CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206709Orig1s000
207223Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: **APPROVAL WITH PMC**

NDA 207223
Review #01

Drug Name/Dosage Form	Stiripentol Powder for Oral Suspension
Strength	250 mg and 500 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Biocodex
US agent, if applicable	KM Pharmaceutical Consulting LLC

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	05-SEP-2017	*Amendment*	06-JUN-2018
Amendment	05-MAR-2018	*Amendment*	15-JUN-2018
Amendment	16-MAR-2018	*Amendment*	03-JUL-2018
Amendment	27-MAR-2018	*Amendment*	06-JUL-2018
Amendment	05-APR-2018	*Amendment*	11-JUL-2018
Amendment	23-APR-2018		

Quality Review Team

DISCIPLINE	PRIMARY/SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Charles Jewell/Kasturi Srinivasachar	ONDP
Drug Product	Andrei Ponta/Wendy Wilson-Lee	ONDP
Process and Microbiology	Yaodong Huang/Nallaperumal Chidambaram	OPF
Facility	Laura Fontan/Ruth Moore	OPF
Biopharmaceutics	Kaushalkumar Dave/Angelica Dorantes	ONDP
Regulatory Business Process Manager	Dahlia Walters	OPRO
Application Technical Lead	Wendy Wilson-Lee	ONDP
Environmental	Andrei Ponta/Wendy Wilson-Lee	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Completed	Comments
(b) (4)	Type IV		(b) (4)	-	-	Sufficient information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107979	Treatment of Dravet Syndrome
NDA	206709	Stiripentol Capsules

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends an **APPROVAL** action for NDA 207223 Stiripentol Powder for Oral Suspension, 250 mg and 500 mg.

As part of this action, OPQ is granting an interim dissolution acceptance criterion and recommending a product quality post-marketing commitment (PMC) to finalize the dissolution acceptance criterion based on data collected from the first six commercial drug product batches manufactured. OPQ recommended revisions to the originally proposed dissolution method during the review cycle. The Applicant accepted these revisions but was unable to generate new dissolution data based on the revised method due to lack of available product for testing. An interim acceptance criterion and PMC are recommended in consideration of the unmet medical need, the orphan designation granted this product, and vast clinical experience with this product.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***For*** (b) (4) ***treatment of*** (b) (4) (b) (4) ***seizures associated with Dravet syndrome in patients*** (b) (4)
Duration of Treatment	***Chronic***
Maximum Daily Dose	***50 mg/kg, administered in 2 or 3 divided doses***
Alternative Methods of Administration	***None***

BIOCODEX submitted this 505(b)(1) NDA to support the approval of stiripentol powder for oral suspension for the (b) (4) treatment of (b) (4) seizures in patients with Dravet syndrome (b) (4). Stiripentol was granted orphan designation for the treatment of Dravet syndrome in October 2008. Stiripentol is approved in Europe and other countries including Canada, Japan for the proposed indication under the trade name Diacomit®. Diacomit® has been used in numerous single patient INDs.

B. Quality Assessment Overview

Stiripentol is manufactured (b) (4) (b) (4) (b) (4) Stiripentol is a racemic mixture of two enantiomers from a structure with one chiral center. Both enantiomers are considered active based on nonclinical results. The typical scale of the commercial drug substance synthesis produces from (b) (4) kilograms of stiripentol.

No related impurities are observed above (b) (4)%, solvent impurities are extremely low, and elemental impurities have been demonstrated to be consistently lower than (b) (4)% the levels that would lead to exposure at the recommended permitted daily exposure (b) (4) (b) (4) (b) (4) **The drug substance stability studies support a retest period of (b) (4).**

The drug product is a pale pink powder for oral suspension that contains stiripentol drug substance and the following excipients: povidone, sodium starch glycolate, (b) (4) glucose (b) (4), erythrosine, titanium dioxide, aspartame, (b) (4) carmellose sodium, and hydroxyethyl cellulose. It is available in 250 mg or 500 mg strengths in (b) (4) (b) (4) packet. The drug product is supplied in (b) (4) of 60 packets.

The powder for oral suspension contains (b) (4) manufactured (b) (4) (b) (4) to facilitate administration by the oral route after dispersion in water. The drug product is to be mixed in a glass of water and should be taken immediately after mixing. The proposed commercial drug product formulation has remained unchanged from the one used in the pivotal clinical and bioequivalence study. The excipient-drug substance compatibility study results show that the selected excipients do not have any adverse effect on the stability of the product.

