NDA 216986

NDA APPROVAL

Guerbet LLC
Attention: Gabriel Lebovic
Director of Regulatory Affairs, North America
214 Carnegie Center, Suite 300
Princeton, NJ 08540

Dear Mr. Lebovic:

Please refer to your new drug application (NDA) dated January 21, 2022, received January 21, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Elucirem (gadopiclenol) injection.

This NDA provides for the use of Elucirem (gadopiclenol) injection as a gadolinium-based contrast agent indicated in adult and pediatric patients aged 2 years and older for use with magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in:

- the central nervous system (brain, spine, and associated tissues),
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

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 for the Prescribing Information 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]

[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.
[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.

The SPL will be accessible via publicly available labeling repositories.

We acknowledge your September 14, 2022, submission containing final printed carton and container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Elucirem (gadopiclenol) injection, for intravenous use, shall be 36 months from the date of manufacture when stored at 25°C.

ADVISORY COMMITTEE

Your application for Elucirem was not referred to an FDA advisory committee because this drug is not the first in its class.

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 deferring the submission of your pediatric study for ages 0 years to less than 2 years for this application because this product is ready for approval for use in adults and children of ages 2 years and older and the additional pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4341-1 Conduct a study of approximately 40 neonates and infants aged < 2 years that will receive a single dose of 0.05 mmol/kg gadopiclenol intravenously for the evaluation of the plasma pharmacokinetics profile of gadopiclenol (POP-PK analysis). Safety and imaging data will be collected as secondary endpoints.

The timetable you submitted on September 13, 2022, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2021
Study Completion:	06/2023
Final Report Submission:	12/2023

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.[3]

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

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.

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:

4341-2 Conduct a developmental and perinatal/postnatal reproduction study of gadopiclenol by intravenous (bolus) injection in mice, including a postnatal behavioral/functional evaluation (Sponsor Reference No. GDX-33-073). The study will examine the safety of gadopiclenol following perinatal exposure through repeated dosing in pregnant dams. The study will provide safety data assessing behavioral, neurological, and histopathology findings. The study will examine the pharmacokinetics of gadopiclenol including gadolinium retention in the brain and other organs/tissues.

The timetable you submitted on September 13, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission,:	08/2022
Final Protocol Submission:	06/2023
Study/Trial Completion:	08/2024
Final Report Submission:	05/2025

4341-3 Conduct an intravenous (bolus) injection juvenile toxicity study of gadopiclenol in mice (Sponsor Reference No. GDX-33-072). The study will examine the safety of gadopiclenol in juvenile animals, following repeated administration. The study will provide safety data assessing

behavioral, neurological, and histopathology findings. The study will also examine the pharmacokinetics of gadopiclenol including gadolinium retention in the brain and other organs/tissues.

The timetable you submitted on September 13, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2022
Final Protocol Submission:	04/2023
Study/Trial Completion:	08/2024
Final Report Submission:	05/2025

4341-4 Conduct a prospective longitudinal cohort study with one or more matched control group(s) to evaluate the effects of repetitive gadopiclenol administration on a comprehensive battery of neurobehavioral testing over the course of at least five administrations. The study should be sufficiently powered to exclude a prespecified magnitude of decline. As a secondary objective, study patients should also have the option of providing blood and urine samples at the time of reimaging, so that normative estimates of gadolinium concentration across an extended range of post-administration timepoints may be documented.

We acknowledge that you will participate in the existing ODYSSEY study with the other GBCA sponsors.

The Interim Report should contain a summary of patient enrollment listed by:

- Study initiation (first patient enrolled at each site)
- Number of patients at each site listed by condition under yearly contrast MRI surveillance
- Number of patients receiving gadopiclenol
- Number of patients providing blood and urine samples for gadolinium levels
- Number of dropouts

The timetable you submitted on September 13, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2022
Final Protocol Submission:	07/2023
Interim Report #1 Submission:	04/2024
Interim Report #2 Submission:	04/2025
Interim Report #3 Submission:	04/2026
Interim Report #4 Submission:	04/2027
Study/Trial Completion:	04/2028

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 123673 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

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

---

[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.

[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

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.

If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at 301-796-1994 or via email at sharon.thomas@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Alex Gorovets, M.D.
Deputy Director
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- 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/

ALEXANDER GOROVETS
09/21/2022 09:19:08 AM