CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206709Orig1s000
207223Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency Memo: Diacomit (stiripentol)
Version: 2018-01-24

Date:	August 1, 2018
Reviewer	Elisa Braver, PhD Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Associate Division Director:	Wei Hua, PhD, MHS, MS Division of Epidemiology I
Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Diacomit (stiripentol)
Application Type/#:	NDA 206709 and NDA 207223
Applicant/Sponsor:	Biocodex SA
OSE RCM #:	2018-1274

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Stiripentol is a derivative of α -ethylene alcohol and has a chemical structure that is completely different from other currently marketed antiepileptic agents. It mechanism is thought to be acting as an allosteric modulator of the c-aminobutyric acid (GABA)A receptor.[a] Stiripentol is designated as an orphan drug.

Diacomit (stiripentol) has a proposed indication for (b) (4) treatment of (b) (4) (b) (4) seizures associated with Dravet syndrome in patients (b) (4). Dravet syndrome is a rare form of epilepsy that begins during infancy with frequent seizures that can be prolonged; the condition generally is associated with a mutation in SCN1A genes. Based on an incidence rate of 1 per 37,000 children, there may be nearly 2,000 children with this disease in the United States, according to the clinical reviewer.[b] The seizures can result in developmental delays and even sudden death and do not respond to first-line epilepsy drugs. The drug is already approved for use in Canada and Europe.

1.2. Pregnancy Exposure Registry

There are no adequate data on the developmental risks associated with the use of stiripentol in pregnant women. Instead of requiring a separate pregnancy exposure registry, stiripentol will be included in the North American Antiepileptic Drug (NAAED) Pregnancy Registry, which monitors pregnancy outcomes in women exposed to anti-epileptic drug during pregnancy (http://www.aedpregnancyregistry.org/).

1.3. Describe the Safety Concern – Pregnancy Risk

Only limited human data are available to establish whether stiripentol poses a risk of adverse pregnancy outcomes. The following information is from the draft clinical review.[c] The Integrated Summary of Safety submitted by the Sponsor did not identify any reports of exposure during pregnancy during the clinical trials or in the published literature. The Sponsor reported a search in the Biocodex pharmacovigilance database through June 2016 for any pregnancy event recorded with stiripentol either during the clinical development of the drug or during the commercialization of the drug and identified 3 cases. All 3 cases were non-Dravet patients in which the drug was added to carbamazepine; no adverse pregnancy or infant outcomes were

[a] Steven Dinsmore. Division of Neurology Products, CDER. Draft clinical review. May 29, 2018.
[b] Ibid..

[c] Steven Dinsmore. Division of Neurology Products, CDER. Draft clinical review. May 29, 2018.

reported for 2 of the 3 cases and the outcome for the third case was unknown.

(b) (4) the following information about what is known about the drug in terms of reproduction.[d] In a three-generation study, stiripentol was tested on the development of the progeny of Sprague-Dawley rats up to maturity. Stiripentol was administered daily orally at dose levels of 0, 50, 200, and 800 mg/kg to groups of 24 females over a period of 15 days prior to mating, during the mating period, and throughout pregnancy and lactation. The high dose level of 800 mg/kg caused a significantly increased incidence of delayed ossification of fetuses. No other treatment-related effects were seen on pup bodyweights and their physical behavior development as well as on auditory and visual functions. The pups developed normally without any drug-related effects until adulthood. The no-effect observed dose level for maternal and embryo-fetal toxicity was 200 mg/kg/day which is 4 times the clinical human dose of 50 mg/kg/day. No drug-related teratogenicity was observed.

The effects of stiripentol on embryo-fetal development also were determined in mice and rabbits.[e] Groups of 25 pregnant mice received stiripentol at dose levels of 0, 50, 200, or 800 mg/kg on days 6-16 of gestation daily by oral gavage. No effects were seen on the number of live and dead fetuses, but the number of resorptions was increased at the two higher dose levels. Possible teratogenic effects of stiripentol were also evaluated in the rabbit. Groups of 18-28 pregnant rabbits were given stiripentol on days 8-21 of gestation daily by oral gavage at dose levels of 0, 50, 200, or 800 mg/kg. No effect was seen on fetal bodyweight. The drug did not induce gross, visceral, or skeletal malformations.

1.4. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

[d] (b) (4)

[e] (b) (4) A study by Finnell et al. (1999) provided additional information on mice. Finnell RH, Bennett GD, Mather GG, Wlodarczyk B, Bajpai M, Levy RH. Effect of stiripentol dose on phenytoin-induced teratogenesis in a mouse model. Reprod Toxicol. 1999 Mar-Apr;13(2):85-91.

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of childbearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of [redacted] (b) (4) A study by Finnell et al. (1999) provided additional information on mice. Finnell RH, Bennett GD, Mather GG, Wlodarczyk B, Bajpai M, Levy RH. Effect of stiripentol dose on phenytoin-induced teratogenesis in a mouse model. Reprod Toxicol. 1999 Mar-Apr;13(2):85-91.

statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☒ Electronic database study without chart review

☐ Other, please specify:

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population

☐ Exposures

☒ Outcomes

☐ Covariates

☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure

corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

The following language (still in draft form) has been proposed for PMRs related to pregnancy outcomes:

> *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 finalized PMR language will be issued upon approval.

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/s/

ELISA R BRAVER
08/02/2018

KIRA N LEISHEAR
08/02/2018

WEI HUA
08/02/2018

JUDITH W ZANDER
08/03/2018

MICHAEL D NGUYEN
08/03/2018

ROBERT BALL
08/03/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 2, 2018
To:	Billy Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: (Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	DIACOMIT (stiripentol)
Dosage Form and Route:	capsules, for oral use powder, for oral suspension
Application Type/Number:	NDA 206709 NDA 207223
Applicant:	KM Pharmaceutical Consulting LLC

1 INTRODUCTION

On October 27, 2015 and October 30, 2015, respectively, KM Pharmaceutical Consulting LLC submitted for the Agency's review an original New Drug Application (NDA) 206709 and 207223, for Stiripentol capsules, for oral use and powder, for oral suspension. The purpose of this submission is to seek approval in the United States for (b) (4) treatment of (b) (4) seizures associated with Dravet Syndrome, (b) (4) . On December 11, 2015, the Applicant submitted DIACOMIT for proprietary name approval, which was found acceptable by the Agency on March 2, 2016.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on November 13, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for DIACOMIT (stiripentol) capsules, for oral use and powder, for oral suspension.

2 MATERIAL REVIEWED

- Draft DIACOMIT (stiripentol) MG and IFU received on October 27, 2015, and received by DMPP and OPDP on July 24, 2018.
- Draft DIACOMIT (stiripentol) Prescribing Information (PI) received on October 27, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 24, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
08/02/2018

DHARA SHAH
08/02/2018

SHARON W WILLIAMS
08/02/2018

LASHAWN M GRIFFITHS
08/02/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 31, 2018

To: Steven Dinsmore, M.D.
Division of Neurology Products (DNP)

LaShawn Dianat, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for DIACOMIT (stiripentol) capsules, for oral use, and powder, for oral suspension

NDA: 206709, 207223

In response to the DNP consult request dated November 13, 2015, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for DIACOMIT (stiripentol) capsules, for oral use, and powder, for oral suspension (Diacomit).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Tracy Peters) on July 23, 2018, and are provided below.

Medication Guide/IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 6, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DHARA SHAH
07/31/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 11, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 207223 and NDA 206709
Product Name and Strength:	Diacomit (stiripentol) for oral suspension 250 mg and 500 mg, and Diacomit (stiripentol) capsules 250 mg and 500 mg
Applicant/Sponsor Name:	Biocodex
FDA Received Date:	July 6, 2018
OSE RCM #:	2017-1862-2 and NDA 2015-2550-4
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products requested that we review the revised container labels and carton labeling for Diacomit (stiripentol) capsules and Diacomit (stiripentol) for oral suspension (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[a,b]

2 CONCLUSION

The revised container labels and carton labeling for Diacomit capsules and Diacomit for oral suspension are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rider B. Label and Labeling Review for Diacomit (NDA 207223). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 28. RCM No.: 2017-1862-1.
[b] Rider B. Label and Labeling Review for Diacomit (NDA 206709). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 28. RCM No.: 2015-2550-3.

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/s/

BRIANA B RIDER
07/11/2018

LOLITA G WHITE
07/11/2018

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 21, 2018

To: William Dunn, M.D., Director
Division of Neurology Products (DNP)

Through: Dominic Chiapperino, Ph.D., Director
Martin Rusinowitz, Lead Medical Officer
Silvia Calderon, Ph.D., Lead Pharmacologist
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Stiripentol, NDAs 206709 and 207223
For NDA 206709: Capsules containing 250 mg and 500 mg stiripentol intended for oral administration
For NDA 207223: Powder for Oral Suspension (b) (4) containing 250 mg and 500 mg stiripentol.
IND Number: 107979
Indication(s): (b) (4) treatment of (b) (4) seizures associated with Dravet syndrome, (b) (4)
Sponsor: Biocodex SA
PDUFA Goal Date: August 20, 2018

Materials Reviewed:

Abuse-related preclinical and clinical data in NDA 206709 (eCTD Original Submission dated November 10, 2015 and eCTD Sequence 0038 dated December 20, 2017), as well as the draft label submitted to NDA Sequence 0044 on March 27, 2018.

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request dated November 13, 2015 by the Division of Neurology Products (DNP) to the Controlled Substance Staff (CSS) for involvement in the review of NDA 206709 for stiripentol (Diacomit) submitted by Biocodex SA (US agent is KM Pharmaceutical Consulting, LLC)). The abuse potential of stiripentol has not previously been determined. It is not controlled under the federal Controlled Substances Act (CSA).

In Europe, stiripentol is marketed under the name DIACOMIT in capsules containing 250 mg and 500 mg of stiripentol. It is indicated for adjunctive treatment of generalized tonic-clonic and clonic seizures associated with Dravet syndrome, in patients (b) (4). The recommended daily dosage of DIACOMIT is 50 mg/kg administered in 2 or 3 divided doses. DIACOMIT is not recommended as monotherapy for Dravets syndrome. Patients should be dosed body weight.

CSS was not involved in the early stage of development of stiripentol under IND 107979. At the pre-NDA meeting held on December 16, 2013, CSS did provide comments on the need for preclinical and clinical data for purposes of assessing the abuse potential and possible placement of stiripentol under the CSA. The Sponsor submitted the requested abuse-related data) to the Agency under the original NDA (NDA 206709) on November 10, 2015. As noted in the subsequent CSS filling document for NDA 206709 (DARRTS, NDA 206709, January 6, 2016, Author: James M. Tolliver, Ph.D.), the Sponsor did not provide any studies necessary for CSS to assess the abuse potential of stiripentol. In response to this lack of information, the Division agreed to file NDA 206709 under a rolling review during which time the Sponsor would be required to submit the necessary studies for CSS to conduct a review of the abuse potential for stiripentol. On January 14, 2016, the Sponsor confirmed their agreement that the NDA be reviewed on a rolling review basis.

Via letter dated December 20, 2017, Sponsor submitted to NDA 206709 the following documents relevant to the assessment of the abuse potential of stiripentol.

- Study (b) (4) 1551 – Physical dependence study
- Study 160736 – Physical dependence study (precipitated signs with flumazenil)
- Study (b) (4) 1552 – Drug discrimination study (midazolam)
- Study (b) (4) 1657 – Drug discrimination study (pentobarbital)
- Study (b) (4) 1553 – Self-administration study
- Studies 100005313, 100027874, and 100030847 – Receptor binding studies.
- Eight Factor Analysis Document Supporting the Non-Control of Stiripentol under the CSA

Following a preliminary review of the pre-clinical studies it was determined that an oral human abuse potential study would not be required.

In September 2017, Biocodex SA submitted a second NDA, namely NDA 207223, for Stiripentol, powder for oral suspension (b) (4). Indication for use was also as (b) (4) treatment of (b) (4) seizures associated with Dravet syndrome, in patients (b) (4). No additional preclinical pharmacology or clinical studies were submitted. Under this additional NDA, no studies were provided pertaining to the assessment of an abuse potential for stiripentol. Via letter dated January 19, 2018, sent to the Division, the Sponsor cross referenced the relevant abuse potential assessment for stiripentol as provided under NDA 206709.

Dravet syndrome, also known as 'Severe Myoclonic Epilepsy in Infancy' (SMEI), is a rare form of epilepsy resulting from a mutation or deletion of the *SCN1A* gene that encodes for the pore-forming subunit of the type 1 voltage-gated sodium channel ($Na_v1.1$) found in the brain and the heart. Seizures are frequent and of multiple seizure types, including status epilepticus. In addition to epilepsy, individuals with Dravet's syndrome generally have motor and cognitive impairment as well as behavioral abnormalities. The onset is during the first year of life in a normal developing child.

Individuals with Dravet syndrome require throughout their lives extensive care to manage seizures as well as the other co-morbitities associated with the syndrome.

Below is provided as assessment of the information provided under NDA 206709 pertaining to the assessment of the abuse potential of stiripentol.

2. Conclusions

1. Overall Conclusion: Data provided in NDA 206-709, as well as data from examination of the scientific and medical literature, indicate that stiripentol does not have a potential for abuse. Therefore, stiripentol is not recommended for control under the CSA.

2. Based upon the negative findings of the preclinical data (in vitro and in vivo) and the lack of possible signals of abuse potential in the available clinical studies, there was no need for the Sponsor to conduct an oral human abuse potential (HAP) study.

3. The results of the rat intravenous (IV) self-administration Study (b) (4) 1553 indicate that stiripentol, even with blood levels 78% to 359% of the maximum blood levels achieved clinically, did not demonstrate reinforcing effects. Stiripentol self-administration was not statistically significantly higher than that produced by vehicle control. At the same time, rats did self-administer one dose of midazolam (Schedule IV benzodiazepine) at levels significantly above that of vehicle control. Rats used in this study were trained with and showed good self-administration of heroin (Schedule I).

4. Drug discrimination Study (b) (4) 1552 demonstrated that, in rats trained to discriminate midazolam (Schedule IV) from saline, stiripentol did not generalize to midazolam (Schedule IV). At single intraperiotoneal (i.p.) doses of 75, 150, and 300 mg/kg, less than 16% midazolam-appropriate responding was achieved. These doses of stiripentol were well tolerated and did not impact operant responding compared to vehicle control. At the highest stiripentol dose (300 mg/kg i.p.) maximum plasma levels of stiripentol were about 2-fold that of the maximum stiripentol concentrations following treatment of Dravet syndrome in children. The positive control comparator, pentobarbital (Schedule II), showed complete generalization at a dose of 7.5 mg/kg i.p.

5. Drug discrimination Study (b) (4) 1657 demonstrated that in rats trained to discriminate i.p. pentobarbital (Schedule II) from i.p. saline, stiripentol administered i.p. did not generalize to pentobarbital (Schedule II). At single i.p. doses of 75 and 300 mg/kg, less than 19% pentobarbital-appropriate responding was achieved, indicating no generalization. At a dose of 150 mg/kg i.p. a mean of 28.2% pentobarbital-appropriate responding was achieved, indicating a low of partial generalization. Behavioral disruption was observed with only one rat receiving a 150 mg/kg i.p. dose. Study validation was achieved by demonstrating a dose-response for sodium pentobarbital-appropriate responding following increasing doses ranging from 1 mg/kg to 5 mg/kg sodium pentobarbital. At the highest stiripentol dose (300 mg/kg i.p.) maximum plasma levels of stiripentol were about 2-fold that of the maximum stiripentol concentrations following treatment of Dravet syndrome in children.

6. In Study 160736, fumazenil-precipitated withdrawal, as determined by statistically significant reductions in the maximum electroshock threshold, was not observed in mice treated twice daily for three days with i.p. stiripentol (75 mg/kg or 150 mg/kg) but was observed in mice treated twice daily with i.p. diazepam (8 mg/kg or 16 mg/kg). Comparisons were to mice given repeated i.p. injections of vehicle followed by injection with flumazenil. The stiripentol concentrations achieved in mice were multiples (up to 4-fold) of the human maximum placement concentrations (15.6 ± 1.2µg/mL) as measured in children with Dravet Syndrome treated with the recommended therapeutic dose (~50 mg/kg/day).

7. In Study (b) (4) 1551, repeated treatment for 28 days with stiripentol (150 mg or 300 mg orally, twice daily) and diazepam (10 mg/kg escalated to 30 mg/kg) resulted in physical and behavioral effects generally not observed with vehicle treatment alone, thereby indicating the administration of pharmacologically active doses. Upon discontinuation of these treatments many of these effects diminished over the 7-day discontinuation phase. However, following discontinuation of stiripentol (300 mg) or diazepam, symptoms suggestive of physical dependence were observed. Specific signs observed more prominently during the withdrawal phase and found in common between stiripentol and diazepam included Straub tail, increased body tone, hunched posture, and increased locomotor activity.

8. Overall, the basic animal studies indicate that stiripentol displays central nervous system (CNS) depressant effects (sedation, ataxia, anticonvulsant, and potentiation of barbiturate-induced sleeping time). Although showing little direct binding to the $GABA_A$ or $GABA_B$ receptors per se, stiripentol can block the reuptake of GABA and, more importantly, function as a positive $GABA_A$ receptor modulator. This receptor modulation appears to be produced at a binding site distinct from where other benzodiazepines or barbiturates act as positive $GABA_A$ receptor modulators.

9. Adverse events (AEs) potentially associated with abuse potential were not observed in four Phase 1 pharmacokinetic studies utilizing healthy adult volunteers. Each of the four studies used healthy male subjects ranging 6 to 26 in number. Three studies involved single dose administration while the fourth study involved multiple dose (14 days) administration. All doses were oral with single doses ranging from 500 mg to 2,400 mg.

10. AEs potentially associated with abuse potential and attributed to stiripentol were not observed in eight clinical studies in which stiripentol was used as add-on (adjuvant) therapy in children and, in some cases, adults with Dravet syndrome. In these studies, stiripentol was used with other anticonvulsants, and not alone, as therapy for Dravet syndrome. In these studies, there was no evidence of abuse, withdrawal, or diversion of stiripentol. Considering the severity of Dravet syndrome as well as the age group of such patients, it is not surprising that AEs associated with abuse potential, as well as evidence of abuse or diversion, were not found (although abuse and diversion could also be applicable for caregivers or clinical trial personnel). In addition, stiripentol was added to dosage regimens involving other anticonvulsants [i.e., clobazam (Schedule IV), valproate] whose concentrations in blood increased due to stiripentol-induced suppression of drug-metabolizing enzymes. Under such conditions, it would not be possible to associate stiripentol as the causal agent for any AEs observed.

11. On October 30, 2017, Biocodex (the Sponsor) conducted a query of its "safety database" for stiripentol covering spontaneous AE reporting dating back to 2007 and documented in Japan or the European Union. No cases were documented of AEs possibly associated with abuse of stiripentol. There were no documented cases of actual abuse, diversion, or withdrawal.

12. A search of the scientific and medical literature (MedLine), dating back to the early 1980s, did not reveal any findings of possible abuse or withdrawal involving stiripentol.

3. Recommendations

Based on our findings, as captured in the Conclusions section, we recommend the following:

1. Based on the totality of the data examined, the substance stiripentol should not be scheduled under the federal Controlled Substances Act (CSA). There is no evidence of an abuse potential associated with stiripentol.

2. The Division should consider not inserting "Section 9 DRUG ABUSE AND DEPENDENCE" into the combined label for DIACOMIT Capsules (NDA 206709) and DIACOMIT (b) (4) (NDA 207223). Stiripentol is not a controlled substance under the CSA. There is no evidence of abuse potential associated with stiripentol.