The specification, as amended, is considered appropriate to ensure the identity, purity, strength, potency, and quality of the final drug product. No new impurities or degradants were identified for the drug product. The content of elemental impurities in the drug product as well as in the drug substance is less than the (b) (4)% of PDE (limits set for oral form with daily doses of not more than 10 grams per day).

The primary stability results and annual stability results show that both 250 mg and 500 mg strength powders are stable at least up to 36 months at 25°C/60% RH storage conditions. No significant changes were observed and all results remained within the proposed specification. **Based on the stability data reviewed and in accordance with ICH Q1E, we grant the proposed product shelf-life of 36 months when stored at 25°C/60% RH conditions.**

The drug product manufacturing process consists of (b) (4), (b) (4) (b) (4) The same manufacturing process proposed for commercial production was used in development except for batch size. (b) (4) (b) (4) (b) (4) **The overall manufacturing inspection recommendation for NDA 207223 is APPROVAL based on acceptable recommendations for all facilities listed in the application.**

The Biopharmaceutics review for this submission is focused on the evaluation of the data supporting approval of the proposed dissolution method and acceptance criterion for Stiripentol Powder for Oral Suspension; 250 mg, 500 mg.

- ***Dissolution Method:*** For the proposed Stiripentol Powder for Suspension, the Applicant proposed using the same dissolution method, as the one for the Stiripentol Capsules submitted under NDA 206709 [*900 mL of Sodium lauryl sulfate (SLS) 1.2% solution adjusted to pH 4.5 using USP Apparatus 2 at 75 rpm*]. However, dissolution data were not provided for the proposed product.

  The Applicant provided comparative dissolution data for the proposed capsules under NDA 206709 and the proposed powder under this NDA, using a previously proposed dissolution method (b) (4) (b) (4). The results show similar dissolution profiles for the Stiripentol capsules and powder products and it is expected that the dissolution profiles of the Stiripentol Capsules and Stiripentol Powder for Injection will be similar with the proposed dissolution method. Therefore, the proposed dissolution method is acceptable on an interim basis for the quality control testing of Stiripentol Powder for Suspension, 250 mg and 500 mg.

- ***Dissolution Acceptance Criterion***: The Applicant proposed a dissolution acceptance criterion of Not less than (b) (4) % (Q) at (b) (4) minutes; however, the dissolution data supported a tighter acceptance criterion. The FDA recommended to implement an acceptance criterion of 'Not less than (b) (4) % (Q) at 20 minutes, on an interim basis, for the dissolution test of the proposed Stiripentol Powder for Suspension; 250 mg, 500 mg. On May 15, 2018, the Applicant agreed to this recommendation.

- ***Post-Marketing Commitment***: Because the proposed drug product is NOT currently available to perform the dissolution studies, the Applicant agreed to provide dissolution profile data using the proposed dissolution method for the first six manufactured commercial batches of each strength of Stiripentol Powder for Oral Suspension (250 mg, 500 mg) as well as a final proposal for the dissolution acceptance criterion as part of a Product Quality Post-Marketing Commitment. On May 15, 2018, the Applicant agreed to the terms of the PMC.

The claim of categorical exclusion meets the requirements 21 CFR 25.31(b) and include a statement of no extraordinary circumstances in accordance with 21 CFR 25.31 (d). **The claim of categorical exclusion is acceptable.**

C. Special Product Quality Labeling Recommendations

None.

D. Final Drug Product Risk Assessment

From Initial Risk Identification		Review Assessment		
Critical Quality Attributes	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Assay	**Low**	(b) (4)	**Acceptable**	
Content Uniformity	**Low**		**Acceptable**	
Dissolution	**Medium**		**Acceptable**	An interim dissolution acceptance criterion is granted; PMC to finalize the dissolution criterion
Microbial Contamination	**Low**		**Acceptable**	
Solid State	**Medium**		**Acceptable**	(b) (4)
(b) (4)	**Low**		**Acceptable**	
Delivered Mass	**Medium**		**Acceptable**	
Container Integrity	**Medium**		**Acceptable**	
(b) (4) Integrity	**Medium**		**Acceptable**	Confirm validation (b) (4) during next inspection
(b) (4) Size	**Low**		**Acceptable**	
Palatability	**Medium**		**Acceptable**	
Reconstitution Time	**Medium**	Instructions for Use (IFU) detail the steps for reconstitution; Development data demonstrate that the suspension is stable for up to (b) (4) in water; Instructions to drink immediately are included in the IFU	**Acceptable**	

42 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

LABELING

I. Package Insert

(b) (4)

[redacted]

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Diacomit (stiripentol) powder for oral suspension
Dosage form, route of administration	Powder for oral suspension
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	250 mg, 500 mg

Is the information accurate? ☒ Yes ☐ No

2. *Section 2 Dosage and Administration*

DIACOMIT Powder for Oral Suspension

DIACOMIT should be mixed in a glass of water and should be taken immediately after mixing during a meal.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation	The drug product is to be mixed in a glass of water and taken immediately.

