage reduction and interruption by comparing the safety and activity of gedatolisib 180 mg 3-weeks-on, 1-week-off versus a lower dose of gedatolisib in patients with PIK3CA-wild type, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer. Additionally, conduct a comparative analysis of dose-and exposure-response relationships for the two dosing regimens. Incorporate systematically assessed patient-reported outcome assessments to evaluate tolerability and conduct exploratory exposure response analyses.

The timetable you submitted on July 6, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 03/2027
Final Protocol Submission: 09/2027
Trial Completion: 06/2030
Final Report Submission: 12/2030

5031-2 Conduct a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and to determine a safe and appropriate dosage of gedatolisib in patients with moderate-to-severe 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 July 6, 2026, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 09/2026
Trial Completion: 09/2027

Final Report Submission: 12/2027

5031-3 Conduct a clinical drug interaction trial to evaluate the effect of P-gp and BCRP inhibitors on the pharmacokinetics of gedatolisib to assess the magnitude of gedatolisib exposure change and serious potential risk of increased drug toxicity and to inform an appropriate drug interaction management strategy for coadministration of gedatolisib with P-gp and BCRP inhibitors. This trial should be designed and conducted in accordance with the Guidance for Industry "M12 Drug Interaction Studies".

The timetable you submitted on July 6, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 03/2027
Final Protocol Submission: 06/2027
Trial Completion: 09/2028
Final Report Submission: 03/2029

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 104846 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

[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.

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:

5031-4 Complete the ongoing clinical trial, study 1 of VIKTORIA-1 (Study CELC-G-301), entitled "A Phase 3, Open-Label, Randomized, Two-Part Study Comparing Gedatolisib in Combination with Palbociclib and Fulvestrant to Standard-of-Care Therapies in Patients with HR-Positive, HER2-Negative Advanced Breast Cancer Previously Treated with a CDK4/6 Inhibitor in Combination with Nonsteroidal Aromatase Inhibitor Therapy", to provide the final overall survival (OS) analysis.

The timetable you submitted on July 6, 2026, states that you will conduct this study according to the following schedule:

Trial Completion:	12/2026
Final Report Submission:	03/2027

Submit the final OS analysis and datasets in the final report submission.

5031-5 Conduct adequate analytical and clinical validation studies to support revisions to the labeling of gedatolisib to specify the use of an FDA-authorized in vitro companion diagnostic device to accurately and reliably identify patients who do not harbor a PIK3CA mutation and for whom gedatolisib therapy is indicated.

The timetable you submitted on July 6, 2026, states that you will conduct this study according to the following schedule:

Study Completion:	11/2028
Final Study Report:	05/2029

The final study report should be accompanied by a labeling supplement to incorporate information about the use of an FDA-authorized companion diagnostic device.

Submit clinical protocols to your IND 104846 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/subjects 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 guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*

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

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[6].

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] https://www.uspnf.com/

If you have any questions, contact Kristie Oh, Regulatory Project Manager, at Kukhwa.oh@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Director
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROMEO A DE CLARO
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