3. The Division should consider keeping in Section 5.3 of the proposed combined label for DIACOMIT Capsules (NDA 206709) and DIACOMIT (b) (4) (NDA 207223) the warning and precautions concerning "Withdrawal Symptoms." This would include the recommendation that DIACOMIT be "withdrawn gradually" and that, in the event that a rapid withdrawal of stiripentol is required, patients be closely monitored.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

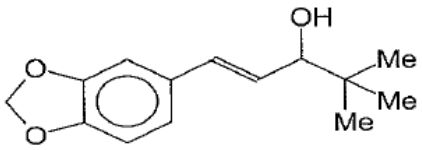
Chemical Characterization of Stiripentol.

Stiripentol is the international non-proprietary name (INN) for a drug having the following chemical names:

- (±)-(E)- 4,4-dimehyl-1-(3,4-methylenedioxyphényl)-1-pentene-3-ol.
- 4,4-dimethyl-1-(1,3-benzodioxol-5-yl)-1-pentene-3-ol
- 1-penten-3-ol, 1-(1,3-benzodioxol)-4,4-dimethyl

Laboratory code names for stiripentol include D306 and (b) (4).

The chemical structure of stiripentol (copied from Module 2.3.S for Drug Substance as provided under the original NDA 206709 submission).



The 3,4-methylenedioxyphenyl constituent to the stiripentol structure gives some structural similarity to 3,4-methylenedioxyamphetamines. The chemical structure of stiripentol for the most part does not resemble benzodiazepines, barbiturates, or other controlled sedatives.

The Chemical Abstracts Service (CAS) registry number for stiripentol is 49763-96-4.

Stiripentol has a molecular formula of $C_{14}H_{18}O_3$ and a molecular weight of 234.29 Daltons.

The stiripentol molecule has an asymmetric carbon atom (in the 3 position) resulting in two optical isomers. The synthesis process described under NDA 206709 yields a racemate.

Physical properties of stiripentol are listed below.

- White to pale yellow crystalline powder.
- Solubility
  - Practically insoluble in water
  - Sparingly soluble in chloroform
  - Soluble in acetone, ethanol, ether, acetonitrile, and dichloromethane.
- pKa = 14.2
- Melting point of 75°C with decomposition at 190°C as determined by differential scanning calorimetry

The very limited solubility of stiripentol in water suggests that this drug will be difficult to abuse by IV injection.

The synthesis of stiripentol [redacted] (b) (4)

To-Be-Marketed Formulations of 250 mg and 500 mg Capsules (NDA 206709) and [redacted] (b) (4) (NDA 207223)

Stiripentol at dosage strengths of 250 mg and 500 mg will be marketed as capsules and [redacted] (b) (4) for oral administration. Stiripentol is not formulated for any other routes of administration.

Excipients included in stiripentol capsules include povidone, sodium starch glycolate, and magnesium stearate. The fill mass for the 250 mg and 500 mg capsules are (b) (4) mg and (b) (4) mg, respectively.

The 250 mg and 500 mg (b) (4) dosage strengths contain powder at a total mass of (b) (4) mg and (b) (4) mg, respectively. Excipients in the powder include povidone, sodium starch glycolate, (b) (4) glucose (b) (4), erythrosine, titanium dioxide, aspartame, (b) (4) flavor, carmellose sodium, and hydroxyethylcellulose.

1.2 Potential Drug Isomers

The stiripentol molecule has an asymmetric carbon atom (in the 3 position) resulting in two optical isomers, namely (-)-stiripentol and (+)-stiripentol. The synthesis process as described in the NDA yields a racemate mixture. Stiripentol as present in the to-be-marketed formulations (capsules or (b) (4)) is a racemate. Both isomeric forms have anticonvulsant activity (see below under Section 2 Nonclinical Pharmacology).

1.3 In Vitro Manipulation and Extraction Studies

In vitro manipulation and extraction studies were not requested or submitted. There is currently no basis to investigate any possible advantages to manipulation of the proposed formulation for abuse purposes.

2. Nonclinical Pharmacology

Under the original NDA 206709 application Sponsor described a variety of pre-clinical studies examining the general pharmacology of stiripentol. These studies were collectively described in detail under Module 2.4 Nonclinical Overview. Individual studies were described in depth under Study BC.098/GB found under Module 4.2.1.1. Results relevant to an abuse potential assessment of stiripentol are briefly mentioned below.

Preclinical behavioral studies demonstrate that stiripentol has sedative effects.

- In the open-field test,
  - Rats administered i.p. 50, 100, or 200 mg/kg stiripentol showed dose-dependent reductions in locomotor activity by 4 to 58%.
  - Mice, receiving i.p. 50 or 100 mg/kg stiripentol showed no decrease in exploratory behavior but some decreased basal motor activity
  - Mice, receiving oral stiripentol (250, 500, 750, or 1000 mg/kg) showed, at 30 minutes to two hours post administration, no effects on exploratory behavior but some reductions in basal motor activity.
- In mice, stiripentol (doses of 100 mg/kg i.p. and higher) potentiated the depressant effects of several benzodiazepines such as diazepam (2 mg/kg i.p.), oxazepam (100 mg/kg i.p.), flunitrazepam (10 mg/kg i.p.), and lorazepam (50 or 100 mg/kg i.p.) in mice.

- In mice, stiripentol at doses of 200 and 400 mg/kg i.p. when given with alcohol at doses of 3,000 or 4,000 mg/kg i.p., dose-dependently potentiated alcohol-induced sedation by increasing the percentage of animals affected by narcosis and prolonged sleeping time.
- In mice, stiripentol (10, 50, 100, 150, and 200 mg/kg i.p.; 25 and 50 mg/kg oral) dose-dependently potentiated duration of sleep induced by hexobarbital (70 mg/kg i.p.). A similar effect was observed with stiripentol (100 mg/kg i.p.) and phenobarbital (75 mg/kg i.p.). Part of this potentiation likely involved cytochrome P450 inhibition by stiripentol, resulting in decreased metabolism of barbiturates.

Stiripentol administered i.p., but not orally, had effects on the rotorod test.

- Oral doses of stiripentol (up to 2,000 mg/kg) had no effect on the rotarod test in mice.
- Intraperiotonel doses to mice of stiripentol of 400, 500, and 600 mg/kg dose-dependently decreased performance on the rotarod test.
- At the 600 mg/kg i.p. dose, impaired activity in the rotarod test was evidenced by inability to remain on the rotarod, decreased motor activity and decreased respiration with cyanosis; animals recovered within 1 hour. The same symptoms were observed at the 1,200 mg/kg i.p. dose, but lasted longer (2 hours). At the 1,800 mg/kg i.p. dose, decreased motor activity, spasticity, "ataxia," reduced rotarod performance, sedation, ptosis, muscle relaxation, loss of righting reflex, and decreased respiration with cyanosis were observed.

An important focus of preclinical in vivo studies has been an assessment of the anticonvulsant effects of stiripentol using various animal models. This was expected considering that under NDA 206709, stiripentol is under development as an anticonvulsant for Dravet syndrome. Below is a summary of the results from these studies.

- In mice, stiripentol does not antagonize convulsions produced my bicuculline, picrotoxin, or strychnine.
- In mice, stiripentol (400 mg/kg to 1,200 mg/kg, oral) dose-dependently and time-dependently antagonized metrazol-induced seizures. The effect was maximal at 1 hour (earlier time points were not studied) and was still present at 6 hours.
- In rats, stiripentol antagonized maximum electroshock seizures and subcutaneously evoked metrazol seizures. Effective doses (i.e., 600 mg/kg orally) achieved levels of stiripentol in rat blood that was similar to levels (17 to 30 mg/L range) achieved following therapeutic doses in epileptic patients.
- Both (+)-stiripentol and (-)-stiripentol have some anticonvulsant activity as demonstrated in the maximum electroshock assay and the subcutaneous metrazol assay.
- In the rat lithium-pilocarpine model of status epilepticus treatment with stiripentol (10 mg/kg to 1,000 mg/kg) given at the beginning of Stage 3 seizures, dose- dependently reduced seizures, with the dose of 1,000 mg/kg completely abolishing seizures. Such seizures are also effectively treated with diazepam.
- In the rat model of petit mal, stiripentol at doses in the range of 125 mg/kg to 500 mg/kg significantly and dose-dependently reduced the duration of paroxysmal EEG activity indicative of epileptic activity.
- Stiripentol (100 mg/kg oral) reduced metrazol-induced EEG spike-and-wave activity and prevented seizures and death in rabbits.
- In a genetic model of Dravet's syndrome developed in mice, stiripentol elevated seizure-inducing body temperature and decreased the duration of hyperthermic seizures in young (1-month old) but

not in older (>5 months old) mice. The schedule IV benzodiazepine, clobazam, was also effective in this model.

It should be noted that, with respect to an anticonvulsant effect, a "supra-additive synergy" results when stiripentol is combined with valproate and/or a benzodiazepine. This synergistic effect is the preclinical basis for the use of stiripentol (b) (4) in the treatment of Dravet syndrome. Stiripentol is not recommended as a monotherapy in Dravet syndrome. Preclinical findings demonstrating this synergy are given below.

- Treatment of mice with either 200 mg/kg stiripentol or with 37 mg/kg valproate combined with 0.25 mg/kg diazepam resulted in only 20% and 10%, respectively, of mice protected against metrazol-induced seizures. However, when all three drugs were combined (200 mg/kg stiripentol, 37 mg/kg valproate, 0.25 mg/kg diazepam), 100% of the mice were protected from metrazol-induced seizures. This supra-additive synergy provides preclinical support for the use of stiripentol as an adjuvant for treatment of Dravet's disorder.
- With respect to the genetic model of Dravet's syndrome developed in mice, the combination of stiripentol with the benzodiazepine, clobazam, provided a synergistic protection against hyperthermic seizures as observed in young and in older mice.

Both the sedative effects and anticonvulsant effects produced by stiripentol suggest that this drug may act via the GABAergic system. With respect to the effects on the GABAergic system, the overall preclinical data suggest:

- Stiripentol does not bind to $GABA_A$ or $GABA_B$ receptors. (See Section 2.1 Receptor Binding and Functional Assays below)
- Stiripentol, at relevant pharmacological concentrations, can block the reuptake of GABA into rat frontal cortex synaptosomes and can inhibit GABA transaminase in the rat (Poisson et al., 1984, Segmann et al 1978)
- Stiripentol acts as a positive allosteric $GABA_A$ modulator.

Studies have demonstrated that stiripentol acts as an allosteric positive $GABA_A$ receptor modulator. The site of action appears to be different from that of benzodiazepines, barbiturates, and neuromodulators . These studies are briefly discussed below.

- Quilicini et. al. (2006), using voltage clamp techniques in hippocampal slices, found that stiripentol (30 to 300 μM) in a dose-dependent manner increased the duration and frequency of miniature inhibitory $GABA_A$ receptor-mediated currents (IPSCs) without modifying amplitude or rise time. These effects were not mediated at the benzodiazepine or neurosteroid binding sites, not at the GABA transporter level.
- Fisher (2009, 2011), using patch-clamp techniques demonstrated the stiripentol was an allosteric modulator at $GABA_A$ receptors. Mammalian cells were transfected with recombinant $GABA_A$ receptors containing selected combinations of α, β, and γ subunits. Stiripentol in a dose dependent manner potentiated the responses to $GABA_A$ receptor subtypes including $\alpha1\beta3\gamma2L$ and $\alpha3\beta3\gamma2L$ with EC50 values of 35.5 and 24.6 μM, respectively. Greatest potentiation was observed at $GABA_A$ receptors containing α3 and δ subunits. Based on inhibition studies, the site of action of stiripentol for having a modulatory effect is different from where other $GABA_A$ allosteric modulators bind, including benzodiazepines, barbiturates, and neurosteroids.
- Grosenbaugh and Mott, using patch clamp techniques showed that stiripentol and clobazam acts at different sites to prolong the decay time for inhibitory post-synaptic currents (IPSC) in cells of the

dentate gyrus of rats. Combining the two drugs together results in a prolongation of IPSC decay that is longer than that produced by either drug alone. Flumazenil has no effect of the stiripentol induced prolongation of the decay of IPSCs.

It should be noted that allosteric modulatory activity at the $GABA_A$ receptor is observed for selected drugs regulated under the CSA. These drugs include:

- Benzodiazepines (Schedule IV)
- Barbiturates (Schedules II and IV)
- Methaqualone (Schedule I)
- Carisoprodol (Schedule IV)

Considering the number of subunits (α, β, γ, and δ) available, there are a variety of pentameric combinations possible for the $GABA_A$ receptor/ionophore complex. These, in turn, make possible various binding sites of drugs. Benzodiazepines and barbiturates bind at sites associated with abuse potential. Stiripentol binds at a site unique from that of benzodiazepines or barbiturates. Based on the behavioral studies (drug discrimination and drug self-administration), the site of action for stiripentol appears not to be associated with an abuse potential.

2.1 Receptor Binding and Functional Assays

The binding of stiripentol to various receptors was reported in the following three studies: 100027874, 100005313, and 100030847.

Study 100005313

As part of the overall in vitro pharmacology assessment for stiripentol Study 100005313 was conducted over the period of September 17 – 21, 2012 by (b) (4). The final report was dated September 24, 2012. Using competitive receptor binding assays stiripentol was found not be bind to AMPA, kainite, NMDA, glycine or phencyclidine receptors located in rat cerebral cortex. Four doses of stiripentol were evaluated ranging from 1×10^{-5}M to 3×10^{-4}M. For all five radioligands used, stiripentol at a dose of 3.0×10^{5}M provided less than 11% inhibition of binding. This low level of inhibition, in the micromolar range, indicates that stiripentol shows little binding to these five receptors. Studies 100027874 and 100030847.

Stiripentol, at concentrations of 0.1, 1, 10, and 100 μM, were evaluated in competitive binding studies to a variety of receptors. Most receptors were human recombinant proteins. Most of the receptors were transfected to Chinese hamster ovary cells; however, a few were inserted into either SH-SYSY cells or HEK-293 cells. Binding was also evaluated for benzodiazepine (diazepam) and chloride channels both obtained from rat cerebral cortex. Stiripentol binding was also examined for human recombinant norepinephrine, dopamine, and serotonin transporters in CHO cells and for the GABA transporter in rat cerebral cortex. Radioactive ligands (agonist or antagonist) demonstrating high affinity were utilized for all receptors, channels, and transporters that were used in the competitive binding assays.

Stiripentol, at a concentration of 100 μM, produced less than 20% radioligand inhibition at the following sights: alpha receptors (1A, 2A, 2B, and 2C), beta receptors (1 and 2), benzodiazepine receptor,

cannabinoid 1 receptor, dopamine receptors (1 and 2), GABA receptor (A1), acetylcholine muscarinic receptors (1, 2, 3, 4, and 5), opioid receptors (μ, δ, κ), serotonin receptor (1A, 3), and GABA transporter.

To the extent that binding took place, stiripentol at high concentrations caused inhibition of radioligand binding at cannabinoid 2 receptors, serotonin receptors (5-HT2A, 5-HT2B), chloride channel, norepinephrine transporter, and dopamine transporter. For these specific assays, the Sponsor conducted more detailed dose response curves as reported in Study 100030847. Competitive binding results are shown below in Table 1.

Table 1. Mean (N = 2) Percentage Inhibition of Reference Drug Binding to Receptors, Channels, and Transporters by Stiripentol at Concentrations of 10 and 100 μM. (Note: At a stiripentol concentration of 1 μM, less than 20% inhibition of reference drug binding was observed.) (Source: Study 100030847)

Receptor, Channel, or transporter	Reference Drug (Radioligand)	Cell Type	K_i (μM)	Mean % Inhibition of Controlled Binding	
				10 μM Stiripentol	100 μM Stiripentol
Cannabinoid 2	WIN-55212-2	CHO	34	10.3	67.0
Serotonin 5HT2A	(±) DOI	HEK-293	28	19.3	75.8
Serotonin 5HT2B	(±) DOI	CHO	18	18.0	65.7
Serotonin 5HT2C	(±) DOI	HEK-293	73	-7.0	49.8
Chloride Channel	Picrotoxinin	Rat Cerebral Cortex	17	29.2	98.3
Norepinephrine Transporter	Protriptyline	CHO	3.6	64.8	95.8
Dopamine Transporter	BTCP	CHO	2.8	65.1	95.5

Table 1 also provides the Ki values for binding. Stiripentol showed a binding to the cannabinoid 2 subtype receptor with a Ki of 34 μM. For the serotonin 2A, 2B, and 2C receptor subtypes, Ki values for stiripentol binding were 28, 18, and 73 μM, respectively. For the norepinephrine and dopamine transports, Ki values were 3.6 and 2.8 μM, respectively. No binding to acetylcholine or norepinephrine receptors was observed.

2.2 Safety Pharmacology/Metabolites

Zhang et al. (1990) identified 15 metabolites in urine collected over 24 hours from rats receiving a single oral dose of 200 mg/kg stiripentol. One metabolite, designated 1-(3-methoxy-4-hydroxyphenyl)-4,4-dimethyl-1-penten-3-one, constituted 17.9% of the original stiripentol dose. This metabolite originated from the oxidative scission of the methylenedioxy ring via the cytochrome P-450 system to generate catechol derivatives. The pharmacological activity of this metabolite is not known. With respect to all remaining metabolites, the recovery was well less than 10 % of the initial stiripentol dose.

Moreland et al., (1986) examined urinary and fecal metabolites of stiripentol following the oral administration of a single 600 mg or 1200 mg dose of stiripentol to two healthy male subjects. Two metabolites were isolated from urine that constituted >10% of a 600 mgs oral dose given to one human subject. One metabolite identified as 1-(3,4-dihydroxyphenyl)-4,4-dimethyl-1-penten-3-ol constituted 10.7% of the total dose collected at 12 hours. The other metabolite was 1-(3-methoxy-4-hydroxyphenyl)-4,4-dimethyl-1-penten-3-ol, constituting 11.8% of the initial stiripentol dose. This

metabolite has been shown to have anticonvulsant activity. (Levy et al., 1983). Both metabolites resulted from oxidative scission of the methylenedioxy ring of stiripentol via the cytochrome P-450 system.

Ten additional metabolites, as identified by Moreland et al., (1986), each constituted less than 10% of the initial stiripentol dose.

2.3 Findings from Safety Pharmacology and Toxicology Studies

Discussions regarding the effects of stiripentol with respect to locomotor activity, inclined plain (roto-rod) test, sedative potentiating effects of barbiturates, physical dependence, drug discrimination, and drug self-administration have been described at other locations in this document (Sections 2.0, 2.1, 2.4, and 2.5). Overall, these studies do not suggest substantial safety issues with stiripentol, including from an abuse potential perspective. Although stiripentol exerts sedative effects, it does not appear to act at the same sites as benzodiazepine (Schedule IV) or barbiturates (Schedules II and IV). Stiripentol does not generalize to benzodiazepines. Stiripentol appears to be devoid of reinforcing effects, in contrast to that seen with benzodiazepines or barbiturates. Abrupt withdrawal following long-term oral administration of stiripentol at a dose of 300 mg in rats appears to evoke a weak withdrawal syndrome suggesting limited physical dependence.

2.4 Animal Behavioral Studies

Study (b) (4) 1552 – Discrimination to Midazolam

As part of the preclinical behavioral abuse potential assessment of stiripentol, Sponsor conducted Study (b) (4) 1552 entitled "Evaluation of the Discriminative Properties of Stiripentol and the Reference Comparator Sodium Pentobarbital in Rats Trained to Discriminate Midazolam from Saline." This study was conducted between July 2016 and March 2017 by (b) (4), with a final study report dated June 2017. The overall finding of this study was that stiripentol did not show stimulus generalization to midazolam, a Schedule IV benzodiazepine.