Is the information accurate? ☒ Yes ☐ No

3. ***Section 3 Dosage Forms and Strengths***

3 DOSAGE FORMS AND STRENGTHS

(b) (4) Powder for Oral Suspension (b) (4) pale pink flavored powder packaged in packets. Each packet contains either 250 or 500 mg of stiripentol.

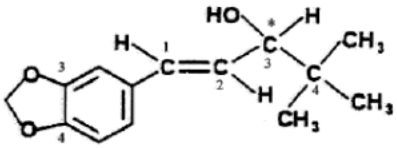
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Powder for oral suspension
Strengths: in metric system	250 mg, 500 mg
Active moiety expression of strength with equivalence statement (if applicable)	Not Applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Pale, pink flavored powder packaged in packets.

Is the information accurate? ☒ Yes ☐ No

4. ***Section 11 Description***

11 DESCRIPTION

Table 7. Description

Proprietary Name	DIACOMIT
Established Name	Stiripentol
Dosage Forms	Powder for Suspension
Route of Administration	Oral
(b) (4)	
Chemical Name	4,4-dimethyl-1-[3,4-(methylendioxyphenyl)-1-pentene-3-ol
Structural Formula	 * : identifies an asymmetric carbon.

Stiripentol is a white to pale yellow crystalline powder with a bitter taste; it is practically insoluble in water (at 25°C), sparingly soluble in chloroform, and soluble in acetone, ethanol, ether, acetonitrile, and dichloromethane. (b) (4) (b) (4) The melting point is approximately 75°C. The pKa is 14.2, and measurement of the partition coefficient (water-octanol) provides a Log P value of 2.94. The molecular formula is $C_{14}H_{18}O_3$ and the molecular weight is 234.3.

DIACOMIT packets contain 250 mg or 500 mg of stiripentol. DIACOMIT packets also contain the following inactive ingredients: aspartame, carmellose sodium, erythrosine, glucose, hydroxyethylcellulose, povidone, sodium starch glycolate, sorbitol, titanium dioxide, (b) (4) flavour.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Not Present
Dosage form and route of administration	Oral: 250 mg, 500 mg
Active moiety expression of strength with equivalence statement (if applicable)	Not Applicable
Statement of being sterile (if applicable)	Not Applicable
Pharmacological/ therapeutic class	Not present
Chemical name, structural formula, molecular weight	Accurate
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	pKa, melting point, Log P present

Is the information accurate? ☒ Yes ☐ No

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

NDC 68418-7941-6: Cartons of 60, 250 mg packets
NDC 68418-7942-6: Cartons of 60, 500 mg packets

Store (b) (4) in a dry place. Store in original package to protect from light.

DIACOMIT Powder for (b) (4) Suspension manufactured by:
BIOCODEX
1, avenue Blaise Pascal
60000 BEAUVAIS
France

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	250 mg, 500 mg
Available units (e.g., bottles of 100 tablets)	Carton of 60 packets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pink powder for oral suspension. NDC number included.
Special handling (e.g., protect from light)	Protect from Light
Storage conditions	15 - 30°C
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Biocodex, France

Reviewer's Assessment of Package Insert: ***Adequate***

Revisions identified and will be communicated to the Applicant as part of DNP labeling negotiations. The PI is adequate assuming Applicant accepts edits.

II. Labels:

1. ***Container Labels***

(b) (4)

(b) (4)

[redacted]

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Diacomit (stiripentol) for oral suspension	Diacomit (stiripentol) for oral suspension
Dosage strength	250 mg, 500 mg	250 mg, 500 mg
Net contents	250 mg, 500 mg	60 packets
"Rx only" displayed prominently on the main panel	Complies	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies	Complies
Lot number and expiration date (21 CFR 201.17)	Complies	Complies
Storage conditions	15 - 30°C	15 - 30°C
Bar code (21CFR 201.25)	Complies	Complies
Name of manufacturer/distributor	Biocodex, France	Biocodex, France
And others, if space is available	Not applicable	Not applicable

Reviewer's Assessment of Labels: ***Adequate***

The carton and container labels comply with all regulatory requirements from a CMC perspective.

