



NDA 206709
NDA 207223

NDA APPROVAL

Biocodex SA
c/o KM Pharmaceutical Consulting, LLC
Attention: Kathleen Clarence-Smith, M.D., Ph.D.
1825 K Street, Suite 520
Washington, DC 20006

Dear Dr. Clarence-Smith:

Please refer to your New Drug Applications (NDAs), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for the following:

Application	Drug Product	Submitted on	Received on
NDA 206709	Diacomit (stiripentol) capsules, for oral use, 250 mg and 500 mg	December 20, 2017	December 20, 2017
NDA 207223	Diacomit (stiripentol) powder, for oral suspension, 250 mg and 500 mg	January 19, 2018	January 19, 2018

These new drug applications provide for the use of Diacomit (stiripentol) capsules and powder for oral suspension for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older taking clobazam.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information and Medication Guide). 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on July 6, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate these submissions as “**Final Printed Carton and Container Labels for approved NDA 206709**” and “**Final Printed Carton and Container Labels for approved NDA 207223.**” Approval of these submissions by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your applications for Diacomit (stiripentol) capsules and powder for oral suspension were not referred to an FDA advisory committee because the safety profile of Diacomit is acceptable for the proposed indication.

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 these drug products for this indication have 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 adverse maternal, fetal, or infant outcomes resulting from the use of Diacomit.

Furthermore, the new pharmacovigilance system that FDA is required to establish 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:

3462-1 Studies to characterize the in vivo metabolic profile of orally administered stiripentol in the species and strains used in the pivotal developmental toxicity and carcinogenicity studies.

The timetable you submitted on August 20, 2018, states that you will conduct this study according to the following schedule:

Final protocol submission: 10/2020
Study completion: 10/2021
Final report submission: 04/2022

3462-2 Bridging toxicokinetic studies to document steady-state plasma exposures to stiripentol and any major human metabolites under the conditions used in the pivotal developmental toxicity and carcinogenicity studies.

The timetable you submitted on August 20, 2018, states that you will conduct this study according to the following schedule:

Final protocol submission: 04/2022
Study completion: 12/2022
Final report submission: 04/2023

3462-3 An embryofetal development study of stiripentol in rat.

The timetable you submitted on August 20, 2018, states that you will conduct this study according to the following schedule:

Final protocol submission: 04/2022
Study completion: 10/2022
Final report submission: 04/2023

3462-4 An embryofetal development study of stiripentol in rabbit.

The timetable you submitted on August 20, 2018, states that you will conduct this study according to the following schedule:

Final protocol submission: 04/2022
Study completion: 10/2022
Final report submission: 04/2023

3462-5 A pre- and postnatal development study of stiripentol in rat.

The timetable you submitted on August 20, 2018, states that you will conduct this study according to the following schedule:

Final protocol submission: 04/2022
Study completion: 11/2022
Final report submission: 05/2023

3462-6 A juvenile animal toxicology study of stiripentol in one species, with selection of species based on interspecies comparison of in vivo metabolic profiles.

The timetable you submitted on August 20, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission: 04/2022
Final protocol submission: 10/2022
Study completion: 10/2023
Final report submission: 04/2024

3462-7 Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Diacomit (stiripentol) during pregnancy compared to an unexposed control population.

The timetable you submitted on July 30, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 05/2019
Final Protocol Submission: 06/2020
Study Completion: 08/2027
Final Report Submission: 08/2028

In addition, we have determined that only clinical trials (rather than nonclinical or observational studies) will be sufficient to identify an unexpected serious risk of QT interval prolongation and any unexpected serious risks resulting from altered pharmacokinetics of stiripentol due to hepatic impairment or drug-drug interactions.

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

3462-8 Conduct a thorough QT trial for Diacomit as per the ICH E14 guidelines.

The timetable you submitted on July 30, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2018
Final Protocol Submission:	06/2019
Trial Completion:	02/2020
Final Report Submission:	09/2020

3462-9 Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Diacomit (stiripentol) 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 August 2, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2019
Final Protocol Submission:	03/2020
Trial Completion:	09/2021
Final Report Submission:	09/2022

3462-10 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of rifampin, a CYP3A, CYP2C19, and UGT inducer, on the single dose pharmacokinetics of Diacomit (stiripentol) in healthy volunteers, and to assess the magnitude of the decrease in stiripentol exposure. You should also evaluate metabolite concentrations if any of the identified metabolites is less polar than the parent drug (stiripentol) and has an AUC \geq 25% of the AUC of stiripentol. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry.”

The timetable you submitted on August 9, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2020
Final Report Submission:	09/2020

3462-11 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of caffeine (a sensitive CYP1A2 substrate) in healthy volunteers to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "[Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry.](#)"

The timetable you submitted on August 9, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2020
Final Report Submission:	09/2020

3462-12 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of a CYP2B6 sensitive substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "[Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry.](#)"

The timetable you submitted on August 9, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2020
Final Report Submission:	09/2020

3462-13 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of a CYP3A4 sensitive substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "[Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry.](#)"

The timetable you submitted on August 9, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2020
Final Report Submission:	09/2020

3462-14 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of a CYP2C19

sensitive substrate in healthy volunteers to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "[Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry.](#)"

The timetable you submitted on August 9, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2020
Final Report Submission:	09/2020

- 3462-15 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of a P-gp sensitive substrate in healthy volunteers to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "[Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry.](#)"

The timetable you submitted on August 9, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2020
Final Report Submission:	09/2020

- 3462-16 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of a BCRP sensitive substrate in healthy volunteers to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "[Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry.](#)"

The timetable you submitted on August 9, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	09/2019
Trial Completion:	03/2020
Final Report Submission:	09/2020

Submit clinical protocol(s) to your IND 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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 COMMITMENT NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3401-1 Submission of a Post-Marketing Commitment (PMC) report with final dissolution acceptance criterion based on data from the first six commercial batches of the powder for oral suspension drug product under a Prior Approval Supplement (PAS) to the NDA.

The timetable you submitted on May 15, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/19

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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 LaShawn Dianat, PharmD, Regulatory Project Manager, at (240) 402-7713.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Office Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Prescribing information and Medication Guide

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/

ROBERT TEMPLE
08/20/2018