Female, Lister Hooded rats were trained to distinguish between the psychoactive effects of i.p. injections of midazolam (0.5 mg/kg) and saline (1 ml/kg) in a 2-choice, lever-pressing model using sweetened milk as food reinforcement. Stiripentol was evaluated after administration by the i.p. route using an interval of 120 min between dosing and testing. The reference comparator selected for this experiment was sodium pentobarbital (Schedule II). Groups of 6-9 rats were intraperitoneally injected with sodium pentobarbital (3.0, 5.0, and 7.5 mg/kg i.p.) and evaluated in the drug-discrimination test 15 min after dosing. During testing there were ≥75% correct lever presses in response to the drug cue and saline in the 10 minutes test preceding test compound evaluation (Test Compound or Reference Comparator) and a mean of ≥75% correct lever-presses in the 4 drug cue and saline cue tests preceding test compound. When rats have achieved 4 correct saline and midazolam test sessions, they progressed to test compound evaluation.

Prior to drug discrimination testing, Stiripentol at doses of 75 mg/kg, 150 mg/kg, and 300 mg/kg injected i.p. were found to be well tolerated and not to influence operant responding compared to vehicle control. Considering that stiripentol is not very soluble in water, stiripentol solutions were made up using Tween 80 at 5% in sterile saline solution. This vehicle solution for stiripentol did reduce operant responding of rats for the sweetened milk rewards.

Full generalization was defined as ≥75% lever-press responses on the sodium pentobarbital lever. Partial generalization was defined as 25.1 - 74.9% lever-press responses on the sodium pentobarbital lever. Less than or equal to 25 lever press responses was considered no generalization.

Single administration of stiripentol at 75, 150, and 300 mg/kg generalized to the saline cue at all doses. Stiripentol evoked no sedative euphoriant (benzodiazepine-like) psychoactive effects at any of the doses tested with mean percentage generalization to the midazolam (0.5 mg/kg i.p.) cue of 15.2 ± 37.3% (n = 7), 14.1 ± 32.7% (n = 7), and 8.3 ± 15.0% (n = 7) at 75, 150 and 300 mg/kg i.p., respectively.

Sodium pentobarbital at the lowest dose of 3.0 mg/kg i.p. showed no generalization to midazolam (mean of 17.7 $\pm$ 17.1 % midazolam-appropriate responding). At the higher doses of 5.0 mg/kg and 7.5 mg/kg i.p. partial midazolam generalization was achieved (means of 61.9 $\pm$ 45.2% and 68.5 $\pm$ 39.1% appropriate midazolam responding). When examining individual data, in the case of the highest dose of sodium pentobarbital, six rats displayed full generalization to midazolam (>80% midazolam appropriate responding) without any disruption of pressing.

The plasma concentrations of stiripentol in rat plasma samples (pre-dose, 1.0, 2.0, and 3.0 hr post-dose) were determined in the groups of 5 rats treated with stiripentol 75, 150, and 300 mg/kg i.p.. The mean observed Cmax was 4.20 µg/mL for the 75 mg/kg group, 12.29 µg/mL for the 150 mg/kg group and 28.53 µg/mL for the 300 mg/kg group. The Cmax for stiripentol achieved after i.p. injection of the 300 mg/kg dose of stiripentol was approximately 2-fold higher than the Cmax value (15.6 $\pm$ 1.2 ug/mL) found in children with Dravet Syndrome treated with the recommended therapeutic dose of 50 mg/kg per day.

Overall the results of this study indicate stiripentol, at the doses examined, does not generalize to midazolam in rats trained to discriminate midazolam from saline.

Study (b) (4) 1657 – Discrimination to Pentobarbital

As part of the preclinical abuse potential assessment for stiripentol, the Sponsor conducted Study (b) (4) 1657 entitled "Evaluation of the Discriminative Properties of Stiripentol in Rats Trained to Discriminate Sodium Pentobarbital from Saline." This study was conducted between March and August of 2017 by (b) (4), with a final study report dated September 2017. The overall results of this study indicate that stiripentol does not generalize to sodium pentobarbital.

Female, Lister Hooded rats were trained to distinguish between the psychoactive effects of i.p. injections of sodium pentobarbital (5.0 mg/kg) (Schedule II) and saline (1 ml/kg) in a 2-choice, lever-pressing model using sweetened milk as a food reinforcer. Stiripentol was evaluated after administration by the intraperitoneal (i.p.) route using an interval of 120 min between dosing and testing at doses of 75 mg/kg, 150 mg/kg, and 300 mg/kg. These doses were selected based on a preliminary study demonstrating that

at these doses stiripentol produced few sedative effects. Drug discrimination was tested at 2 hours following i.p injection of stiripentol based on a previous study (Study (b) (4)1552) demonstrating that in Lister Hooded rats maximum stiripentol plasma levels were seen at 2 hours post i.p. injection. During the testing period rats had to achieved 4 correct saline and sodium pentobarbital test sessions (≥ 75% correct lever presses), before they progressed to test compound evaluation. Following injection of test compound (sodium pentobarbital or stiripentol) the percentage of responses on the sodium pentobarbital lever was determined during the 10-minute test sessions.

Full generalization was defined as ≥75% lever-press responses on the sodium pentobarbital lever. Partial generalization was defined as 25.1 - 74.9% lever-press responses on the sodium pentobarbital lever. Less than or equal to 25 lever press responses was considered no generalization.

When administered by the i.p. route and tested 120 min. after dosing, a single administration of stiripentol at 75 and 300 mg/kg generalized to the saline cue. Stiripentol evoked no sedative barbiturate-like psychoactive effects at 75 and 300 mg/kg with mean percentage generalization to the sodium pentobarbital (5.0 mg/kg) cue of 18.4 ± 20.7% (n = 6) and 9.4 ± 4.3% (n = 6), respectively. At 150 mg/kg i.p. stiripentol produced a low partial response of 28.2 ± 19.5% (n = 7, with 1 rat displaying disrupted behaver).

Study validation was achieved by showing a dose-response for sodium pentobarbital appropriate responding following i.p. injections of 1.0 mg/kg, 2.5 mg/kg, and 5.0 mg/kg sodium pentobarbital tested at 15 minutes following injection.

For this study, pharmacokinetic analysis of plasma stiripentol was not determined. Instead this study relied upon the pharmacokinetic results of study (b) (4)1552 using the same rat strain. Measured concentrations indicated systemic exposure of the animals to stiripentol concentrations were detected 1, 2, and 3 hours after administration in all animals. Mean observed Cmax values were 4.20 µg/mL for the 75 mg/kg group, 12.29 µg/mL for the 150 mg/kg group, and 28.53 µg/mL for the 300 mg/kg group. At the highest dose of 300 mg/kg, the maximum stiripentol concentration of 28.53 µg/mL represented a 2-fold higher stiripentol concentration than that found in measured in children with Dravet Syndrome treated with the recommended therapeutic dose (~50 mg/kg/day).

Study (b) (4)1553 – Intravenous Self-Administration Study in Rats

As part of the abuse potential evaluation of stiripentol, Sponsor submitted Study (b) (4)1553 entitled "Evaluation of the Potential Reinforcing Effects of Stiripentol and a Reference Comparator Using an Intravenous Self-Administration Procedure in Heroin-Maintained Rats." This study was conducted at the (b) (4). The study period was September 14, 2016 to December 18, 2016. The overall finding of this study is that stiripentol was not a positive reinforcer.

Following training to press a lever for food pellets using a fixed ratio 3 (FR 3) schedule of reinforcement, adult, Sprague-Dawley rats were implanted with intravenous catheters. Rats were then trained to self-administer heroin (0.05 mg/kg/infusion initial training dose, 0.015 mg/kg/infusion IV for

final training dose) on a FR3 schedule of drug reinforcement. Robust self-administration of heroin was defined as 3 consecutive sessions where the mean number of heroin infusions was ≥12.

Prior to conducting self-administration studies, pharmacologically active doses of stiripentol were determined by observing the effects of a single, bolus, intravenous injection of a range of doses on FR3 responding for food rewards and other behaviors. Stiripentol produced few effects on general behavior apart from very mild ataxia and mild/very mild decreased body tone at the highest dose of 10 mg/kg IV tested. Active pharmacological doses observed and selected for the IV self-administration study included 0.2, 1.0 and 5.0 mg/kg/infusion, IV.

Stiripentol was solubilized in 45% (w/v) Trappsol in deionized water. Heroin and midazolam were prepared using physiological saline.

When the operant responding of the rats had been extinguished (defined as 3 consecutive sessions where the mean number of saline infusions was ≤ 6 infusions/2 hr session), by giving them daily access to the non-reinforcer, saline (0.5 ml/kg IV) on a FR3 schedule, stiripentol and the comparator, midazolam (Schedule IV), were evaluated across a range of pharmacologically active doses to determine whether it would substitute for heroin in the model. Stiripentol (0.2, 1.0, and 5.0 mg/kg/infusion, IV; n = 8 rats/group) or midazolam (0.001, 0.0015, and 0.00225 mg/kg/infusion, IV; n = 8 rats/group) were substituted in the paradigm to determine whether they would maintain self-administration at levels above those of the saline vehicle (0.5 ml/kg IV) across a range of doses. The rats could lever-press for a maximum of 20 infusions/2 hour session (in addition to the non-contingent injection) in daily sessions. Rats were tested 5-6 days/week.

Determination of a positive reinforcing effect was based on a statistically significant increase in the mean number of IV injections received for rats in the three sessions of each condition, saline, heroin, or stiripentol. Results are provided below.

- Statistical mean (± SEM) for the number of IV injections of heroin were 16.4 ± 0.6 (N = 25) Thereby demonstrating that heroin was well self-administered as might be expected for a Schedule I opioid.
- Saline was not IV self-administered, as demonstrated by a statistical mean (+ SEM) for the number of IV injections of 4.1 ± 0.3.
- When rats (N = 8) were given access to stiripentol at the three doses of 0.2, 1.0, and 5.0 mg/kg/injection, the statistical mean (+ SEM) for the number of IV injections 5.4 ± 1.5, 4.9 ± 1.2, and 5.6 ± 1.0, respectively. The number of injections at all three does was not statistically significantly ($p<0.05$) higher when compared to saline, indicating a lack of reinforcing effect.
- When rats (N = 8) were given access to midazolam at the three doses of 0.001, 0.0016, and 0.00225 mg/kg/injection, the statistical mean (+ SEM) for the number of IV injections 5.8 + 1.3, 7.3 + 1.5, and 4.9 + 1.5, respectively. Only at the dose of 0.0016 mg/kg/injection was the number of injections of midazolam statistically significantly ($p=0.01$) higher when compared to saline, supporting a positive reinforcing effect of midazolam.

Because the rats self-administered multiple infusions of the test compound, the estimated Cmax concentrations were achieved by the cumulative dose of stiripentol that was taken by the rats for each of the doses that were tested in the model, i.e., 0.2, 1.0 and 5.0 mg/kg/infusion, IV. The cumulative doses of stiripentol comprising the group mean intake of infusions/2 hr session + the 1 non-contingent dose

used to start the sessions was 1.376, 6.230, 33.0 mg/kg IV for the doses of 0.2, 1.0, and 5.0 mg/kg/infusion, IV, respectively. The maximum plasma levels of stiripentol in rats ranged from 78 % to 359 % of its clinical Cmax at the two highest doses. The reinforcing potential of stiripentol has been investigated across concentrations that are 12.14 and 56.03µg/mL at respective cumulated doses of 6.23mg/kg (medium dose) and 33mg/kg (high dose).

2.5 Tolerance and Physical Dependence Studies in Animals

Study Report (b) (4) 1551 – Physical Dependence Study – Spontaneous Withdrawal

As part of the abuse potential assessment of stiripentol, the Sponsor submitted Study 1551 entitled "Determination of the Potential of Stiripentol to Induce Pharmacological Tolerance and Physical Dependence on Withdrawal." This study was conducted November-December, 2016, by (b) (4) The final study report is dated September 2017. The study was provided via letter dated December 20, 2017, from the Sponsor submitted to NDA 206709. This study showed that, upon abrupt discontinuation of prolonged oral Stiripentol administration, a withdrawal syndrome was evoked.

Seventy (70), male Sprague-Dawley rats were used (58 rats for the tolerance/dependence experiment [50 main study; 6 pilot study; 2 spares] and 12 rats for blood sampling for measurement of Stiripentol in plasma [2 groups of 5 rats/group for blood sampling; 1 spare rat/group]). Five groups of rats (10 rats/group) were studied.

Following a 7-day baseline phase during which the rats received vehicle PO once a day, the animals were dosed at 8:00 am and 8:00 pm each day for 28 days:

- Group A - vehicle-treated group, deionized water at 10 ml/kg, orally by gavage, twice daily
- Group B - morphine at 30 mg/kg/dose oral twice daily (60 mg/kg/day).
- Group C - diazepam (10 mg/kg oral twice daily for 5 days [20 mg/kg/day on Days 1 to 5]; 15 mg/kg oral twice daily for 13 days [30 mg/kg/day on Days 6 to 18]; and 20 mg/kg oral twice daily for 10 days [40 mg/kg/day on Days 19 to 28]).
- Group D - Stiripentol (150 mg/kg oral bid [300 mg/kg/day])
- Group E - Stiripentol (300 mg/kg bid oral [600 mg/kg/day]).

It is notable that this study included a cohort of rats repeatedly treated with morphine. The dose used was sufficient to produce noticeable physiological effects. With termination of treatment, as would be expected, a withdrawal syndrome was observed. Morphine was selected as a second positive control for purposes of validating the study, a function also of the use of diazepam which had previously been shown in the same laboratory to produce physical dependence. However, considering the very different mechanism of action of morphine it is questionable that this treatment has much relevance with respect to assessing physical dependence associated with stiripentol. A more appropriate second positive control, along with diazepam (Schedule IV), might have been a Schedule II barbiturate. This review will focus on treatments with vehicle control, stiripentol, and diazepam.

At the end of the 28-day dosing phase, drug treatment ceased abruptly and animals were subjected to a 7-day spontaneous drug withdrawal period. Behavioral and physical signs were looked for twice-daily

starting at 09.00 hours and 16.30 hours. Physiological measurements of body weight, food intake, and water intake were taken once-daily during the baseline period, drug dosing phase, and the drug withdrawal phase.

Physical and behavioral effects observed are listed below.

- Vehicle Control
    - ON-DOSE PHASE - Behavioral/physical signs observed with "sporadic frequency" included rearing, wet dog shakes, escape attempts, increased body tone, increased irritability, increased reactivity to sound, increased locomotor activity, tail rattling, and increased respiration
    - WITHDRAWAL PHASE – "Occasional" observation of digging, escape attempts, increased body tone, increased locomotor activity, increased reactivity to sound, exophthalmos
- Stiripentol 150 mg
    - ON-DOSE PHASE – Increased locomotor activity documented on Day 23 was the only effect observed in > 40% of rats. Behaviors that were observed in <40% of rats on any day were ataxia/rolling gait, hunched posture, subdued behavior, Straub tail, escape attempts, increased body tone, increased reactivity to sound, increased irritability, piloerection, and stained fur and noses. Very occasional signs were head weaving, rearing, head shakes, vacuous chewing, tail rattling, explosive movements, exophthalmos, and erratic and increased respiration.
    - WITHDRAWAL PHASE - Most behavioral and physical signs seen in the on-dose phase decreased upon termination of treatment. Most frequent behavioral signs during withdrawal were increased body tone, rearing, and locomotor activity (≥ 40%).
- Stiripentol 300 mg
    - ON-DOSE PHASE - Hunched posture and Straub tail were observed in ≥40% of rats. Signs observed in <40% of rats that were sporadically observed across the 28-day on-dose phase were ataxia/rolling gait, subdued behavior, rearing, escape attempts, increased locomotor activity, head shakes, increased body tone, increased reactivity to sound, increased irritability, piloerection, and erratic respiration.
    - WITHDRAWAL PHASE - Behavioral and physical signs observed in the on-dose phase generally diminished indicating that these effects were due to the treatment with 300 mg stiripentol. Signs that occurred at a higher frequency in the withdrawal period were Straub tail, increased body tone, increased locomotor activity, piloerection, subdued behavior, hunched posture. These signs were considered part of a physical withdrawal syndrome.
- Diazepam
    - ON-DOSE PHASE – Physical and behavioral signs of an active drug effect as seen in ≥ 40% of rats included Ataxia/rolling gait, hunched posture, subdued behavior, head weaving, escape attempts, increased locomotor activity, vacuous chewing, exophthalmos, erratic respiration, “drunk” (the rats showed a peculiar, weaving, uncoordinated gait and lack of acute awareness of their environment that was reminiscent of drunkenness) and flattened body posture. Other signs occurring in <40% on a number of on-dose days included head shakes, decreased body tone, increased reactivity to sound, increased irritability, and tail rattling.
    - WITHDRAWAL PHASE - Signs including ataxia/rolling gait, hunched posture, head weaving, head shakes, escape attempts from cage, vacuous chewing, exophthalmos, and

"drunk" that had been observed in the on-dose phase gradually decreased in frequency and severity over the 7-day withdrawal period. Typical signs of diazepam-dependence included subdued behavior, Straub tail, increased body tone, increased locomotor activity, and increased reactivity to sound.

The overall findings indicate that repeated treatment with stiripentol (150 mg or 300 mg orally, twice daily) and diazepam resulted in physical and behavioral effects generally not observed with vehicle treatment alone. Upon discontinuation of these treatments many of these effects diminished over the 7-day discontinuation phase. However, following discontinuation of stiripentol (300 mg) or diazepam, symptoms suggestive of physical dependence were observed. Specific signs were observed more prominently during the withdrawal phase and found in common between stiripentol and diazepam, including subdued behavior, Straub tail, increased body tone, hunched posture, and increased locomotor activity.

Study Report 160736 – Precipitated Withdrawal Using Flumazenil.

As part of the abuse potential assessment of stiripentol, Sponsor submitted Study 160736 entitled "Evaluation of a Selected Bicodex Test Substance Using the Flumazenil-Precipitation Withdrawal Test in the Mouse." This study was conducted July 17-20, 2017 in (b) (4). The original study was provided via letter dated December 20, 2017, submitted to NDA 206709. The overall finding of this study was that flumazenil-precipitated withdrawal could be evoked in mice treated repeatedly with diazepam (Schedule IV) but not with stiripentol.

The specific aim of the study was to test whether stiripentol may induce physical withdrawal symptoms after cessation of repeat-dosing treatment (twice daily i.p. for 3 days) using the flumazenil-precipitated withdrawal test in male mice.

A total of 160 mice were used in the study in groups of 15 mice. Mice were treated i.p. twice daily for three days with either stiripentol (75 mg/kg or 150 mg/kg), diazepam (8 mg/kg or 16 mg/kg), or vehicle. On the fourth day, mice received IV injections of 2.5 mg/kg flumazenil five minutes before beging subjected to electroconvulsive (ECS) shock. For each group the ECS threshold was determined.

Results from this study are listed below:

- When compared to vehicle control, the repeated i.p. injection of stiripentol ((75 mg/kg or 150 mg/kg) in the absence of any flumazenil challenge had no effect on the ECS threshold.
- The repeated i.p. injection of 75 mg/kg stiripentol followed by flumazenil did not result in a significant difference in ECS threshold compared to that produced in mice given repeated vehicle control followed by flumazenil.
- A statistically significant increase of 9% was observed in the ECS threshold following flumazenil challenge in mice treated with 150 mg/kg stiripentol compared to in mice treated with vehicle control.
- In mice following repeated i.p. injection of 8 mg/kg and 16 mg/kg diazepam, but without any flumazenil challenge, there was a significant ($p<0.001$) reduction (24%) in ECS threshold on Day 4 as compared to that seen in mice receiving repeated vehicle control but without flumazenil challenge.

- In mice receiving repeated i.p. injections of 8 mg/kg and 16 mg/kg diazepam, followed by flumazenil injection, there were statistically ($p<0.001$) significant reductions in ECS threshold of 24% and 37% when compared to mice receiving vehicle control and challenged with flumazenil.

Differences in body weight during the study were not observed. No other signs or behaviors were documented.