List of Deficiencies: Revisions identified and will be communicated to the Applicant as part of DNP labeling negotiations.

Overall Assessment and Recommendation: Adequate

Andrei Ponta

Digitally signed by Andrei Ponta
Date: 7/25/2018 04:39:16PM
GUID: 53b58e0b00004a630e714ee170af4c26

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/25/2018 04:42:47PM
GUID: 50816dbc000085595ca3284bbca465a8

31 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

QUALITY ASSESSMENT

BIOPHARMACEUTICS	
Application No./Submission Date	NDA 207223, Dated 09/05/2017
Applicant Name	Biocodex
Product Name	Stiripentol Powder for Suspension; 250 mg, 500 mg
Route of Administration	Oral
Clinical Division	Neurology Products
Primary Reviewer	Kaushalkumar Dave, Ph.D.
Secondary Reviewer	Angelica Dorantes, Ph.D.
RECOMMENDATION	**ADEQUATE**

REVIEW SUMMARY

Submission: The Applicant is seeking approval for NDA 207223 for Stiripentol Powder for Suspension; 250 mg, 500 mg, via 505(b)(1) route as an (b) (4) treatment of (b) (4) (b) (4) seizures associated with Dravet syndrome. The Applicant is also seeking approval of Stiripentol Capsules, 250 and 500 mg, submitted under NDA 206709 on 11/10/2015 (reviewed separately).

Review: The Biopharmaceutics review for this submission is focused on the evaluation of the data supporting approval of the proposed dissolution method and acceptance criterion for Stiripentol Powder for Suspension; 250 mg, 500 mg.

- ***Dissolution Method:*** For the proposed Stiripentol Powder for Suspension, the Applicant proposed using the same dissolution method, as the one for the Stiripentol Capsules submitted under NDA 206709 [*900 mL of Sodium lauryl sulfate (SLS) 1.2% solution adjusted to pH 4.5 using USP Apparatus 2 at 75 rpm*]. However, dissolution data were not provided for the proposed product.

  The Applicant provided comparative dissolution data for the proposed capsules under NDA 206709 and the proposed powder under this NDA, using a previously proposed dissolution method (b) (4) (b) (4). The results show similar dissolution profiles for the Stiripentol capsules and powder products and it is expected that the dissolution profiles of the Stiripentol Capsules and Stiripentol Powder for Injection will be similar with the proposed dissolution method. Therefore, the proposed dissolution

method is acceptable on an interim basis for the quality control testing of Stiripentol Powder for Suspension, 250 mg and 500 mg.

- ***Dissolution Acceptance Criterion***: The Applicant proposed a dissolution acceptance criterion of Not less than (b)(4)% (Q) at (b)(4)minutes; however, the dissolution data supported a tighter acceptance criterion. The FDA recommended to implement an acceptance criterion of 'Not less than (b)(4)% (Q) at 20 minutes' for the dissolution test of the proposed Stiripentol Powder for Suspension; 250 mg, 500 mg. On May 15, 2018, the Applicant agreed to this recommendation.

- ***Post-Marketing Commitment***: Because the proposed drug product is NOT currently available to perform the dissolution studies, the Applicant was requested to provide as a Post-Marketing Commitment (PMC), dissolution profile data using the proposed dissolution method for the first six manufactured commercial batches of each strengths of Stiripentol Powder for Suspension; 250 mg, 500 mg. The Applicant was also requested to provide under the PMC submission, their proposal for the final dissolution acceptance criterion of the powder for suspension drug product. On May 15, 2018, the Applicant agreed to the terms of the PMC.

Recommendation: The following dissolution method and acceptance criterion are acceptable **on an interim basis** for the quality control testing of Stiripentol Powder for Suspension; 250 mg, 500 mg, at release and on stability.

Interim Dissolution Method and Acceptance Criterion for Stiripentol Powder for Suspension; 250 mg, 500 mg	
Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	75 rpm
Volume	900 ml
Medium	1.2% solution adjusted to pH 4.5
Temperature	37.0 ± 0.5 C
Acceptance Criterion	Not less than (b)(4)% (Q) at 20 minutes

From a Biopharmaceutics perspective, NDA 207223 for Stiripentol Powder for Suspension; 250 mg, 500 mg, is recommended for **APPROVAL with a PMC**.