Blood samples were collected from six animals at each dose at sampling times of 0.5, 1, 2, and 24 hours after the last administration on the third day. The mean observed maximum plasma levels of stiripentol were 47.5 µg/mL for the 75 mg/kg group and 62.4 µg/mL for the 150 mg/kg group at 30 min post dosing. These levels were multiples (up to 4-fold) of the human maximum placement concentrations (15.6 ± 1.2µg/mL) as measured in children with Dravet Syndrome treated with the recommended therapeutic dose (~50 mg/kg/day).

Overall, benzodiazepine-like, flumazenil-precipitated withdrawal, as specifically defined by a decrease in the ECS threshold, was observed for flumazenil challenge in mice repeatedly dosed (2x daily for three days) with diazepam (Schedule IV benzodiazepine) but not with mice treated repeatedly with stiripentol.

3. Clinical Pharmacology

3. 1 Absorption, Distribution, Metabolism, Elimination (ADME)

The pharmacokinetics of stiripentol has been examined in mice, rats (Pieri et al 1982), monkeys (Lin and Levy, 1983), and human volunteers (Levy et al., 1983; Levy et al., 1984; Moreland et al., 1986; Peigne et al., 2014; Proposed Label for DIACOMIT).

In rats stiripentol is absorbed from the GI tract. It undergoes an extensive first past metabolism to a series of metabolites. Following IV injection of tritiated-stiripentol, radioactivity is found in various organs as well as in the cerebellum and medulla indicating good peripheral distribution as well as entry into the CNS. Maximum plasma concentrations are achieved at around 2 hours.

In the Rhesus monkey the PK of a 40 mg dose of stiripentol was evaluated following oral, IV , and i.p. injection. While stiripentol could be absorbed across the GI tract following oral administration, the bioavailability was only about 21% due to the large first pass effect in the liver. Likewise, again due to the large hepatic metabolic effect, the bioavailability of intraperitoneal injection was only 25% to 28%. At higher i.p. doses of 80 mg and 120 mg bioavailability due to first pass effect was 32% and 34%, respectively. Stiripentol undergoes extensive biotransformation. Stiripentol that is not metabolized e is glucuronidated. The volume of distribution suggests that stiripentol is well distributed including into the extravascular space with protein binding. The slow egress of stiripentol back into the circulation allows for a longer terminal distribution phase.

The overall findings from studies conducted in healthy adult volunteers on the PK of stiripentol are (b) (4) These findings are listed below.

- Stiripentol is orally absorbed with a median time to peak plasma concentration of 2 to 3 hours. The absolute bioavailability in humans has not been determined.

- Stiripentol binds extensively to circulating plasma proteins (about 99%).
- Systemic exposure to stiripentol increases in a way that is more than dose proportional. Initial studies in healthy subjects receiving doses of 500 mg, 1,000 mg, and 2,000 mg, showed that plasma AUC increases more than proportionately with dose. The half-life of elimination ranges from 4.5 hours to 13 hours, increasing with dose.
- On the basis of in vitro studies, the main liver cytochrome P450 isoenzymes involved in metabolism are considered to be CYP1A2, CYP2C19, and CYP3A4.

3.2 Drug/Product Interactions

A number of studies have examined the interaction of stiripentol with other drugs (Levy et al., 1984; Tran et al., 1997; Cazali et al., 2003; Giraud et al., 2006; Patsalos, 2013; Yamamoto et al., 2014; Jullien et al., 2015).

Stiripentol Effects of Pharmacokinetic of other Drugs.

In studies using human liver microsomal preparations stiripentol inhibited the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4 (Tran et al., 1997). These coenzymes are involved in the metabolism of a number of anticonvulsant drugs (See Review by Patsalos 2013) potentially used in combination with stiripentol.

Clinically, stiripentol may be administered with either carbamazepine or phenytoin. Stiripentol slows down the metabolism of carbamazepine and phenytoin by inhibiting CYP3A4 and CYP2C9/CYP2C19, respectively. The result is a reduction in clearance with a concomitant increase in drug exposure (Patsalos, 2013).

Of importance to the treatment of Dravet's syndrome is the coadministration of stiripentol with clobazam (Schedule IV benzodiazepine) as well as with other anticonvulsants (i.e., phenytoin). The inhibition of CYP3A4 and CYP2C19 by stiripentol reduced the clearance of clobazam (Schedule IV benzodiazepine and its active metabolite norclobazam resulting is plasma levels 2 to 3 times that found in the absence of stiripentol administration Cazali et al., 2003; Giraud et al., 2006; Patsalos 2013; Yamamoto et al., 2014; Jullien et al., 2015).

Due to an inhibitory effect on CYP2CP and CYP2C19, stiripentol in epileptic patients reduces the clearance of phenobarbital (Schedule IV barbiturate) and thereby increases plasma levels of phenobarbital (Levy, 1984; Patsalos, 2013).

Effects of Other Drugs on the Pharmacokinetics of Stiripentol

Co-administration of stiripentol with carbamazepine, phenytoin, phenobarbital, or primidone results in an increased clearance of stiripentol accompanied by a substantial reduction in stiripentol plasma concentrations. This reduction in stiripentol concentration may result from an induction of CYP3A4 and CYP2C19 enzyme activity by the co-administered drugs.

The cytochrome P450 isoenzymes involved in the metabolism of clobazam are also involved in the metabolism of stiripentol. With the co-administration of clobazam, the clearance of stiripentol is reduced resulting in an increase in stiripentol plasma concentration by as much as 25%. (May et. al., 2012)

3.3 Special Considerations

It is important to note that stiripentol is used medically only in combination with other anticonvulsant drugs to treat Dravet syndrome and other epilepsies. It is not used alone. The relative importance of different mechanism(s) for the supra additive anticonvulsant effects observed by these combinations is not clearly known. One mechanism may relate to stiripentol acting as a positive modulator at a unique pentameric GABA receptor site that is synergistic to that of the site produced by another anticonvulsant such as a benzodiazepine (i.e., Clobazam). A second mechanism would be stiripentol-induced inhibition of cytochrome P450 coenzymes involved in the metabolism of concomitant anticonvulsants such as clobazam thereby leading to elevated blood levels of these drugs and possible active metabolites (i.e. norclobazam). The relative contribution of each to the supratherapeutic effects of drug combinations commonly used is not known.

As will be noted below, considering that stiripentol is not used alone but in combination with other anticonvulsants including benzodiazepines (i.e., Clobazam) and that stiripentol can have significant drug PK interactions with these additional anticonvulsants, it is problematic attempting to interpret AEs, from an abuse potential perspective, as pertaining to stiripentol.

4. Clinical Studies

4.1 Human Abuse Potential Studies

The Sponsor was not required to conduct a human abuse potential study. The results of pre-clinical studies did not indicate a need for a human abuse potential study. In addition, no signals of abuse potential were found during the clinical development program for stiripentol.

4.2 Adverse Event Profile Through all Phases of Development

In support of the clinical development program of stiripentol under NDA 206709, Sponsor submitted the following Phase 1 PK and tolerability studies conducted on healthy adult volunteers.

- Study Report RCLA098 – Greig - Pharmacokinetic Study Comparing Racemic Stiripentol and Stiripentol Isomers in Healthy Volunteers
- Stiuni Report – Study of Pharmacokinetics, Safety, Tolerability of Stiripentol (DIACOMIT) Following Single Oral Administration of 500 mg, 1,000 mg, 2,000 mg Stiripentol to Male Healthy Volunteers.
    - This study was documented in the medical literature (Peigne et al., 2014. Epilepsy Research, 108: 909-916

- Pons Report – A Study of the Influence of Stiripentol on the Activity of Cytochromes P-450, 1A2, 2D6, and 3A in Healthy Volunteers.
- STP611 – STIVAL Report – Bioavailability Study of Stiripentol After Single Oral Administration of Two 500 mg Stiripentol Formulations (Capsule and (b) (4) in 24 Health Male Volunteers.

Table 2. Adverse Events Documented in Phase 1 Pharmacokinetic Studies Conducted with Health Adult Male Volunteers. (Data were obtained from the Integrated Summary of Safety Document under NDA 206709)

Study Designation	Design	Adverse Events
Study Report RCLA098 – Greig	• Phase I, randomized, crossover trial in 6 healthy males aged 18 to 40 years old • Single oral dose of each of 4 different STP racemic and isomeric preparations (1,200 mg of each isomer; 1,200 mg and 2,400 mg of racemic STP).	One subject each reported gastralgia and headache.
Pons Report	• Open-label, 14-day repeated dose Phase I trial in 13 healthy males to study the effect of an oral administration of STP for 14 days on the activities of CYP1A2, CYP2D6, and CYP3A, evaluated by test compounds using non-invasive methods. • STP was orally administered in two daily doses during meals, in the morning and the in evening. • The STP dosage was 1,000 mg (500 mg twice a day) on Day1, 2,000 mg (1,000 mg twice a day) on Day2, 3,000 mg (1,500 mg twice a day) from Day 3 to Day 13, and 1,500 mg in the morning on Day 14	• Five subjects (Nos. (b) (6) and (b) (6)) had minor neuropsychiatric disorders: asthenia (1 subject), insomnia (2 subject), nervousness (1 subject), and irritability (1 subject). These AEs occurred between Day 4 and Day 5 on average and persisted for four to five days. Additional AEs included gastric burning, nausea, abdominal pain, and neutropenia (one each). • One subject withdrawn prematurely. This Subject No (b) (6) experienced a gastrointestinal disorder (nausea), irritability and insomnia starting on Day 1 of treatment and STP was discontinued on Day 2 after the evening dose.
Stiuni Report	• Phase I, randomized, crossover trial in 12 healthy males 18 to 40 years of age. • Purpose study the pharmacokinetics, safety and tolerability of single oral doses of STP (500; 1,000; or 2,000 mg).	One subject (No (b) (6)) experienced 2 AEs (rhinitis and pharyngitis); these AEs were moderate in severity and were considered unlikely related to STP.
STIVAL Study	• Phase I, randomized, crossover trial in 24 healthy males 18 to 45-years old • Compared the relative bioavailability of the 2 formulations of STP ((b) (4) and capsule) after a single oral dose (2 x 500 mg).	4 subjects (Nos. (b) (6)) experienced 5 AEs. One subject (No (b) (6)) reported AEs of hot flush in both treatment periods (i.e., after a single 1,000 mg dose administered either as a capsule or as a (b) (4)

As can be seen from Table 2, none of the AEs reported in the four studies are indicative of abuse potential for stiripentol.

Within the scientific and medical literature, several studies have examined the PK of stiripentol in healthy adult human volunteers (Levy et al., 1983; Levy et al., 1984; Moreland et al., 1986). The studies

cited do not overlap with the PK studies in healthy adult human volunteers noted in the NDA submission. The literature articles cited only a small number of AEs, none of which were indicative of abuse potential.

Efficacy Studies Involving Dravet Syndrome Patients – Evaluation of Reported Adverse Events.

In the Integrated Summary of Safety document provided under the initial submission for NDA 206709, the Sponsor provided a detailed examination of the AEs documented in eight studies examining the efficacy of stiripentol in patients with Dravet syndrome or, in some cases, other intractable forms of epilepsies. It should be noted that AEs indicative of abuse potential were not seen in these studies. These studies are listed below.

1. STEV Study — Non-Pivotal Single-Blind and Open-Label Study – 2 Centers in France
2. STICLO France — Pivotal Double-Blind, Controlled Study – 14 Centers in France
3. STICLO Italy — Pivotal Double-Blind, Controlled Study – 6 Centers in Italy
4. STP-1 — Non-Pivotal Single-Blind and Open-Label Study – 11 Centers in Japan
5. STILON — Non-Pivotal, Open-Label, Long-Term Study – 39 Centers in France
6. TAU-EAP — Non-Pivotal, Open-Label, Long-Term Study – 77 Centers in France
7. DIAVEY — Non-Pivotal, Open-Label, Long-Term Study – 57 Centers in France
8. STIPOP — Population Pharmacokinetic Study in Children with Dravet Syndrome (Post-Approval Study) – 13 Centers in France

The following general comments apply to these studies.

- Stiripentol was administered orally either as capsules or from oral suspensions prepared from (b) (4)
- Stiripentol was an add-on medication, and NOT used alone. Stiripentol was added to an already existing dosage regimen involving other anticonvulsant drugs such as, frequently, clobazam and valproate, and less often carbamazepine, diazepam, or phenobarbital. As already noted, the addition of stiripentol had the potential to inhibit the clearance of some of these additional drugs thereby increasing blood levels of the parent or metabolite. The comparison was to a second group of patients on anticonvulsant drugs without stiripentol.
- The patients in these studies tended to be children ranging in age from 1 to 18 years old with Dravet syndrome or, less often, other severe intractable epilepsies. Several of the trials also included adults with Dravet syndrome (children who managed to reach adult age). Based upon what is known about Dravet syndrome, it is likely that many of these patients also had cognitive and motor development problems.

Tables 3 and **4** below document the AEs involving nervous system and psychiatric disorders specifically reported for subjects in the pivotal placebo controlled studies and the non-pivotal studies, respectively. As noted from these tables AEs indicative of a potential for abuse were rarely observed in these studies. No information was provided on the single cases of "psychotic disorder" or "mood altered" which may or may not be abuse potential related. AEs such as "insomnia" or "sedation" are not specific for abuse potential.

Table 3. Number of Subjects Experiencing Nervous System Disorders and Psychiatric Disorders as Observed in the Pivotal Placebo Controlled Studies - Pooled Data from STICLO France and STICLO Italy. (Data obtained from Table 2-27 on page 89 of the Integrated Summary of Safety Document.) (N = Number of Subjects)

Adverse Event Designation (Preferred Terms)	Pooled STICLO FRANCE and ITALY (Number of Subjects Experiencing Adverse Events)	
	Stiripentol (N = 33)	Placebo (N = 31 Total)
Nervous System Disorders		
Ataxia	9	7
Balance disorder	1	0
Convulsions	1	2
Dysarthria	4	0
Epilepsy	0	1
Hemiparesis	0	1
Hyperkinesia	0	1
Hypotonia	6	4
Mental Impairment	1	0
Motor disfunction	0	1
Myoclonic epilepsy	2	0
Somnolence	22	7
Status epilepticus	0	1
Tremor	6	3
Psychiatric Disorders		
Aggression	3	0
Agitation	9	5
Insomina	4	2

Table 4. Number of Subjects Experiencing Nervous System Disorders and Psychiatric Disorders as Observed in the Six Non-Pivotal Studies (Data obtained from Tablet 3-28 of the Integrated Summary of Safety Document) (N = Number of Subjects)

Adverse Events (Preferred Terms)	Non-Pivotal Studies					
	STEV (N=24)	STILON (N=45)	STIPOP (N=35)	STP-1 (N=30)	TAU-EAP (N=210)	DIAVEY (N=152)
Nervous System Disorders						
Altered States of Consciousness	0	1	0	0	0	0
Aphasia	0	1	0	0	0	0
Apraxia	0	0	0	0	2	0
Ataxia	5	1	0	14	2	8
Clumsiness	0	0	0	0	0	1
Convulsions	0	0	1	0	0	4
Coordination Abnormal	0	0	0	0	0	1

Attention Disturbance	0	0	0	1	0	0
Dizziness	0	0	0	0	0	1
Dysarthria	1	0	0	0	0	1
Dystonia	0	1	0	0	0	0
Epilepsy	0	13	0	1	5	2
Febrile Convulsions	0	0	0	0	0	2
Headache	0	0	0	1	0	0
Hyperkinesia	3	0	0	1	0	0
Hypotonia	4	2	0	2	3	5
Motor Dysfunction	0	0	0	0	1	0
Myoclonic Epilepsy	0	1	0	0	1	0
Myoclonus	0	2	0	0	0	0
Restlessness	0	0	0	0	0	1
Sedation	0	0	0	0	0	5
Sleep Phase Disturbance	0	0	0	1	0	0
Somnolence	8	1	0	21	11	14
Status Epilepticus	0	0	0	2	3	4
Tremor	1	0	0	7	0	1
Psychiatric Disorders						
Abnormal Behavior	0	2	0	0	0	2
Aggression	2	2	0	0	1	11
Agitation	1	1	0	2	6	0
Apathy	0	0	0	0	0	1
ADHD Disorder	0	0	0	1	0	0
Depression	1	0	0	0	0	0
Eating Disorder	0	0	0	0	0	2
Histrionic Personality	0	0	0	0	1	0
Initial Insomnia	0	0	0	2	1	1
Insomnia	6	0	0	1	3	3
Irritability	0	0	0	0	0	4
Logrrhea	0	0	0	1	0	0
Middle Insomnia	0	0	0	0	1	0
Mood Altered	0	0	0	0	0	1
Psychotic Disorder	0	0	0	0	0	1
Restlessness	0	0	0	1	0	1
Sleep Disorder	0	1	0	1	5	2

In the pivotal and non-pivotal studies, no documentation was provided on actual abuse or dependence either by the patients studied or possible care givers. Considering the age of the subjects and the severity associated with Dravet syndrome, it is unlikely that the patient population would abuse stiripentol or report AEs indicative of abuse potential.

4.3 Safety Profile

The data that have been reviewed under NDA 206709 collectively indicate that stiripentol does not have a potential for abuse. As such, from an abuse potential perspective, stiripentol does not appear to present safety issues. (b) (4) The

results of the AE assessments during the clinical development program as well as documented effects observed under the Biocodex Safety Database, demonstrate few AEs indicative of safety issues which can be associated with stiripentol treatment. At least some of the effects may be in part related to the metabolic interactions occurring when stiripentol is administered with anticonvulsant drugs subject to cytochrome P-450 metabolism.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There was no evidence of abuse, misuse, or diversion of stiripentol during the clinical trials.

4.5 Tolerance and Physical Dependence Studies in Humans

No studies were conducted in humans regarding tolerance and physical dependence.

5. Regulatory Issues and Assessment

Via letter dated March 5, 2018, the Sponsor submitted a revised combined label for DIACOMIT Capsules (NDA 206709) and DIACOMIT (b) (4) (NDA 207223) (DARRTS, SN 0042, eCTD 0043, March 5, 2018). This label does not contain a Section 9 ABUSE AND DEPENDENCE but does contain a Section 5.3 Withdrawal Symptoms.
This is acceptable considering that stiripentol does not, based on the available data, have an abuse potential and, as such, should not be recommended for scheduling under the CSA. Stiripentol thus becomes another example of a drug with CNS effects that do not appear to have reinforcing effects suggestive of abuse potential, but may produce some limited physical dependence with repeated dosing. Such drugs are not scheduled under the CSA.

The current proposed label contains a Section 5.3 Withdrawal Symptoms" with the following language:

> (b) (4)
> *As with* (b) (4) *AEDs, DIACOMIT should be withdrawn gradually to minimize the* (b) (4) *increased seizure frequency.*
>
> *In situations where rapid withdrawal of DIACOMIT is* (b) (4) *required, appropriate monitoring is recommended.*

This language seems reasonable with respect to stiripentol.

There is no indication of the need for REMS or post marketing commitments or requirements as related to abuse or dependence.

The Division of Neurology is not taking NDA 206709 to an Advisory Committee meeting.

6. Other Relevant Information

Search of the Scientific and Medical Literature

A detailed examination of the scientific and medical literature as presented in PubMed did not identify any studies, nonclinical or clinical, providing support for an abuse potential associated with stiripentol. No AEs suggestive of abuse potential were documented in the Phase 1 PK studies conducted using normal healthy adult volunteers as reported in submission for NDA 206709 or the medical literature (Levy et al., 1983; Levy et al., 1984; Moreland et al., 1986; Peigne et al., 2014).

Examination of Post-Marketing Reactions in the Biocodex Safety Database

On pages 24 and 25 of the Integrated Summary of Safety, the Sponsor provided a history for the approval of stiripentol in other countries. On January 4, 2007, the European Medicines Agency (EMA) granted marketing authorization with conditional authorization for stiripentol (trade name: DIACOMIT®) for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with Dravet syndrome whose seizures are not adequately controlled with clobazam and valproate. On January 8, 2014, the European Union Commission switched the 2007 conditional license of Diacomit® into a full marketing authorization after the Committee for Medicinal Products for Human Use (CHMP)/EMA final evaluation of the completion of the Marketing Authorization Holder (MAH) commitments. Stiripentol has also been approved in Canada (December 21, 2012), and Japan (September 28, 2012). In Europe, Canada, and Japan, stiripentol is approved as adjunctive therapy for the treatment of generalized tonic-clonic and tonic seizures in Dravet syndrome added on to valproate and clobazam when the seizures are not adequately controlled with these two treatments. The approved stiripentol product in these countries is recommended at a dose of 50 mg/kg/day.

Biocodex has kept a safety database which includes

- all spontaneous reports for stiripentol (including DIAVEY post-marketing study, cohort TUA-EAP, JAPAN PMS),
- all AEs from clinical studies started since 2007 and at least possibly related to stiripentol, serious AEs from clinical studies started before 2007 and at least possibly related to stiripentol.

On October 30, 2017, the Sponsor (Biocodex) conducted a search of its safety database using MedDRA Preferred Terms under a MedDRA Standardized Medical Query (SMQ) for "Drug abuse, dependence" and for "Drug Withdrawal." Both "broad scope" and "narrow scope" terms were looked for. A total of 56 terms were covered. Examples included but were not limited to: drug abuse, drug dependence, drug use disorder, drug use overdose, intentional overdose, neonatal complications of substance abuse, substance abuse, substance dependence, drug withdrawal, accidental overdose, dependence, drug detoxification, drug diversion, drug level increased, drug screen, intentional product use issue, overdose, prescription drug used without a prescription, substance-induced mood disorder, substance-induced psychotic disorder, drug rehabilitation, and withdrawal syndrome. Additional terms looked for included euphoria, perceptional, distortion, cognitive, hallucination, addiction, impaired control, compulsive, craving, and mood disorders.

The results of the search of the safety database conducted on October 30, 2017, were included in an "Eight Factor Analysis Document" provided my Biocodex regarding stiripentol. This document was submitted to NDA 206709 on December 22, 2017, along with the selected pre-clinical abuse potential related studies.

A search of the safety database revealed the following reports:

- Three cases of "accidental overdose" occurred in two 1-year old children and one 19-month old child.
- One case of "drug level increased" involving sodium valproate following stiripentol treatment.
- One "prescribed overdose" was of stiripentol upon admission of a child to the hospital
- One case of "cognitive disorder" in which a child reported experienced "cognitive slowing."
- One case of "flat affect" in which an 11-year old patient presented with "flat emotions and younger behavior" 9 months after start of stiripentol.
- One case of "impulsive behavior" in a child who displayed "highly excitable, impulsive, and uncontrollable behavior" after start of stiripentol treatment.
- One case of "mood instability" with drowsiness from a 7-year old while treated with stiripentol, valproate, topiramate and rufinamide for Dravet syndrome.
- One case of a 23-year old female Dravet patient displaying "emotional instability and diarrhea following treatment with 500 mg per day stiripentol.
- One case of a 29-year old Japanese patient experiencing "emotional instability, hyperkinesia, and impaired appetite following an increase in dose of stiripentol.
- One case of a 20-year old Japanese female Dravet patient displaying "dyskinesia, affect lability, somnolence and salivary hypersecretion following treatment with stiripentol powder.
- Six cases of "Mood altered (Bad mood) in Japanese patients (2, 3, 18, 20, 36, and 36 years old) following treatment with 250 mg per day stiripentol (capsule or (b) (4)). Somnolence was documented in most of these cases.

The cases cited above do not support an abuse potential for stiripentol. The results of an examination of the Biocodex Safety Database do not support that stiripentol has an abuse potential.

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/s/

JAMES M TOLLIVER
05/21/2018

SILVIA N CALDERON
05/21/2018

MARTIN S RUSINOWITZ
05/21/2018

DOMINIC CHIAPPERINO
05/21/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 28, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 206709
Product Name and Strength:	Diacomit (stiripentol) capsules 250 mg and 500 mg
Applicant/Sponsor Name:	Biocodex
FDA Received Date:	March 27, 2018
OSE RCM #:	2015-2550-3
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products requested that we review the revised carton labeling and container labels for Diacomit (stiripentol) capsules (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling and container labels for Diacomit (stiripentol) capsules are acceptable from a medication error perspective. We have no further recommendations at this time.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Rider B. Label and Labeling Review for Diacomit (NDA 206709). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 02. RCM No.: 2015-2550-2.

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/s/

BRIANA B RIDER
03/28/2018

LOLITA G WHITE
03/29/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 13, 2017

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: LaShawn Dianat, RPM
DNP

Subject: QT-IRT Consult to NDA 206709

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 06/27/2017 regarding the sponsor's request for TQT waiver. The QT-IRT reviewed the following materials:

- Sponsor's clinical study report and an ECG report submitted to Sequence 0020;
- Sponsor's cover letter describing the ECG acquisition and analysis in Study STP-1; and
- Highlights of clinical pharmacology and cardiac safety submitted to Sequence 0030.

The Division has asked for the IRT's input on whether the sponsor's analysis of data from Phase 3 Study STP-1 is sufficient as an assessment of QT prolongation risk or whether a formal QT study would be required.

1. QT-IRT Response to the Division

We recommend that the sponsor conducts a TQT study as per the ICH E14 guidelines. The sponsor should submit the protocol for our review and comments. Our recommendation is based on the following:

- The clinical study STP-1, in which ECGs were collected following oral dosing of up to 50 mg/kg/day of stiripentol in patient population, cannot be used as a substitute for a TQT study. The study lacks a placebo control and the exposures may not cover the highest clinically relevant scenario of exposures with therapeutic dosing (e.g. when

stiripentol is given to patients with hepatic impairment; the drug is eliminated by hepatic metabolism and that impact of hepatic impairment on exposures has not been studied yet).

- Furthermore, in this study the post-treatment ECGs were collected only at C_{trough} at Week 16 and C_{trough} at Week 52. Thus, these ECGs are not adequate to quantify the effect of stiripentol on the QTc interval.

2. BACKGROUND

Product Information

Stiripentol (ME2080) is an antiepileptic drug which originated in Biocodex SA in France in 1978. Clinical studies commenced in Europe in the 1980s and reactions to it in severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome) among various convulsions and convulsive syndromes have been seen as highly favourable. This drug received orphan drug designation on 5th December 2001 in the EU based on a subsequent clinical investigation. In addition, it received Authorization for Temporary Use in France as an unlicensed drug limited to SMEI and was used from January 2003. This drug received approval with some conditions in January 2007 in the EU, and is presented as clinically effective under the name of DIACOMIT® in France and Germany in 'methods for the concomitant use of clobazam and valproic acid in patients with intractable generalized tonic-clonic seizures in whom sufficient effects of clobazam and valproic acid are not observed in SMEI.

Sponsor's position related to the question

The Sponsor believes that the ECG data in the "Report on the results of Electrocardiogram analysis" for Study STP-1 by (b) (4), is adequate to serve as an alternative to a "Thorough QT/QTc Study" as described in the "Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs."

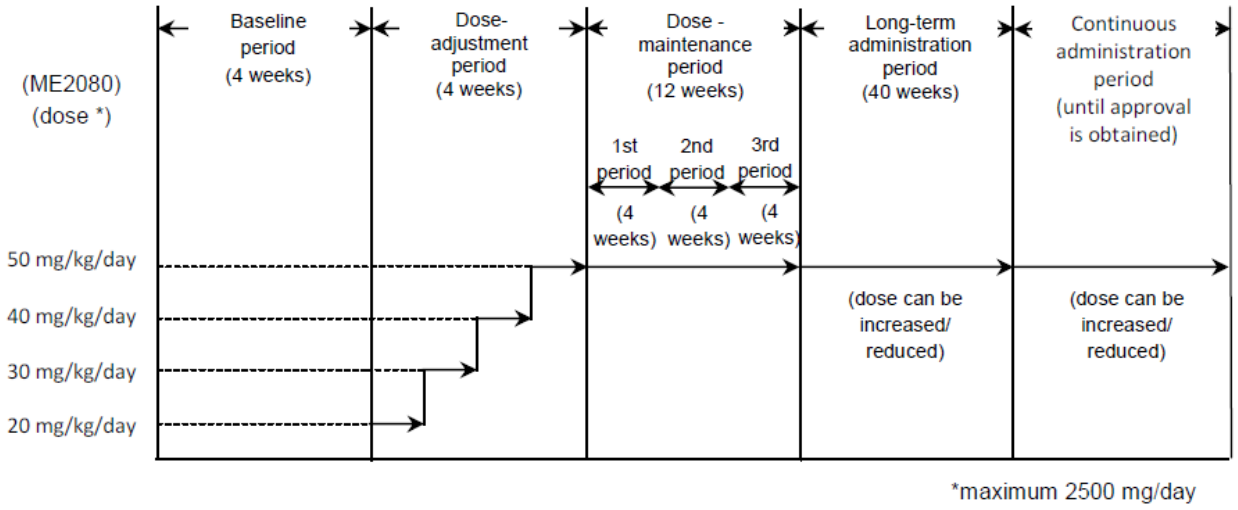
Summary of QTc assessments in Study STP-1

Design: Phase III trial in Japanese Dravet patients. This was an open-label study (not randomized trial). There was no concurrent placebo group or positive control group.
ECG methodology: Sponsor conducted an ECG central reading evaluation in addition to the site reading.

- 12-lead ECG data collected from sites were converted to digital.
- ECGs were measured on three consecutive beats by trained cardiologists using the QT analyze system ((b) (4)).
- The ECG interval duration measurements were performed in Lead II.
- This QT analyze system was developed and validated by (b) (4) to meet ICH E14 guidance requirement; (1) digital data, (2) central reading by trained cardiologists, (3) blind patient information in the system, (4) same reader reads all ECGs per patient, (5) provide the information of the morphological change of T-U wave, and (6) validated system accuracy and detectability of QT measurement.

Sample size: A total of 24 stiripentol (STP) (ME2080)-naïve Dravet syndrome patients (Groups 1 and 2) were enrolled in the STP-1 trial. ECGs were analyzed in patients 1 to 18 years of age

(Group 1; N=20) and in patients 19 to 30 years of age (Group 2; N=4). Patients were analyzed in 3 groups:
• Group 1 (N=20): STP-naïve patients, 1 to 18 years of age (mean ± SD = 5.7 ± 4.3 years, range: 1 – 18 years);
• Group 2 (N=4): STP-naïve patients, 19 to 30 years of age (mean ± SD = 22.8 ± 1.3 years, range: 21 – 24 years); and
• Group 3 (N=6): patients previously treated with STP, 1 to 30 years of age (mean ± SD = 15.0 ± 5.6 years, range: 10 – 24 years).
Treatment/Dosing: Shown in figure below.



ECG Time points:

Group	Cardiac report	Description
Group 1 and 2	Baseline	Baseline (prior to STP treatment) / Before ME2080 dosing on Day 1 of dose adjustment period
	At the end of 3rd Phase	End of Week 16 / At the end of dose maintenance period
	At the end of long-term administration period	At the end of long-term administration period
Group 3	At the end of 3rd Phase	At the entry of long-term administration period
	At the end of long-term administration period	At the end of long-term administration period

Results:

- No subject had an absolute value for either QTcF or QTcB that exceeded 450 ms.
- Four subjects had a 30 to 41 ms prolongation of QTcF and/or QTcB between baseline and end of Week 16, but no subject had a prolongation that exceeded 60 ms.
- Similar to the results obtained during the short-term administration portion of the trial (baseline to end of Week 16), there was no difference in mean QTcF and QTcB at end of trial.
- No subject had a prolongation of QTcF or QTcB >60 ms.
- No subject in any analysis group had an absolute value for QTcF and/or QTcB >450 ms, except for one subject ((b) (6) , 24 years old, Group 3). This subject had QTcB

values of 469 ms at baseline and 466.2 ms at the end of the long term administration period).

- Data collected in Dravet syndrome patients receiving STP in combination with various AEDs did not detect any impact of STP on QTc, both in short- and long-term treatment.
- In addition, there was no correlation between QTcF or QTcB and STP (ME2080) plasma concentration (Cmin).
- There was no adverse event related to QT prolongation in this study.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Table 1: Highlights of clinical pharmacology and cardiac safety

Therapeutic dose and exposure	The daily dosage of DIACOMIT is 50 mg/kg administered in 2 or 3 divided doses. Patients should be dosed according to body weight. Higher doses were not tested in the pivotal trials. The mean doses for STICLO France and STICLO Italy were 48.8 ± 2.8 mg/kg/day and 50.2 ± 4.7 mg/kg/day, respectively. In the pivotal trials, the mean Cmin at the end of the 8-week treatment period in STICLO France and STICLO Italy were 10.0 ± 3.6 mg/L (Min-Max: 6.0 to 18.8 mg/L) and 10.5 ± 2.67 mg/L (Min-Max: 5.7 to 14.0 mg/L).	
Maximum tolerated dose	Higher doses were not tested in the pivotal trials. The mean doses for STICLO France and STICLO Italy were 48.8 ± 2.8 mg/kg/day and 50.2 ± 4.7 mg/kg/day, respectively.	
Principal adverse events	**Somnolence and Drowsiness** Initiation of treatment with DIACOMIT (b) (4) (b) (4) is associated with somnolence/drowsiness in up to 67% of patients. Prescribers should monitor patients for somnolence and drowsiness, particularly when DIACOMIT is used concomitantly with other central nervous system (CNS) depressants, and should consider adjusting the dosage of concomitant clobazam or other AEDs. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of DIACOMIT added on to other AEDs is known. **Anorexia/Loss of Appetite and Weight Decreased** Treatment with DIACOMIT has been reported to be associated with loss of appetite in up to 46% of patients, and weight decreased in up to 28% of patients. Given the frequency of these AEs, the growth of children treated with DIACOMIT should be carefully monitored. In some cases, decreasing the dose of concomitant valproate by 30% per week can be helpful to minimize loss of appetite and weight decreased. See detailed information of most common adverse reactions in Appendix I.	
Maximum dose tested	Single Dose	2,000 mg in healthy volunteers {STIUNI}
	Multiple Dose	3,000 mg (1,500 mg twice a day) for 10 days in healthy volunteers {PONS} 121.9 mg/kg/day in Dravet syndrome patients (TAU-EAP trial) 75.5 mg/kg/day in Dravet syndrome patients (STP-1)

Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax 14.0 mg/L (35%) and AUC 86.0 mg.hr/L (31%) for 2000 mg {Table 1 of Peigne et al STIUNI}
	Multiple Dose	In STP-1, the mean (%CV) Cmax was 13.03 mg/L (37.5%). The mean (%CV) AUCo-t was 41.56 mgxhr/L (43.3%).
Range of linear PK	0-25mg/kg/day in half of patients and 0-40 mg/kg/day (or higher) in other half {based on Figure 2.7.2-5 reproduced from Figure 3 of May et al, 2012}	
Accumulation at steady state	Accumulation ratios (Rac) were calculated in the STIVAL study (PO50211/STP166) comparing single oral administration of 2x500 mg capsules and (b) (4), with multiple dosing with once a day (dosing interval = 24 hr), twice daily (dosing interval = 12 hr) and three times daily (dosing interval = 8 hrs). Rac values for these three regimens were 1.42, 2.20 and 3.01, respectively for capsules and 1.35, 2.03 and 2.75, respectively for (b) (4)	
Metabolites	DIACOMIT is extensively metabolized, 13 different metabolites having been found in urine. The main metabolic processes are oxidative cleavage of the methylenedioxy system and glucuronidation, although precise identification of the enzymes involved in each pathway has not yet been achieved. Active moieties in plasma are the two STP enantiomers: two metabolites tested in rats had no anticonvulsant activity and three metabolites resulting from cleavage of the methylenedioxy ring (p-OH, m-OH and di-OH) could not be detected in human plasma.	
Absorption	Absolute/Relative Bioavailability	The absolute bioavailability of DIACOMIT is not known since an intravenous formulation is not available for testing.
	Tmax	Tmax is reached about 1.5 hours.
Distribution	Vd/F or Vd	The population PK study (STIPOP) yielded values for apparent volume of distribution in 35 children (1 to 17.6 years) with Dravet syndrome (receiving VPA and CLB). As body weight increased from 10 to 60 kg, the apparent volume of distribution increased from 32.0 to 191.8 L.
	% bound	DIACOMIT binds extensively to circulating plasma proteins: percent bound = 98.9% {Report Cyprotex CYP1477R2}.
Elimination	Route	DIACOMIT metabolites are excreted mainly via the kidney. Urinary metabolites of DIACOMIT accounted collectively for the majority (73%) of an oral acute dose whereas a further 13-24% was recovered in feces as unchanged drug.
	Terminal t½	The half-life of elimination ranges from 4.5 hours to 13 hours, increasing with dose.

Elimination (con't)	CL/F or CL	In Dravet syndrome patients, clearance is decreased after repeated administration of DIACOMIT, probably due to inhibition of the cytochrome P450 isoenzymes responsible for its metabolism. The population PK study (STIPOP) yielded values for apparent oral clearance (CL/F) in 35 children (1 to 17.6 years) with Dravet syndrome (receiving VPA and CLB). As body weight increased from 10 to 60 kg, the apparent oral clearance increased from 2.60 to 5.65 Lhr.
Intrinsic Factors	Age	The effects of age on the pharmacokinetics of DIACOMIT have not been studied. Pediatrics: A population pharmacokinetic study was conducted in 35 children with Dravet syndrome (median age 7.3 years) treated with DIACOMIT, valproate and clobazam. The data were best fitted with a one compartment model with first order absorption and elimination processes. Clearance and volume of distribution were related to body weight. As a result, elimination half-life increased from 8.5 hr (for 10 kg) to 23.5 hr (for 60 kg). The population estimate for the absorption rate constant ka was 2.08 hrs^{-1} (standard deviation of random effect = 122%).
	Sex	The effects of gender on the pharmacokinetics of DIACOMIT have not been studied.
	Race	The effects of race on the pharmacokinetics of DIACOMIT have not been studied.
	Hepatic & Renal Impairment	There is no formal study of the pharmacokinetics and metabolism of DIACOMIT in patients with renal impairment. However, since DIACOMIT metabolites are eliminated mainly through the kidney. (b) (4) (b) (4) There has been no formal study of the pharmacokinetics of DIACOMIT in patients with liver impairment. However, since the drug is mainly metabolized by the liver. (b) (4) (b) (4)

Extrinsic Factors	Drug interactions	In vivo drug interaction studies examining the inhibitory effects of STP on the metabolism of antiepileptic drugs were performed, including drugs used in Dravet syndrome such as VPA and CLB. No dosage adjustment should be needed for co-administration of VPA. With clobazam, the increases in clobazam concentrations are much less than those involving norclobazam because this latter metabolite is metabolized principally by CYP2C19. Under clinical conditions, these increases are independent of STP concentration because therapeutic concentrations are higher than inhibition constants. Also, these STP effects are CYP2C19 genotype dependent since the norclobazam/clobazam ratio is genotype dependent, as shown in an Asian patient population. STP tends to transform intermediate metabolizers into poor metabolizers and to elevate NCLB concentrations in extensive metabolizers. But it has no effect on NCLB concentration in poor metabolizers. The overall net result is a reduction of interindividual variability in plasma concentrations of that metabolite in any population. The results of these in vivo studies are all consistent with predictions based on in vitro data. Those in vitro studies showed that inhibition constants are below therapeutic concentrations for five CYP enzymes (1A2, 2B6,2C8,2C19, 3A4) but not for CYP2C9 {Report 100029108 available for submission}. In vitro studies measuring mRNA level suggested that STP has a potential for induction toward CYP1A2 (2 of 3 livers), CYP2B6 (1of 3 livers), and CYP3A4 (1of 3 livers) {Report 100029108 available for submission}. Because therapeutic concentrations are above inhibition constants, in vivo interaction studies show that STP behaves as an inhibitor with no evidence of induction. In vitro studies evaluated the substrate and/or inhibitor potential of STP for P-glycoprotein (P-gp), BCRP, OATP1B1and OATP1B3, OAT1 and OAT3, and OCT2. STP is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. STP is not a significant inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. The inhibition constants for P-gp and BCRP were at the high end and low end of therapeutic concentrations, respectively (Report 16BCDXP1R2 available for submission}.