Primary Biopharmaceutics Reviewer/Date:

Kaushalkumar Dave, Ph.D. 05/18/2018
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch 1
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer/Date:

I agree with Dr. Dave assessment and recommendation

Angelica Dorantes, Ph.D. 05/18/2018
Biopharmaceutics Branch Chief
Division of Biopharmaceutics-Branch 1
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSSESSMENT

1. LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0000	09/05/2017	Original NDA Submission
0007	04/23/2018	Quality/Response to Biopharmaceutics Information Request
-	05/15/2018	Quality/Response to Biopharmaceutics IR via an Email (Appendix 2)

2. DRUG PRODUCT

The proposed drug product, Stiripentol Powder for Suspension; 250 mg, 500 mg, is described as a (b) (4) containing a pale-pink powder. It is (b) (4) (b) (4) (b) (4) (b) (4) The two strengths of the proposed product are varying only in the total fill weight/quantity. The composition of the proposed product is presented in Table 1.

Table 1: Composition of Stiripentol Powder for Suspension; 250 mg, 500 mg

Names of ingredients	Unit formula		Percentage formula (approx.)	Function	Reference for the control
Stiripentol	250.000 mg	500.000 mg	(b) (4)	Active substance	Certificate of analysis
Excipients:				(b) (4)	
Povidone					European Pharmacopoeia, Current edition monograph (b) (4)
Sodium starch glycolate (b) (4)					European Pharmacopoeia, Current edition monograph (b) (4)
(b) (4) glucose					In-house monograph
Erythrosine (b) (4)					In-house monograph
Titanium dioxide (b) (4)					European Pharmacopoeia, Current edition monograph (b) (4)
Aspartame (b) (4)					European Pharmacopoeia, Current edition monograph (b) (4)
(b) (4)					In-house monograph
Carmellose sodium					European Pharmacopoeia, Current edition monograph (b) (4)
Hydroxyethylcellulose					European Pharmacopoeia, Current edition monograph (b) (4)
(b) (4)					European Pharmacopoeia, Current edition monograph (b) (4)
(b) (4					
					(b) (4)

3. BCS DESIGNATION

The Applicant did not request BCS designation. However, the Applicant believes that stiripentol is a BCS Class II compound. Please refer to the 'Biopharmaceutics Review' section of NDA 206709 for the drug substance solubility and permeability information and the review thereof[1].

4. DISSOLUTION TEST

Dissolution Method: For the proposed Stiripentol Powder for Suspension, 250 mg and 500 mg, under NDA 207223, the Applicant proposed using the same dissolution method, as the one for the Stiripentol Capsules; 250 mg, 500 mg submitted under NDA 206709 [900 mL of Sodium lauryl sulfate (SLS) 1.2% solution adjusted to pH 4.5 using USP Apparatus 2 at 75 rpm]. However, the Applicant did not provide any dissolution data with this dissolution method for the proposed Stiripentol Powder for Suspension product. Therefore, via an Information Request (IR) sent on 03/23/2018, the Applicant was requested to provide data/information justifying the selection of the proposed dissolution method for quality control of the proposed drug product. Also, the Applicant was requested to provide data justifying the selection of the type and level of the surfactant used in the proposed dissolution method. In the response to the IR dated 04/23/2018, the Applicant provided data from the dissolution method development report submitted under NDA 206709 to justify the selection of the proposed dissolution method. The Applicant argued that the dissolution method used for Stiripentol Capsules is also suitable for the proposed Stiripentol Powder for Suspension. To support the argument, the Applicant provided comparative dissolution data (**Figure 1**) for the proposed capsules under NDA 206709 and the proposed powder under this NDA, using a previously proposed (under NDA 206709) dissolution method (b) (4) (b) (4) .

(b) (4)

[1] http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a0e4cf

The Applicant also stated in the IR response, dated 04/23/2018, that the proposed dissolution method was developed/revised during the review of NDA 206709 and unexpired or undergoing stability-testing batches are NOT available for the proposed powder for suspension to collect dissolution data with the proposed dissolution method.