Extrinsic Factors (con't)	Drug interactions (con't)	There are limited in vitro data suggesting that STP is a substrate for several CYPs (CYP1A2, CYPC19, CYP3A4). Although in vivo studies that investigate inhibition of STP metabolism are not available, such interactions are not expected to be significant for two reasons: (i) because of the multiplicity of CYPs and metabolic pathways participating in STP metabolism, and (ii) the fact that STP inhibits CYPs involved in its own metabolism. Evidence suggests that STP metabolism is inducible by potent inducers such as phenytoin and phenobarbital which is consistent with the roles of glucuronidation and the three CYPs involved in its metabolism.
	Food Effects	The effect of food on the bioavailability of STP has not been studied.
Expected High Clinical Exposure Scenario	Most of Dravet syndrome patients (397 of 529) have been dosed less than 60 mg/kg/day. There are 127 Dravet syndrome patients who have been dosed 60 mg/kg/day or higher (supra-therapeutic dose) which includes 11 patients treated with >100 mg/kg/day. No PK parameter for these patients is available. No cardiac safety events such as QT prolongation, syncope, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flatter, or torsade de pointes were reported in these patients.	
Preclinical Cardiac Safety	The cardiovascular effects of STP were examined in a variety of tests in dogs, rats, rabbits, and guinea pigs as a safety pharmacology. See Appendix II	
Clinical Cardiac Safety	See Appendix III	

Appendix II: Preclinical Cardiac Safety

The cardiovascular effects of STP were examined in a variety of tests in dogs, rats, rabbits, and guinea pigs.

Effects of STP on Blood Pressure, Heart Rate, and Stroke Volume

STP (2.5 and 5 mg/kg iv) was tested for its effects on the cardiovascular system in groups of 2 mongrel dogs weighing 10-15 kg per dose [4.2.1.1; BC. 114/GB]. As shown in Table 3 below, slight decrease in blood pressure and heart rate were seen at both STP doses.

Table 3. Mean Change from Baseline Values of Cardiovascular Parameters in Dogs Administered STP 2.5 or 5.0 mg/kg iv

Parameter	Time after Injection								
STP Dose	30 sec	1 min	2 min	5 min	10 min	15 min	20 min	25 min	30 min
Aortic pressure									
STP 2.5 mg/kg iv	-11%	-11%	-7%	3%	2%	1%	1%	3%	2%
STP 5.0 mg/kg iv	-19%	-21%	-18%	-8%	-6%	-8%	-8%	-11%	-8%
Cardiac rate									
STP 2.5 mg/kg iv	-7%	-6%	-6%	-6%	-5%	-5%	-6%	-7%	-7%
STP 5.0 mg/kg iv	-3%	-4%	-6%	-6%	-8%	-7%	-7%	-8%	-5%
Stroke volume									
STP 2.5 mg/kg iv	2%	0%	3%	3%	0%	0%	1%	6%	2%
STP 5.0 mg/kg iv	5%	-3%	3%	0%	-3%	-7%	-7%	-5%	-3%

Source: [4.2.1.1; BC. 114/GB, Section 3-4-1]
STP=stiripentol; mg/kg=milligram per kilogram; iv=intravenous; sec=second; min=minute

Effects of STP on Capillary Permeability and Resistance

Effects on capillary permeability were determined as diffusion of Trypan Blue, injected ip, through the dermis of female albino rats weighing 150-170 g. STP given at a dose of 100 mg/kg ip to groups of 10 rats did not affect capillary permeability [4.2.1.1; BC. 114/GB].

Capillary resistance was tested in groups of 20 male Wistar rats weighing 200 g by inducing petechiae in the ear by applying different pressures for varying time periods. No effect of STP was seen at a dose of 200 mg/kg ip [4.2.1.1; BC. 114/GB].

Effects of STP on Vertebral Artery Blood Flow

The effects of STP on cerebral circulation were also studied. Groups of 3 dogs weighing 10-15 kg were each given STP at doses of 2.5, 5, or 10 mg/kg iv. A moderate (mean 24%) increase in vertebral artery flow, independent of dose, and a transient early (within 1 minute of drug administration) slight dose-dependent fall in blood pressure were also seen in this study [4.2.1.1; BC. 114/GB].

Appendix III: Clinical Cardiac Safety

Phase I Studies in Healthy Volunteers

ECGs were performed in the following 3 studies (STIUNI, STIVAL, and Greig); ECGs were not performed in the Pons trial. No clinically significant changes in ECG parameters were reported in the 3 Phase I studies. Some abnormal values were observed but were judged to be clinically not significant by Investigators.

Trial	Number of Subjects	Number of Doses	Dose Levels	Formulation
Greig [5.3.3.1; BC.287]	6	4 single doses	1,200 mg (+) enantiomer; 1,200 mg (-) enantiomer; 1,200 and 2,400 mg racemic STP	300 mg capsules
STIUNI [5.3.3.1; BC.337]	12	3 single doses	500, 1,000, 2,000 mg STP	500 mg capsules
STIVAL [5.3.1.2; BC.481]	24	2 single doses	1,000 mg STP (capsule); 1,000 mg STP ((b) (4))	500 mg capsules; ; containing 500 mg STP

*: one patient was prematurely withdrawn on Day 2 due to AE (nausea, insomnia, and irritability).

In the STIUNI trial, Subject No (b) (6) was found to have a heart rate ≤40 bpm prior to study drug intake on Day 1 of Period 2 (STP 2,000 mg) and Period 3 (STP 1,000 mg). This subject also had a QTc interval >440 ms (441 ms) on Day 1 of Period 2 (STP 2,000 mg) 2 hours after drug administration. Since all other QTc values for this individual were within normal ranges, the abnormal values were judged to not have clinical significance. Subject No. (b) (6) had a first degree atrioventricular block (PR >200 ms) on Day 1 of Period 3, prior to study drug administration. Subject No. (b) (6) had an incomplete right bundle branch block at screening with otherwise normal values.

In the STIVAL trial, all mean values for ECG parameters were within normal limits. Three subjects had minor abnormal values on one ECG recording only at some time during the study, but the abnormalities were judged to be clinically not significant (QRS >115 ms; short PR; left hemiblock anterior).

No ECG abnormalities were reported in the Greig trial.

No cardiac safety events per ICH E14 guidance such as QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths were reported in any of these 3 studies.

Clinical Trials in Dravet Syndrome Patients

Eight clinical trials were conducted in Dravet syndrome patients and are listed below.

Study (Year Started) Report Location	Treatment/ Number of Patients	Study Design/ Treatment Duration and Dose per Protocol	Safety Assessments
Pivotal Double-Blind, Controlled Studies			
STICLO France (1996) [5.3.5.1; BC.299]	STP: 22 [1)] Placebo: 20	Multicenter (14 centers in France), randomized, double-blind, 8-week treatment, STP *vs* placebo, parallel groups, add-on to optimized VPA and CLB treatment STP dose: 50 mg/kg/day	AEs, weight, measurements, physical examination, laboratory tests
STICLO Italy (1999) [5.3.5.1; BC.385]	STP: 12 Placebo: 11	Multicenter (6 centers in Italy), randomized, double-blind, 8-week treatment, STP *vs* placebo, parallel groups, add-on to optimized VPA and CLB treatment STP dose: 50 mg/kg/day	AEs, weight, measurements, physical examination, laboratory tests
Non-Pivotal Single-Blind and Open-Label Studies			
STEV[#,§] (1992) [5.3.5.1; BC.288]	STP: 25 [2)]	Multicenter (2 centers in France), single-blind, add-on. Single-blind, 28-day, placebo run-in followed by STP treatment for 84 days. STP dose: Day 1-28: 60 mg/kg/day Day 29-84: up to 90 mg/kg/day	AEs, neurological & physical evaluations, vital signs (blood pressure, pulse, weight and height), mental status, behavioral symptoms, laboratory tests
STP-1* (2010) [5.3.5.2; BC.609]	STP: 33 [3)]	Multicenter (11 centers in Japan), open-label, add-on to other AEDs Short-term (16 weeks) and long term (>52 weeks) up to drug approval in Japan STP dose: up to 50 mg/kg/day (with dose titration during the 1st 4 weeks)	AEs, vital signs (blood pressure, pulse, temperature, weight), laboratory tests, ECG and EEG, physical examinations
Non-Pivotal Open-Label, Long-Term Studies			
STILON[#] (1999) [5.3.5.2; BC.387]	STP: 45	Multicenter (39 centers in France), open-label, add-on to other AEDs (for most Dravet syndrome patients concomitant AEDs consisted of VPA and CLB) Up to several years Mean STP dose: 43.3±16.0 mg/kg/day	AEs, vital signs (blood pressure, heart rate, weight and height), laboratory tests, neurological evaluations, mental and behavioral evaluations, physical examinations
TAU-EAP (2003) [5.3.5.2; BC.458]	STP: 272 [4)]	Multicenter (77 sites in France), open-label, add-on to other AEDs Up to drug approval in the EU Mean STP dose: 55.2±24.7 mg/kg/day	AEs, height and weight measurements, laboratory tests, EEG, neurological examination

Study (Year Started) Report Location	Treatment/ Number of Patients	Study Design/ Treatment Duration and Dose per Protocol	Safety Assessments
DIAVEY# (2007) [5.3.5.2; BC.627]	STP: 153 5)	Multicenter (57 centers in Europe), open-label, long-term, add-on to other AEDs (Post EMA conditional approval study) STP dose: 50 mg/kg/day (per the SmPC)	AEs, height and weight measurements, laboratory tests, clinical examination, mental and behavioral evaluations
Population Pharmacokinetic Study in Children with Dravet Syndrome (Post-Approval Study)			
STIPOP (2008) [5.3.3.5; STP167]	STP: 35	Multicenter (13 centers in France), population pharmacokinetic study STP dose: 50 mg/kg/day	AEs, height and weight measurements

STP=stiripentol; VPA=valproate; CLB=clobazam
Note that the number of patients in the table does not refer to unique patients. Some patients were treated in several studies (for example, a patient could have been treated in STICLO France, STILON, and TAU-EAP).
*: (b) (4) in partnership with Biocodex conducted the STP-1 clinical trial in Japan.
#: These 3 clinical trials (STEV, STILON, and DIAVEY) enrolled both Dravet and non-Dravet syndrome patients
§: Some STEV patients (but not all) are included in publication by Perez, et al., (1999)

1) One patient in STICLO France who received at least 1 dose of STP was considered non-evaluable because of non-compliance with treatment and non-completion of the patient diary. This patient was totally excluded from efficacy and safety analyses because of missing data.
2) One patient enrolled in STEV completed only the baseline visit and was not included in the treatment period of trial.
3) Three patients were withdrawn before dosing.
4) Sixty-two patients completed only the baseline visit and did not receive study drug.
5) One patient completed only the baseline visit.

ECGs were performed in only one trial (STP-1). In this trial, ECGs were performed at prior to STP treatment, at the end of Week 16 (the end of maintenance period), and at the end of long-term administration period. ECG report of this trial was filed separately in this NDA.

No cardiac safety events per ICH E14 guidance such as QT prolongation, syncope, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths were reported in two pivotal trials.

In non-pivotal trials, no QT prolongation, syncope, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes were reported. There were 11 deaths. The most common cause of death was Sudden Unexpected Death in Epilepsy (SUDEP; n=7); in addition 1 patient (enrolled in the TAU-EAP) died during a seizure, 1 patient (enrolled in DIAVEY) died due to recurrent chest infection 9 months after discontinuing study drug because of lack of efficacy and for two patients (enrolled in DIAVEY) cause of death was unknown. None of the deaths were judged to be related to STP. It should be noted that SUDEP is a frequent cause of death in Dravet syndrome patients.

Concerning the adverse event of seizures, the Sponsor believes that reports of seizures reflect lack of efficacy, since the clinical trials were conducted in patients with Dravet syndrome, a catastrophic epileptic syndrome, and since the primary efficacy endpoint was decrease in the number of seizures.

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/s/

DHANANJAY D MARATHE
10/13/2017

CHRISTINE E GARNETT
10/22/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 4, 2017
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 207223
Product Name and Strength:	Diacomit (stiripentol) powder for oral suspension 250 mg and 500 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Biocodex
Submission Date:	September 5, 2017
OSE RCM #:	2017-1862
DMEPA Primary Reviewer:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

As part of the approval process for Diacomit (stiripentol) powder for oral suspension NDA 207223, the Division of Neurology Products (DNP) requests that we review the proposed Prescriber Information (PI), container label, and carton labeling for areas of vulnerability that could lead to medication error.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	n/a
ISMP Newsletters	n/a
FDA Adverse Event Reporting System (FAERS)*	n/a
Other	n/a
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information (PI) labeling, container label, and carton labeling identified the following areas of needed improvement that may contribute to medication errors:

Highlights and Full Prescribing Information

1. The Dosage and Administration section of the Highlights of Prescribing Information and Section 2.1 Dosing Information of the full PI uses a total daily dose expression of (b) (4) (b) (4). We are concerned that the dose expression is not clear and may be misinterpreted (b) (4) which may lead to error of improper dose leading to overdose.

Full Prescribing Information (FPI)

1. In Section 3 *Dosage Forms and Strength* and Section 16 *How Supplied/Storage and Handling*, the 250 mg strength is not consistently expressed with a corresponding unit of measure (i.e., mg).
2. The NDC numbers in Section 16 *How Supplied/Storage and Handling* of the FPI will need to be updated to align with the revised NDC numbers on the carton and container (see Section 4.2, recommendation A.2).
3. Section 2.3 *Important Administration Instructions* does not state in what volume of water to mix the product.
4. Section 2 *Dosage and Administration* does not indicate if and how to measure and administer doses that fall outside of 250 mg increments. For example, doses less than 250 mg, doses between 250 mg and 500 mg, etc.
5. The presentation of the finished dosage form (i.e., powder for oral suspension) is not consistent with USP requirements.

Carton Labeling and Container Label, 250 mg and 500 mg strengths

1. It is not immediately clear that the designated strength (i.e., 250 mg, 500 mg) is per unit (one packet).
2. The NDC numbers assigned to the container labels and carton labeling are not appropriate.
3. The intended expiration date format has not been submitted for evaluation.
4. The presentation of the finished dosage form (i.e., powder for oral suspension) is not consistent with USP requirements.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the labels and labeling where additional important information should be added or information should be revised in order to help ensure the safe use of the product. We provide recommendations below in Sections 4.1 and 4.2 to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights and Full Prescribing Information- Section 2 *Dosage and Administration*

1. The dosing instructions are expressed as (b) (4) (b) (4) which lacks clarity and may lead to overdose. Postmarketing evidence suggests that ambiguous course dosing leads to errors[1] and we are concerned that the dose expression may be misinterpreted as (b) (4) (b) (4) which may lead to error of improper dose leading to overdose. The dosing instructions should be clarified and revised to state: "The

[1] Institute for Safe Medication Practices. Safety briefs: Ambiguous course dosing leads to errors. ISMP Med Saf Alert Acute Care. 2014; 19(25): 2-3.

total daily dosage of DIACOMIT should be divided into 2 or 3 doses. If possible, consider adding a table similar to:

Dose (mg/kg)	**Dosing Interval**
16.67 mg/kg	Every 8 hours
25 mg/kg	Every 12 hours

B. Full Prescribing Information

1. In Section 3 *Dosage Forms and Strengths* and in Section 16 *How Supplied/Storage and Handling*, the 250 mg strength is not expressed with a corresponding unit of measure (i.e., mg). We recommend that throughout the PI, each strength have a corresponding unit of measure 'mg' after the numeric value (i.e., revise "250 or 500 mg" to read "250 mg or 500 mg").
2. In Section 16 *How Supplied/Storage and Handling,* if applicable, revise the NDC numbers to ensure consistency with the below carton labeling and container label recommendations. See Section 4.2, recommendation A.2.
3. As presented, the presentation of the finished dosage form (i.e., powder for oral suspension) is not consistent with USP requirements. The dosage form should be revised to state "for oral suspension" throughout the PI labeling.
4. Section 2.3 *Important Administration Instructions* states *"*DIACOMIT should be mixed in a glass of water and should be taken immediately after mixing during a meal". However this section does not instruct what volume of water to use. We are concerned that users may not use the necessary volume of water required to form the suspension.
5. Section 2 *Dosage and Administration* of the FPI does not indicate if and how doses that fall outside of 250 mg increments should be measured or administered. We recommend either:
    a) Clarifying that doses should be rounded to the nearest 250 mg increments, if appropriate. Or,
    b) Clarifying how to prepare and administer doses that fall outside of 250 mg increments. For example, mix the entire contents of the 250 mg packet with X mL of water. Administer X mL to achieve a 125 mg dose; discard remaining.

4.2 RECOMMENDATIONS FOR BIOCODEX

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling and Container Label, 250 mg and 500 mg strengths

1. It is not immediately clear that the designated strength (i.e., 250 mg, 500 mg) is per unit (one packet). Revise the strength statement "X mg" to state "X mg per packet" to make it clear that the designated strength is per unit. [2]
2. As currently presented, the last 2 digits (package size identifier) of the NDC number are the same (that is, 6) for both the carton and packets of the individual strengths. Since each carton contains 60 units and each packet is a single unit, we recommend you differentiate the package sizes by using different last 2 digits of the NDC number for the two package configurations (for example, 06 for the carton and 01 for the packet).
3. We note that the carton labeling and container labels do not indicate the proposed expiration date format. Please provide the intended expiration date format for evaluation. We recommend an expiration date format of MMMDDYYYY or MMMYYYY.
4. The presentation of the finished dosage form (i.e., powder for oral suspension) is not consistent with USP requirements. The dosage form should be revised to state "for oral suspension" on all panels of the carton label and container labeling.

[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Diacomit (stiripentol) that Biocodex submitted on September 5, 2017.

Table 2. Relevant Product Information for Diacomit	
Initial Approval Date	N/A
Active Ingredient	Stiripentol
Indication	(b) (4) treatment of (b) (4) seizures associated with Dravet syndrome.
Route of Administration	Oral
Dosage Form	Powder for oral suspension
Strength	250 mg and 500 mg
Dose and Frequency	50 mg/kg/day administered in 2 or 3 divided doses.
How Supplied	Cartons of 60 packets
Storage	Store (b) (4) in a dry place. Store in original package to protect from light.
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 2, 2017, we searched the L:drive and AIMS using the terms, stiripentol to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous label and labeling reviews[3,4,5] for Diacomit (stiripentol) capsules, NDA 022416.

[3] Rider, B. Label and Labeling Review for Diacomit NDA 022416. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 04. RCM No.: 2015-2550.

[4] Rider, B. Label and Labeling Review Memorandum for Diacomit NDA 022416. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 06. RCM No.: 2015-2550-1.

[5] Rider, B. Label and Labeling Review Memorandum for Diacomit NDA 022416. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 02. RCM No.: 2015-2550-2.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[6] along with postmarket medication error data, we reviewed the following Diacomit (stiripentol) labels and labeling submitted by Biocodex on September 5, 2017.

- Container label
- Carton labeling
- Prescribing Information-no image

G.2 Label and Labeling Images

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[6] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

BRIANA B RIDER
10/04/2017

LOLITA G WHITE
10/04/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 2, 2017
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 206709
Product Name and Strength:	Diacomit (stiripentol) capsules 250 mg and 500 mg
Applicant/Sponsor Name:	Biocodex
Submission Date:	March 6, 2017
OSE RCM #:	2015-2550-2
DMEPA Primary Reviewer:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised carton labeling and container labels for Diacomit (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling and container labels for Diacomit are unacceptable from a medication error perspective. Our review of the revised carton labeling and container labels identified the following areas of needed improvement that may contribute to medication errors:

- The product barcode is presented in a horizontal position which may hinder scannability due to container curvature.
- The intended expiration date format has not been submitted for evaluation.

[a] Rider B. Label and Labeling Review for Diacomit (NDA 206709). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 06. RCM No.: 2015-2550-1.

3 RECOMMENDATIONS FOR BIOCODEX

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels, 250 mg and 500 mg
    1. We note that the product barcode appears on panel 1B and is presented in a horizontal position. We are concerned that the barcode may not be able to be scanned due to container curvature. Consider reorienting the barcode to a vertical position to improve the scannability of the barcode. Please address this concern in a manner that does not hinder the readability of other critical information on the container labeling. For example, consider relocating the product barcode to panel 1A and reorienting to a vertical position to improve the utility of the barcode.

B. Carton Labeling and Container Labels, 250 mg and 500 mg
    1. We note that the carton labeling and container labels do not indicate the proposed expiration date format. Please provide the intended expiration date format for evaluation. We recommend an expiration date format of MMMDDYYYY or MMMYYYY.

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/s/

BRIANA B RIDER
10/02/2017

LOLITA G WHITE
10/02/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 6, 2017
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 206709
Product Name and Strength:	Diacomit (stiripentol) capsules 250 mg and 500 mg
Applicant/Sponsor Name:	Biocodex
Submission Date:	March 6, 2017
OSE RCM #:	2015-2550-1
DMEPA Primary Reviewer:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised carton labeling and container labels for Diacomit (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling and container labels are unacceptable from a medication error perspective. Our review of the revised carton labeling and container labels identified the following areas of needed improvement that may contribute to medication errors:

- The established name is not presented in accordance with 21 CFR 201.10(g)(1).
- Currently, the middle digits of the NDC product codes are sequential (i.e., 7939 and 7940) which is not an effective differentiating feature.

[a] Rider B. Label and Labeling Review for Diacomit (NDA 206709). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 04. RCM No.: 2015-2550.

- The presence of the dosage form (i.e., capsules) displayed in the middle right of the PDP, (b) (4) is extraneous and may hinder the readability of other critical information.
- The "peel-back booklet" container label lacks adequate and prominent instructions to inform the user to peel back the label to view important product information (e.g. barcode, warnings, storage instructions). We are concerned that important product information may be overlooked.

3 RECOMMENDATIONS FOR BIOCODEX

We recommend the following be implemented prior to approval of this NDA:

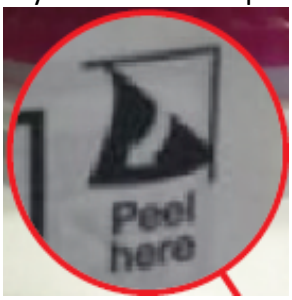
A. Carton Labeling and Container Labels, 250 mg and 500 mg
   1. As presented on the PDP, the presentation of the established name is not consistent with FDA regulations. The presentation of the established name should be revised on all panels of the carton and container labeling in accordance with 21 CFR 201.10(g)(1). For example, add parenthesis to surround the established name as such:

      Diacomit
      (stiripentol)
      Capsule
   2. The NDC number is presented with the use of sequential numbers for the middle digits. Assignment of sequential numbers for the middle digits of the NDC product code numbers (i.e., 7939 and 7940) is not an effective differentiating feature. Post-marketing experience indicates that similarity of the NDC product code numbers has led to selecting and dispensing of the wrong strength. The middle 3-4 digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Please revise the middle digits so they are not sequential. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: xxxx-**XXXX**-xx

B. Carton Labeling, 500 mg
   1. We note the presence of the dosage form (i.e., capsules) displayed in the middle right of the PDP, above the word (b) (4). (b) (4) (b) (4) (b) (4) should be removed to improve the readability of other critical information. (See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; April 2013)*.

C. Container Labels, 250 mg and 500 mg
   1. We note that the "peel-back booklet" container labels lack adequate and prominent instructions on how to peel back the labels. Furthermore, the symbol used to

instruct to peel back the label lacks prominence. We are concerned that critical safety information, such as the warnings, storage instructions, and barcode, may be overlooked. Instructions on how to peel back the label should be added to the container labels and the arrow symbol and instructions should be prominently displayed. See an acceptable example below:



2. We note your product's barcode is located (b) (4) The drug barcode is often used as an additional verification before drug administration and/or dispensing; therefore, it is an important safety feature. We are concerned that the barcode's location is not prominent and may contribute to product selection medication errors (b) (4) (b) (4) Consider relocating the barcode to the immediate container label (1A/1B) to improve the utility and prominence of the barcode.

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/s/

BRIANA B RIDER
07/06/2017

LOLITA G WHITE
07/07/2017

Clinical Inspection Summary

Date	12/29/2016
From	Cara Alfaro, Pharm.D., Clinical Analyst, OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	LaShawn Dianat, Pharm.D., Regulatory Project Manager DNP Steven Dinsmore M.D., Medical Officer DNP
NDA #	206709
Applicant	Biocodex
Drug	Stiripentol
NME	Yes
Therapeutic Classification	Antiepileptic
Proposed Indication(s)	(b) (4) treatment of (b) (4) seizures associated with Dravet syndrome
Consultation Request Date	6/9/2016
Summary Goal Date	12/31/2016 (extended to 1/13/2017)
Action Goal Date	2017
PDUFA Date	Not applicable

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For NDA 206709, four clinical investigator sites and the sponsor (Biocodex) were inspected. These inspections did not reveal significant regulatory violations. Form FDA 483s were issued to two clinical investigator sites (Chiron and Netter) for failure to obtain informed consent when antiepileptic medications were adjusted prior to enrollment in Protocol STICLO France. The clinical investigators responded that these medication adjustments were performed for clinical management and not in preparation for study enrollment. Based on results of the clinical investigator and sponsor inspections, it appears that the data submitted by the sponsor in support of the pending application are acceptable, and the studies appear to have been conducted adequately.

Establishment Inspection Reports (EIRs) have been received and reviewed for all inspections. All four clinical investigator inspections have been classified as No Action Indicated (NAI) and the sponsor inspection has also been classified NAI.

II. BACKGROUND

Stiripentol is being developed for the (b) (4) treatment of (b) (4) seizures associated with Dravet syndrome under NDA 206709. Two foreign clinical studies, one conducted in France (STICLO France) and one conducted in Italy (STICLO Italy) were submitted to support the efficacy and safety of stiripentol in Dravet's syndrome.

Protocol STICLO France
Title: Comparative study of the efficacy of stiripentol used in combination in severe myoclonic epilepsy in infancy
Subjects/Sites: 42 subjects enrolled in 14 sites in France
Study Initiation and Completion Dates: 10/25/1996 – 8/17/1998

STICLO France was a multicenter, randomized, double-blind, parallel group study of stiripentol compared to placebo as add-on treatment to clobazam and valproate sodium therapy. The study included two phases: a 1-month baseline phase followed by a 2-month comparison phase. Included were subjects 3 to 18 years of age, weight $\leq$ 60 kg, diagnosis of Dravet syndrome, experiencing at least four generalized clonic or tonic-clonic seizures per month despite currently receiving clobazam and valproate sodium.

The primary efficacy endpoint was the difference between the number of responders between the two treatment groups. Responder was defined as a $\geq$ 50% decrease in frequency of generalized tonic-clonic or clonic seizures. A preliminary analysis without breaking the blind was planned after enrollment of 40 subjects. Since this analysis showed a significant difference between the two groups on the primary endpoint, the study was stopped. The sponsor reported a higher responder rate in the stiripentol group compared to the placebo group (71.4% vs. 5.0%, $p < 0.0001$).

Protocol STICLO Italy
Title: Comparative study of the efficacy of stiripentol used in combination in severe myoclonic epilepsy in infancy: a double-blind, multicenter, placebo-controlled phase III study
Subjects/Sites: 23 subjects enrolled in 6 sites in Italy
Study Initiation and Completion Dates: 4/20/1999 – 10/20/2000

The study design of STICLO Italy was identical to STICLO France. The primary efficacy endpoint was the difference in the number of responders between the two treatment groups. The sponsor reported a higher responder rate in the stiripentol group compared to the placebo group (66.7% vs. 9.1%, $p < 0.0098$).

Inspections of clinical sites were considered essential to verify the data submitted for this application. Clinical sites for inspection were chosen primarily due to the relatively large contributions to the efficacy outcome. The focus of the clinical site inspections was adherence to protocols (e.g. inclusion/exclusion criteria), protocol deviations, documentation of informed consent prior to subject participation, reporting of adverse events, maintenance of the study blind, and verification of the primary and key secondary efficacy endpoints.

III. RESULTS:

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Site #01 Catherine Chiron, M.D., Ph.D. Inserm U1129 et Centre de Référence Epilepsies Rares Hôpital Necker-Enfants Malades Service de Neuropédiatrie 149, rue de Sèvres 75743 Paris Cedex 15 France	STICLO France Subjects: 15	9/5/2016 to 9/9/2016	NAI
Site #11 Jean-Claude Netter, M.D. Service de Pédiatrie-Néonatalogie CH Intercommunal de Tarbes-Vic en Bigorre Boulevard de Lattre de Tassigny 65013 Tarbes France	STICLO France Subjects: 4	9/12/2016 to 9/14/2016	NAI
Site #01 Anna Rita Ferrari, M.D. Instituto di Neuropsichiatria Infantile Università di Pisa – IRCCS Tella Maris Via dei Giacinti, 2 56018 Calambrone (Pisa) Italy	STICLO Italy Subjects:4	9/12/16 to 9/14/2016	NAI
Site #02 Francesca Darra, M.D. Cattedra di Neuropsichiatria Infantile Policlinico GB Rossi – Borgo Roma piazzale L.A. Scuro 10 37134 Verona Italy	STICLO Italy Subjects: 3	9/19/2016 to 9/21/2016	NAI
Biocodex 1 Avenue Blaise Pascal Beauvais France	STICLO France STICLO Italy	9/12/2016 to 9/16/2016	NAI

Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. **Clinical Investigator:** Catherine Chiron, M.D., Ph.D.; France; Site #01

Protocol STICLO France was not conducted under an IND.

For Protocol STICLO France, eighteen subjects were screened, sixteen subjects were enrolled, and twelve subjects completed the study. Of the four subjects who did not complete the study, three discontinued due to adverse events, and one discontinued due to non-compliance. Source documents describe the adverse events as "status" (Subject (b) (6)), drowsiness/right motor deficit (Subject (b) (6)), and "absences status" (Subject (b) (6)).

Records were reviewed for all eighteen subjects screened and included but were not limited to source documents, CRFs, inclusion/exclusion criteria, adverse event reports, lab reports, concomitant medications, Human Research Ethics Committee and sponsor correspondence, monitoring logs, training records, enrollment logs, test article accountability, protocol deviations, and primary efficacy data. Financial disclosure forms were not completed or available at inspection initiation but were completed by Dr. Chiron and Professor Dulac (sub-investigator) before the close of the inspection. No financial interests were reported. Monitoring visit letters between the sponsor and site were available for the site initiation visit and site closeout visit only.

A Form FDA 483 was issued with the observation that informed consent was not properly documented in that the written informed consent used in the study was not signed by the subject or the subject's legally authorized representative at the time of consent. Based on this finding, the field investigator recommended a Voluntary Action Indicated (VAI) classification.

For eight of the sixteen enrolled subjects, progress notes indicated that antiepileptic medications were adjusted in anticipation of enrollment into the STICLO study, but informed consent documents were not signed until 3 weeks to 6 months later. Dr. Chiron responded to the inspectional observations in a letter dated 9/29/2016. She stated that her clinical practice was to put her patients on a combination of valproate sodium and clobazam at the lowest doses possible to minimize adverse events and control seizures. As she was making these medication adjustments, she started to mention to parents that their child might be a candidate for the STICLO study. Signed informed consent/assent documents were available for all subjects, except Subject # (b) (6), by Visit 1 (start of baseline period, Week 0). Informed consent/assent documents for Subject # (b) (6) were signed on (b) (6) (per source document) while Visit 1 occurred on (b) (6) (per data listing).

OSI Reviewer Comment: Dr. Chiron has stated that the antiepileptic medication adjustments were based on clinical management and were not performed in preparation for subjects to enter into the STICLO study. There is no evidence to dispute Dr. Chiron's statements. Based on Dr. Chiron's response, we have downgraded the inspection to a No Action Indicated (NAI) classification.

It is unknown why the informed consent/assent document for Subject (b) (6) *was obtained two days after Visit 1. According to the schedule of events, study evaluations performed at Visit 1 included informed consent, clinical history, physical examination, verification of screening criteria, recording of seizures, adverse events, and weight. Randomization occurred at Visit 2 (Week 4). Though informed consent/assent appears to have been obtained a few days after Visit 1, no invasive evaluations were performed, and the subject did not receive investigational drug at that visit.*

Six of the sixteen subjects (Subjects (b) (6)) enrolled in the study had laboratory values outside the normal reference range for study inclusion. Per protocol, subjects must have normal laboratory results at study inclusion (CBC, platelets, plasma creatinine, AST and ALT < 3 times the upper limit of normal).

OSI Reviewer Comment: The protocol states that subjects must have normal laboratory results at study inclusion but, other than ALT/AST, does not further define normal laboratory parameters. These protocol deviations were reported to the sponsor and noted in the data listings. Data listings report these deviations as values "<- 2 SD for age". Four of these subjects had laboratory values outside the reference range for one analyte (erythrocytes or neutrophils), while the remaining two subjects had laboratory values outside the reference range for five analytes (erythrocytes, hematocrit, hemoglobin, neutrophils, leukocytes, and/or platelets. For any questionable laboratory values, the clinical investigator should have contacted the sponsor/medical monitor to verify subject eligibility. It is unlikely that inclusion of these subjects would impact efficacy or safety data for this application.

Other than the findings noted above, the study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

2. **Clinical Investigator:** Jean-Claude Netter, M.D.; France; Site #11

Protocol STICLO France was not conducted under an IND.

For Protocol STICLO France, four subjects were screened, four subjects were enrolled, and three subjects completed the study.

Records were reviewed for all four subjects screened and included, but were not limited to, source documents, CRFs, inclusion/exclusion criteria, adverse event reports, lab reports, concomitant medications, Human Research Ethics Committee and sponsor correspondence, monitoring logs, training records, enrollment logs, test article accountability, protocol deviations, and primary efficacy data. Financial disclosure forms were not completed or available at inspection initiation, but were signed by Dr. Netter before the close of the inspection. No financial interests were reported.

A Form FDA 483 was issued with the observation that informed consent was not properly documented in that the written informed consent used in the study was not signed by the subject or the subject's legally authorized representative at the time of consent. Dr. Netter

responded to the inspectional observations in a letter dated 9/29/2016. He stated that the antiepileptic medication adjustments were based on clinical management of the patients and not in preparation for enrollment into the STICLO study.

The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

3. **Clinical Investigator:** Anna Rita Ferrari, M.D.; Italy; Site #01

Protocol STICLO Italy was not conducted under an IND.

For Protocol STICLO Italy, four subjects were screened, four subjects were enrolled, and two subjects completed the study. Two subjects discontinued due to lack of efficacy and adverse events (sleepiness, hypersalivation).

Records were reviewed for all four subjects screened and included but were not limited to source documents, CRFs, inclusion/exclusion criteria, adverse event reports, lab reports, concomitant medications, Human Research Ethics Committee and sponsor correspondence, monitoring logs, training records, enrollment logs, test article accountability, protocol deviations, and primary efficacy data. The site did not have any financial disclosure information for the investigators. Dr. Ferrari stated that financial disclosure was not a requirement in Europe when this trial was conducted.

No significant regulatory violations were noted and no Form FDA 483 was issued. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

4. **Clinical Investigator:** Francesca Darra, M.D.; Italy; Site #02

Protocol STICLO Italy was not conducted under an IND.

For Protocol STICLO Italy, six subjects were screened, four subjects were enrolled, and four subjects completed the study.

Records were reviewed for all four subjects screened and included but were not limited to informed consent documents, source documents, CRFs, inclusion/exclusion criteria, adverse event reports, lab reports, concomitant medications, Human Research Ethics Committee and sponsor correspondence, enrollment logs, test article accountability, protocol deviations, and primary efficacy data. The site did not have any financial disclosure information for the investigators, but reported that there was no investigator compensation for this study.

No significant regulatory violations were noted and no Form FDA 483 was issued. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

5. **Sponsor:** Biocodex, 1 Avenue Blaise Pascal, Beauvais, France

This inspection covered sponsor practices related to Protocols STICLO France and STICLO Italy. Documentation reviewed during this inspection included contracts for services, monitoring logs, SOPs, Independent Ethics Committee correspondence, informed consent forms, adverse events, and investigational product accountability. For the two sites participating in STICLO France, the only available monitoring documents were for initial, pharmacy, and closing monitoring visits. The sponsor stated that they did not have any financial disclosure information for the investigators for the studies since they were conducted approximately 20 years ago. The sponsor stated that there was no compensation for the investigators in the studies.

No significant regulatory violations were noted and no Form FDA 483 was issued.

CC:

Central Document Room/NDA 206709
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/s/

CARA L ALFARO
12/29/2016

SUSAN D THOMPSON
01/05/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 4, 2017
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 206709
Product Name and Strength:	Diacomit (stiripentol) capsules 250 mg and 500 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Biocodex
Submission Date:	November 10, 2015
OSE RCM #:	2015-2550
DMEPA Primary Reviewer:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

As part of the approval process for Diacomit (stiripentol) capsules NDA 206709, the Division of Neurology Products (DNP) requests that we review the proposed Prescriber Information (PI), container label, and carton labeling for areas of vulnerability that could lead to medication error.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	n/a
Human Factors Study	n/a
ISMP Newsletters	n/a
FDA Adverse Event Reporting System (FAERS)*	n/a
Other	n/a
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information (PI) labeling, container label, and carton labeling identified the following areas of needed improvement that may contribute to medication errors:

Highlights and Full Prescribing Information- Section 2 *Dosage and Administration*

1. The Dosage and Administration section of the Highlights of Prescribing Information and Section 2.1 Dosing Information of the full PI uses a total daily dose expression of (b) (4) (b) (4). We are concerned that the dose expression is not clear and may be misinterpreted (b) (4) which may lead to error of improper dose leading to overdose.

Prescribing Information (PI):

1. Section 16 How Supplied/Storage and Handling of the full PI lacks the package configuration (e.g. bottle of 60) as well as appropriate information to facilitate product

identification (e.g., imprinting and NDC number) as required per 21 CFR 201.57. The lack of this identifying information may lead to wrong drug or wrong strength errors.

2. Section 16 How Supplied/Storage and Handling of the full PI and the Medication Guide do not clearly and consistently state handling and storage instructions (e.g. store at room temperature, store in original packaging and protect from light) throughout all of the labels and labeling. We are concerned that the lack of consistent cautionary statements may lead to the inappropriate storage and/or handling of the product and decrease product quality.

Carton Labeling and Container Label, 250 mg and 500 mg strengths

1. As presented on the principal display panel (PDP), the presentation of the finished dosage form (i.e., capsules) is not consistent with USP requirements.
2. The unit of measure (i.e., mg) in the strength expression lacks prominence due to the small font size. The small font size hinders the readability of the unit of measure which may cause misinterpretation of the strength.
3. We note the presence of the following statement "(b) (4) " In accordance with 21 CFR 208.24(d), the label should also state how the Medication Guide is provided (e.g., enclosed, accompanying).
4. (b) (4)
5. The NDC product code numbers are denoted by placeholders (XXXX-XXX-XX). Therefore, we are unable to evaluate whether the NDC product code numbers will adequately differentiate the 250 mg and 500 mg strength products.
6. The current storage statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that this information could be misinterpreted and should therefore be revised for clarity.