The information for Stiripentol Capsules and Stiripentol Powder for Suspension shows that both products are (b) (4) (b) (4) and the Applicant states that these products are expected to show similar dissolution profiles in the proposed dissolution medium. The mean dissolution data presented in Figure 1 show similar dissolution profiles for the Stiripentol capsules and powder products. Therefore, these dissolution data support the Applicant's hypothesis. Based on the provided information under NDA 207223 and NDA 206709, the proposed dissolution method appears to be adequate for the proposed Stiripentol Powder for Suspension and **is acceptable on an interim basis**.

Reviewer's Comment: *It is noted that the previous dissolution method* (b) (4) (b) (4) *was revised by the Applicant during the review of NDA 206709[1] as per the FDA's recommendation, and therefore the currently proposed dissolution method uses* (b) (4) (b) (4)*. The dissolution method proposed under the current NDA was previously accepted for Stiripentol Capsules, 250 mg and 500 mg by the Biopharmaceutics Reviewer, Dr. Fang Wu (refer to the 'Biopharmaceutics Review' section for NDA 206709[1]).*

Dissolution Acceptance Criterion: The Applicant proposed a dissolution acceptance criterion of 'Not less than (b) (4)% (Q) at (b) (4) minutes'; however, the available limited dissolution data supported a tighter acceptance criterion. On 05/11/2018 via an IR, the Applicant was recommended to implement, on an interim basis, an acceptance criterion of 'Not less than (b) (4)% (Q) at 20 minutes' for the dissolution test of the proposed Stiripentol Powder for Suspension; 250 mg, 500 mg. In their response dated 05/15/2018 (Appendix 2), the Applicant agreed to implement this criterion.

5. BRIDGING

There were no in-vitro and/or in-vivo bridging studies needed through development because of the following:

- There were no changes in the composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches;
- There was no change in the manufacturing site for the proposed product. Clinical and exhibit batches were manufactured at the same site as the proposed site for the commercial batches;
- The commercial size is within 10-fold of bio-batch sizes that were used in clinical trials;
- There were no major changes in the manufacturing process in the scale-up.

6. BIOWAIVER

A biowaiver request was NOT needed because the Applicant performed several 'non-pivotal' clinical pharmacokinetics, safety and efficacy studies with Stiripentol Powder for Suspension, 250 mg and 500 mg. Also, the Applicant performed comparative bioavailability studied using the Stiripentol Capsules, 500 mg, and Stiripentol Powder for Suspension, 500 mg. The report of the comparative Bioavailability study will be evaluated by the Clinical Pharmacology reviewer.

7. POST-MARKETING COMMITMENT:

Because Stiripentol Powder for Suspension, 250 mg and 500 mg product is NOT currently available to perform the dissolution studies, the Applicant was requested to provide, as a Post-Marketing Commitment (PMC), dissolution profile data using the proposed dissolution method for the first six manufactured commercial batches of each strengths of Stiripentol Powder for Suspension; 250 mg, 500 mg. The Applicant was also requested to provide under the PMC report, their proposal for the final dissolution acceptance criterion of their powder for suspension drug product. In the Applicant's response dated 05/15/2018, the Applicant agreed to provide the requested dissolution information/data under a PMC-supplement (*refer to the PMC in Appendix 1 and 2*).

The dissolution information/data requested under the PMC are needed to ensure suitability of the proposed specification (method and acceptance criterion) for the dissolution test evaluating the quality of the proposed product, Stiripentol Powder for Suspension; 250 mg and 500 mg.

8. RECOMMENDATION

The FDA acknowledges that the Applicant agreed to the terms of the PMC described in Appendix 1 and they are committed to submit a PMC report with the requested information/data under a PMC-Prior Approval Supplement (PAS) to the NDA within 6 months from the NDA's action date.

From a Biopharmaceutics perspective, NDA 207223 for Stiripentol Powder for Suspension; 250 mg and 500 mg, is recommended for **APPROVAL with a PMC**.

Appendix 1

Agreed-Upon Studies to be Performed Under the PMC

Submission of a Post-Marketing Commitment (PMC) report with the following information/data under a Prior Approval Supplement (PAS) to the NDA within 6 months from the NDA's action date:

- *Dissolution profile data* [redacted] (b) (4) *for each strength of the proposed Stiripentol Powder for Suspension from the first six manufactured commercial batches using the proposed dissolution method*

- *Proposal for the final dissolution acceptance criterion, based on the dissolution data collected from the first six manufactured commercial batches*

Appendix 2

BIOCODEX

7 avenue Gallieni
94257 Gentilly cedex, France
tel. 33 (0)1 41 24 30 00
fax 33 (0)1 41 24 30 01