Container Label, 250 mg and 500 mg strengths

1. The net quantity statement appears in close proximity to the product strength on the container label. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
2. We note the absence of a barcode on the immediate container label. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible.

Carton Labeling, 250 mg and 500 mg strengths

1. The net quantity on the carton labeling [redacted] and we find the statement confusing in its current presentation [redacted].

We note that the carton labeling uses terminology [redacted] and that the container label use the terminology [redacted] on the principle display panel (PDP). We defer to the Office of Pharmaceutical Quality (OPQ) to address this issue.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the labels and labeling where additional important information should be added or information should be revised in order to help ensure the safe use of the product. We provide recommendations below in Sections 4.1 and 4.2 to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights and Full Prescribing Information- Section 2 *Dosage and Administration*

1. The dosing instructions are expressed as [redacted] which lacks clarity and may lead to overdose. Postmarketing evidence suggests that ambiguous course dosing leads to errors[1] and we are concerned that the dose expression may be misinterpreted [redacted] which may lead to error of improper dose leading to overdose. The dosing instructions should be clarified and revised to state: "The daily dosage of DIACOMIT should be administered in 2 or 3 divided doses. If possible, consider adding a table similar to:

Dose (mg/kg)	**Dosing Interval**
16.67 mg/kg	Every 8 hours
25 mg/kg	Every 12 hours

B. Full Prescribing Information- Section 16 *How Supplied/Storage and Handling*

1. We note that the following information is provided in Section 16 of the PI: special handling and storage instructions; the strength of the dosage form in metric system and limited information to facilitate identification of the dosage form (i.e., capsule size and color). However, section 16 of the PI lacks additional information required per 21 CFR 201.57. We recommend you revise section 16 of the PI to include the

[1] Institute for Safe Medication Practices. Safety briefs: Ambiguous course dosing leads to errors. ISMP Med Saf Alert Acute Care. 2014; 19(25): 2-3.

units in which the dosage form is supplied (i.e., bottles of 60), imprint code and National Drug Code number in order to comply with the content requirements outlined in 21 CFR 201.57 and to decrease risk of wrong drug or wrong strength errors.

2. Section 16 of the PI includes the following special handling and storage instructions: (b) (4) However, this is statement does not clearly state the acceptable storage temperature range. Furthermore, the handling and storage instructions in the PI are inconsistent with the cautionary statements present on the carton and container (e.g. store (b) (4) original package to protect from light). We are concerned that the lack of consistent information throughout the labels and labeling may lead to the inappropriate storage and/or handling of the product and pose risk of decreased product quality. We recommend you revise " (b) (4) to "store (b) (4) in a dry place" and add the following statement to Section 16 of the PI: "Store in original package to protect from light."

4.2 RECOMMENDATIONS FOR BIOCODEX

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling and Container Label, 250 mg and 500 mg strengths
    1. As presented on the PDP, the presentation of the finished dosage form (i.e., capsules) is not consistent with USP requirements. The PDP should be revised so the finished dosage form is located either in the same line as the active ingredient (established name) or directly below the active ingredient (established name) on all panels of the carton and container labeling. (See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; April 2013)*.
    2. The small font size of the unit of measure (i.e., mg) in the strength expression lacks prominence and hinders the readability of the unit of measure which may cause misinterpretation of strength. We recommend the font size used for the unit of measure (i.e., mg) be increased to that of the numerical strength (i.e., 250 or 500) to ensure prominence in accordance with 21 CFR 201.15(a)(6).
    3. We note that the presence of the following statement (b) (4) In accordance with 21 CFR 208.24(d), the label should also state how the Medication Guide is provided (e.g., enclosed, accompanying). Revise the statement in a manner such as displayed below to include how the Medication Guide will be provided:

i. “Attention Pharmacist: Dispense the enclosed Medication Guide to each patient.” or
ii. “Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.”

4. (b) (4)

5. The NDC product code numbers are denoted by placeholders (XXXX-XXX-XX). Therefore, we are unable to evaluate whether the NDC product code numbers will adequately differentiate the 250 mg and 500 mg strength products. Provide the intended NDC product code numbers for Agency review.
6. The storage statements do not contain the temperature scale designation (i.e., “°C” or “°F”) after each numerical value. As such, we are concerned that the acceptable storage temperature could be misinterpreted and pose risk of improper storage leading to decrease product quality. Ensure that the degree symbol and temperature scale follows each numeric value denoting temperature ranges. For example, revise (b) (4) to read (b) (4)

B. Container Label, 250 mg and 500 mg strengths
1. The net quantity statement appears in close proximity to the product strength and may contribute to confusion of product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Relocate the net quantity statement away from the product strength, such as to the bottom of the PDP.
2. Your immediate container label lacks a barcode and may lead to risk of improper product selection. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. We recommend you add the product barcode to the immediate container label as required per 21 CFR 201.25(c)(2).

C. Carton Labeling, 250 mg and 500 mg strengths

1. The net quantity is currently presented as [redacted] (b) (4) [redacted] (b) (4) the net quantity statement is confusing. We are concerned that the quantity supplied may be misinterpreted and lead to medication dosing errors. [redacted] (b) (4) [redacted]

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Diacomit (stiripentol) that Biocodex submitted on November 10, 2015.

Table 2. Relevant Product Information for Diacomit	
Initial Approval Date	N/A
Active Ingredient	Stiripentol
Indication	(b) (4) treatment of (b) (4) seizures associated with Dravet syndrome.
Route of Administration	Oral
Dosage Form	Capsule
Strength	250 mg and 500 mg
Dose and Frequency	50 mg/kg/day administered in 2 or 3 divided doses.
How Supplied	250 mg capsules: 60-count 500 mg capsules: 60-count
Storage	Store (b) (4) in a dry place. Store in original package to protect from light.
Container Closure	The capsules are packaged in opaque (b) (4) bottle closed with a (b) (4) (b) (4) cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 23, 2016, we searched the L:drive and AIMS using the terms, stiripentol to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Diacomit (stiripentol) labels and labeling submitted by Biocodex on November 10, 2015.

- Container label
- Carton labeling
- Prescribing Information-no image

G.2 Label and Labeling Images

APPEARS THIS WAY ON ORIGINAL

Container Label: 250 mg strength

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BRIANA B RIDER
01/04/2017

LOLITA G WHITE
01/05/2017

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September, 26, 2016

To: William Dunn, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Diacomit (Stiripentol), NDA 206709, Amendment 14, Presubmission to Rolling Submission – Part 9
Trade Name, dosages, formulations, routes: 250 mg and 500 mg stiripentol capsules for oral administration
Indication(s): (b) (4) treatment of (b) (4) seizures associated with Dravet syndrome (b) (4)
Sponsor: Biocodex

Materials Reviewed:

Three protocols ((b) (4)1551, (b) (4)1552, and (b) (4)1553) submitted for pre-clinical studies to assess the abuse potential of stiripentol.

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request to CSS dated August 11, 2016, by the Division of Neurology Products (DNP) to evaluate and provide comments on three pre-clinical protocols intended to assess the abuse potential of stiripentol. These protocols were submitted by KM Pharmaceuticals Consulting on behalf of the Sponsor, Biocodex, via a letter to the Division dated August 10, 2016. The protocols include:

- Protocol (b) (4) 1551 entitled "Determination of the Potential of Stiripentol to Induce Pharmacological Tolerance and Physical Dependence in Withdrawal."
- Protocol (b) (4) 1552 entitled "Evaluation of the Discriminative Properties of Stiripentol and a Reference Comparator in Rats Trained to Discriminate Midazolam from Saline."
- Protocol (b) (4) 1553 entitled "Evaluation of the Potential Reinforcing Effects of Stiripentol and a Reference Comparator Using a Self-Administration Procedure in Heroin Maintained Rats."

The three studies will be conducted by (b) (4).

The protocols were provided in response to an FDA general advice letter dated February 4, 2016. According to the submission letter, the protocols were designed by the Sponsor following the FDA Draft Guidance for Industry "Assessment of Abuse Potential of Drugs" (January 2010) and in consultation with a specialist experienced in the field of abuse potential evaluation.

2. Conclusions

1. Protocol (b) (4) 1551 stipulates evaluating stiripentol in rodents for spontaneous withdrawal only, and not also for precipitated withdrawal. The protocol should be modified to also evaluate precipitated withdrawal using the benzodiazepine antagonist, flumazenil, and the barbiturate antagonist, benegride. This recommendation is made in part due to previous findings by Gatch et al., (2012) in which carisoprodol, a Schedule IV positive GABAa receptor modulator, following repeated dosing produced minimal, if any, spontaneous withdrawal, but produced a strong precipitated withdrawal response. An additional important modification to the protocol should be the use of a benzodiazepine or barbiturate as the positive control, instead of morphine.

2. Protocol (b) (4) 1552 stipulates evaluation of stiripentol for stimulus generalization to a benzodiazepine (midazolam) but not to a barbiturate. Stiripentol positively modulates all recombinant GABAa receptors tested, including those modulated by benzodiazepines (Fisher, 2011). Stiripentol has positive allosteric modulatory effects on GABAa receptors not modulated by benzodiazepines (Fisher, 2011). In addition, stiripentol acts at a specific locus on the GABAa receptor acted upon only by barbiturates (Quilichini et al., 2006). These results suggest that stiripentol may or may not show generalization to either benzodiazepines or barbiturates, or both. As such, the protocol should be evaluated to include a second cohort of rats trained to discriminate between a barbiturate (i.e., pentobarbital) and saline. This will allow for evaluation of stiripentol for stimulus generalization to benzodiazepines and barbiturates.

3. Protocol (b) (4) 1553 stipulates the use of rats trained to self-administer heroin for assessing the reinforcing effects of stiripentol. This may be acceptable as long as these heroin-trained rats are also shown to self-administer either a benzodiazepine (i.e., midazolam) or barbiturate.

3. Recommendations

CSS has the comments listed below to be conveyed to Sponsor concerning protocol (b) (4) 1551.

1. Stiripentol should be evaluated for spontaneous withdrawal and precipitated withdrawal. The benzodiazepine antagonist flumazenil and the barbiturate antagonist bemegride should be used in an attempt to evoke a precipitated withdrawal following repeated administration of stiripentol and the positive comparator.

2. The use of morphine as the positive comparator for purposes of evaluating the physical dependence potential of stiripentol is not acceptable. Instead, the positive comparator should be a benzodiazepine (i.e., diazepam) or barbiturate scheduled under the federal Controlled Substances Act. For purposes of validation, the repeated administration (28 days) of the benzodiazepine or barbiturate, should upon termination of treatment, result in a spontaneous withdrawal syndrome, and in the presence of an antagonist, result in precipitated withdrawal.

3. There is no need for a valproate/topiramate arm in the study.

4. You have included in the protocol an "Observation Checklist" Behavioral and Physical Signs of Drug Administration and Withdrawal in Rats." Ensure that this checklist accurately reflects signs of withdrawal observed following chronic benzodiazepine or barbiturate administration.

5. The protocol stipulates that behavioral observations during the spontaneous withdrawal phase will be made for 2 minutes twice a day. An observation period of 2 minutes does not seem appropriate for assessing behavioral effects of spontaneous withdrawal. You should consider extending the observation periods out to at least 10 minutes. For examination of spontaneous withdrawal, an alternative observation schedule will be needed. Ensure that the behavioral observations are made by individuals blinded to the treatment given.

CSS has the comments listed below to be conveyed to Sponsor concerning protocol (b) (4) 1552.

1. Your protocol currently provides for evaluating possible stimulus generalization of stiripentol to benzodiazepines (midazolam), but not to barbiturates. It is, however, possible that stiripentol might generalize to one or the other, or both benzodiazepines and barbiturates. This suggests that stiripentol should also be evaluated for stimulus generalization to barbiturates as well as benzodiazepines. You should modify your protocol to include a second cohort of rats trained to distinguish a barbiturate such as pentobarbital from saline and use this cohort to evaluate stiripentol for possible stimulus generalization to barbiturates.

2. The accompanied pharmacokinetic study protocol stipulates determination of stiripentol plasma levels at pre-dose and at 1.5 hours and 2.5 hours following administration of stiripentol at doses of 75, 150, and 300 mg/kg i.p. It is not clear how these sampling time points (1.5 hours and 2.5 hours) compare with the period over which stimulus generalization will be evaluated. Pharmacokinetic sampling with determination of stiripentol plasma concentrations should coincide with the measuring times for stimulus generalization.

CSS has the comments listed below to be conveyed to Sponsor concerning protocol (b)(4)1553.

1. For evaluation of the reinforcing effects of stiripentol, the use of rats trained to self-administer heroin is acceptable as long as self-administration is achieved with substitution of heroin with a benzodiazepine (i.e., midazolam) or a barbiturate, scheduled under the federal Controlled Substances Act.

2. There is no need for sodium valproate or topiramate treatments in this study. These drugs are not expected to produce reinforcing effects and are not scheduled under the federal Controlled Substances Act.

3. Criteria of determining "positive reinforcement" and "non-reinforcement" will be considered during the review of the study results.

II. DISCUSSION

2.4 Animal Behavioral Studies

Sponsor submitted three protocols ((b)(4)1551, (b)(4)1552, and (b)(4)1553) for pre-clinical studies to evaluate stiripentol for physical dependence potential, stimulus generalization, and reinforcing effects.

Tolerance and Physical Dependence with Repeated Dosing of Stiripentol

Sponsor submitted **protocol (b)(4)1551** entitled "Determination of the Potential of Stiripentol to Induce Pharmacological Tolerance and Physical Dependence on Withdrawal" Provided below are some stipulations for this protocol.

- Protocol stipulates that morphine will be used as the positive control in the study. As noted on page 8 of the protocol, the laboratory conducting the study has "previously demonstrated that morphine given twice daily at a fixed dose of 30 mg/Kg produces tolerance and clear signs of moderate physical dependence" and hence it will be selected as a positive control for this study." Morphine is not an appropriate positive control for evaluating the physical dependence of stiripentol, a $GABA_A$ receptor modulator. A benzodiazepine such as diazepam or a barbiturate should serve as the positive control.
- This study only evaluates spontaneous withdrawal following discontinuation after 28 days of dosing. The protocol does not include an examination of precipitated withdrawal, which may be a more sensitive method for detecting physical dependence. Precipitated withdrawal should be evaluated

with regard to chronic stiripentol administration using flumazenil (benzodiazepine antagonist) and bemegride (barbiturate antagonist).

- Following a 7 day baseline observation period, rats will be dosed twice daily for 28 days by gastric gavage. Upon termination of chronic treatment, rats will be evaluated for 7 days for signs of withdrawal.
- For purposes of assessing behavioral/physical effects, protocol (b) (4) 1551 stipulates a 2 minute observation period at 1 hour after morning dosing in the drug administration phase, and two times each day during the drug withdrawal phase. The two-minute observation periods seem a little short and should be extended to 10 minutes observation periods, particularly during the withdrawal phase.
- The number of rats per treatment group will be 10 for purposes of achieving statistical significance testing. This number is based on the experience of the laboratory, presumably from morphine dependence studies, demonstrating that a group size of > 8 rats per group was sufficient to achieve statistical significance for the clinical signs in the on dose and withdrawal periods.
- A standardized checklist of expected withdrawal behaviors for pharmacological drug classes should be used. Changes of body weight and food intake will also be monitored for signs of withdrawal.
- An additional group of rats that will be evaluated be dosed chronically with stiripentol in order to determine the plasma levels of stiripentol during the 28 days of dosing in rats. Animals will be dosed in parallel and kept under the same conditions as the rats in the tolerance and dependence study. This study is intended to demonstrate stiripentol plasma concentrations greater than 3-fold excess of the human exposure at clinical doses.

Discriminative Stimulus Properties of Stiripentol

Sponsor submitted **protocol (b) (4) 1552** entitled "Evaluation of the Discriminative Properties of Stiripentol and a Reference Comparator in Rats Trained to Discriminate Midazolam from Saline." Provided below are some stipulations for this protocol.

- Protocol stipulates both a discrimination study as well as an accompanied pharmacokinetic study.
- The protocol provides for examining for possible stimulus generalization to a benzodiazepine (midazolam) but not for possible stimulus generalization to a barbiturate. Studies at the cellular level suggest that stiripentol produces GABAA receptor facilitation is a manner similar to that of barbiturates. As such, stiripentol should be evaluated for stimulus generalization to both benzodiazepines and to barbiturates, and not just to benzodiazepines.
- Female rats will be trained to discriminate (≥ 75% correct lever choice) between an intraperitoneal (i.p.) injection of midazolam (0.5 – 1.0 mg/kg) and saline (1 ml/kg) using a sweetened milk reward in a 2-choice lever-pressing model with a fixed ratio of 5 (FR5). Dosage of midazolam selected is based upon "in house" experience of performing drug discrimination testing in rats using midazolam as a training cue.
- Stiripentol doses selected by Sponsor are 75, 150, and 300 mg/kg. Each dose will be tested in 6 or more rats. Dose-test interval will be determined by Sponsor. At least a 24 hour washout period will be used.
- "Reference Comparator" drug will be sodium pentobarbital or sodium secobarbital tested at 3 doses given i.p. Doses will be selected by Sponsor. At least a 24 hour washout period will be used.
- Control will be saline solution containing 5% tween 80 (v/v) given i.p.
- Data will be expressed in figures as % generalization to midazolam.

- Testing laboratory criteria for generalization is as follows: full generalization if ≥ 75% lever press responses on the midazolam lever; partial generalization if 26% - 74% lever press responses on the midazolam lever; and no generalization if ≤ 25% lever press responses on the midazolam lever.
- Stiripentol plasma concentrations will be determined in a separate group of rats following i.p. doses 75, 150, and 300 mg/kg.

Potential Reinforcing Effects of Stiripentol

Sponsor submitted **protocol** (b) (4) **1553** entitled "Evaluation of the Potential Reinforcing Effects of Stiripentol and a Reference Comparator Using a Self-Administration Procedure in Heroin-Maintained Rats. Provided below are some stipulations for this protocol.

- Study will be conducted using rats trained to self-administer heroin. It is not clear why heroin trained rats were selected. It is possible that the laboratory conducting the studies have experience primarily with opioids.
- Study is non-GLP but will, according to Sponsor, be performed as close as possible to GLP standards.
- Midazolam will be the positive comparator if, according to Sponsor, it is found to be substitute for heroin.
- Valproate or topiramate are listed as negative comparators that will be tested even though they are pharmacologically different and therefore not expected to substitute for heroin.
- Vehicle is sterile 0.9% saline.
- Rats will be initially trained to lever-press for food reinforcement on a FR-3 schedule of reinforcement, after which rats will be surgically fitted with indwelling venous catheters.
- Rats will be trained to self-administer heroin (0.015 mg/kg/injection or 0.5 mg/kg/injection) on a FR5 schedule of reinforcement. Maximum of 20 injections within a 2 hour period for FR 5 schedule. Robust heroin self-administration (≥ 12 infusions for three consecutive sessions) will be obtained after which saline will be substituted for heroin until extinction is achieved, at which point, test drugs will be evaluated for reinforcing effect using a FR5 schedule of reinforcement during 2 hour sessions.
- There will be 6 rats per dose, with each drug involving separate animals.
- Data will be presented as the mean number of injections received per 2 hour sessions.

III. REFERENCES

Fisher JE (2011). The effects of stiripentol on GABAa receptors. Epilepsia, 52 Suppl. 2: 76-78.

Gatch MB, Nguyen JD, Carbonaro T, and Forster MJ (2012). Carisoprodol tolerance and precipitated withdrawal. Drug and Alcohol Dependence, 123 (1-3): 29-34.

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/s/

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09/26/2016

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