May 15, 2018

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
USA

RE: IR May 11, 2018 Comments NDA #207223

Dear Sir or Madam,

We well noted that:

1. the proposal of providing dissolution data from the upcoming/future commercial batches of the proposed Stiripentol Powder for Suspension; 250 mg, 500 mg, using the proposed dissolution method [900 mL of Sodium lauryl sulfate (SLS) 1.2% solution adjusted to pH 4.5 using USP Apparatus 2 at 75 rpm] is acceptable.
2. FDA recommends implementing, on an interim basis, the acceptance criterion of 'Not less than (b) (4)% (Q) at 20 minutes' for the dissolution test of Stiripentol Powder for Suspension; 250 mg, 500 mg.

Biocodex commits and agrees to submit a Post-Marketing Commitment (PMC) report under a Prior Approval Supplement (PAS) to the NDA submission within 6 months from the NDA's action date with dissolution profile data collected (b) (4) for each strength of the proposed Stiripentol Powder for Suspension from the first six manufactured commercial batches using the proposed dissolution method.

Biocodex commits and agrees to use on an interim basis, the acceptance criterion of 'Not less than (b) (4)% (Q) at 20 minutes' for the dissolution test of Stiripentol Powder for Suspension; 250 mg, 500 mg. A proposal for the final dissolution acceptance criterion, based on the dissolution data collected from the first six manufactured commercial batches will be submitted.

Please feel free to contact me at +33 (0)1 41 24 30 00 or g.renaud@biocodex.fr, if you have any questions regarding this letter.

Sincerely,

Gilles Renaud, PharmD
VP Pharmaceutical Affairs
Biocodex
7 avenue Gallieni, 94250 Gentilly, France
Telephone no: +33 (0)1 41 24 30 00
Email: g.renaud@biocodex.fr

Kaushalkumar Dave

Digitally signed by Kaushalkumar Dave
Date: 5/20/2018 09:35:23PM
GUID: 5575db68006e2262805f2e6449c54250

Angelica Dorantes

Digitally signed by Angelica Dorantes
Date: 6/06/2018 04:44:12PM
GUID: 502d0913000029d59f1c87e0a380c7f7

Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/27/2018 08:55:51AM
GUID: 50816dbc000085595ca3284bbca465a8

Recommendation: APPROVAL

NDA 206709
Review #01

Drug Name/Dosage Form	Stiripentol Capsules
Strength	250 mg and 500 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Biocodex
US agent, if applicable	KM Pharmaceutical Consulting LLC

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	10-NOV-2015	*Amendment*	14-SEP-2017
Amendment	14-JAN-2016	*Amendment*	20-SEP-2017
Amendment	15-JUL-2016	*Amendment*	10-OCT-2017
Amendment	28-SEP-2016	*Amendment*	23-OCT-2017
Amendment	19-DEC-2016	*Amendment*	24-JAN-2018
Amendment	27-JAN-2017	*Amendment*	06-FEB-2018
Amendment	06-MAR-2017	*Amendment*	05-MAR-2018
Amendment	01-AUG-2017	*Amendment*	14-MAR-2018

Quality Review Team

DISCIPLINE	PRIMARY/SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Charles Jewell/Kasturi Srinivasachar	ONDP
Drug Product	Thomas Wong/Wendy Wilson-Lee	ONDP
Process	Rakhi Shah/Akm Khairuzzaman	OPF
Microbiology	Rakhi Shah/Akm Khairuzzaman	OPF
Facility	Thuy Nguyen/Peter Qiu	OPF
Biopharmaceutics	Fang Wu/Kimberly Raines	ONDP
Regulatory Business Process Manager	Dahlia Walters	OPRO
Application Technical Lead	Wendy Wilson-Lee	ONDP
ORA Lead	Caryn McNab	ORA
Environmental	Thomas Wong/Wendy Wilson-Lee	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Completed	Comments
(b) (4)	Type IV	(b) (4)		-	-	Sufficient information provided in the NDA
	Type IV			-	-	Sufficient information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107979	Treatment of Dravet Syndrome
NDA	207223	Stiripentol Powder for Oral Suspension

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 206709 for Stiripentol Capsules, 250 mg and 500 mg.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***For (b) (4) treatment of (b) (4) (b) (4) seizures associated with Dravet syndrome in patients (b) (4)***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***50 mg/kg, administered in 2 or 3 divided doses***
Alternative Methods of Administration	***None.***

BIOCODEX submitted this 505(b)(1) NDA to support the approval of stiripentol for the (b) (4) treatment of (b) (4) seizures in patients with Dravet syndrome (b) (4). Stiripentol was granted orphan designation for the treatment of Dravet syndrome in October 2008. Stiripentol is approved in Europe and other countries including Canada, Japan for the proposed indication under the trade name Diacomit®. The indication, daily recommended dose, contraindications, and warnings are identical across these three regulatory bodies and match what is proposed in this NDA. Diacomit® has also been the drug product used in numerous single patient INDs.

B. Quality Assessment Overview

Stiripentol is a relatively simple molecule manufactured (b) (4) (b) (4) Stiripentol is a racemic mixture of two enantiomers from a structure with one chiral center. Both enantiomers are considered active based on nonclinical results. The typical scale of the commercial drug substance synthesis produces from (b) (4) kilograms of stiripentol.

No related impurities are observed above (b) (4)%, solvent impurities are extremely low, and elemental impurities have been demonstrated to be consistently lower than (b) (4)% the

levels that would lead to exposure at the recommended permitted daily exposure (b) (4) (b) (4) (b) (4). **The drug substance stability studies support a retest period of (b) (4).**

The drug product is an immediate-release capsule formulated with compendial excipients and will be available in two strengths, 250 mg and 500 mg. The formulation and manufacturing process for the 500 mg and 250 mg capsules used in the pivotal clinical study and bioequivalence study is the same as the proposed commercial formulation. The formulations for each strength are dose-proportional. The excipient-drug substance compatibility study results show that the selected excipients do not have any adverse effect on the stability of the capsule product.

The specification, as amended, is considered appropriate to ensure the identity, purity, strength, potency, and quality of the final drug product. No new impurities or degradants were identified for the drug product. The content of elemental impurities in the drug product as well as in the drug substance is less than the (b) (4)% of PDE (limits set for oral form with daily doses of not more than 10 grams per day). The commercial packaging is (b) (4) bottle closed with a (b) (4) cap and is considered suitable based on review of the information submitted.

The primary stability results and annual stability results show that both 250 mg and 500 mg strength capsules are stable at least up to 36 months at 25°C/60% RH storage conditions. No significant changes were observed for test attributes of appearance, disintegration time, specified impurities, unspecified impurities, and microbiological quality for all stability samples at all test time points. The assay values fluctuated within ± 3% with a couple of outliers throughout the stability study periods but all results were within specification. Statistical analysis of the data determined that the observed variance in assay was acceptable based on the standard error. Dissolution results showed that most the samples had (b) (4)% dissolved at the 30 minute-time point. The dissolution results also showed some degree of fluctuation with a downward trend for the 500 mg strength but no trend was observed for the 250 mg strength. All dissolution results remained within the proposed specification of (b) (4)% at 20 minutes. **Based on the stability data reviewed and in accordance with ICH Q1E, we grant the proposed product shelf-life of 36 months when stored at 25°C/60% RH conditions.**

The manufacturing process for Stiripentol capsules includes (b) (4) (b) (4) (b) (4) Following a review of the application and inspectional documents, there are no significant outstanding manufacturing or facility risks that prevent the approval of this application from the facilities perspective. **The manufacturing facilities for NDA 206709 are found to be acceptable.**

The biopharmaceutics assessment focused on the evaluation and acceptability of the data provided to support the; 1) proposed in vitro dissolution method and (2) dissolution acceptance criteria for release and stability. Stiripentol is practically insoluble in water, but is well absorbed following oral administration. Due to the low solubility and presumed high permeability of the drug substance, and the rate limiting step for absorption is presumed to be dissolution.

The clinical studies, STICLO France (study no: BC.299) and STICLO Italy (study no: BC. 385) supporting this submission initiated in 1996 and 1999, respectively, therefore in vitro dissolution data for clinical batches were not available using the current dissolution method. As no changes were reported related to the formulation or manufacturing of the product, the dissolution acceptance criterion recommendation is based on limited dissolution testing data on the drug product registration batches. The final agreed upon in vitro dissolution method and dissolution acceptance criterion (NLT (b)(4)% (Q) of the labeled amount of stiripentol dissolved in 20 minutes) for the drug product are deemed acceptable for quality control.

The claim of categorical exclusion meets the requirements 21 CFR § 25.31(b) and include a statement of no extraordinary circumstances in accordance with 21 CFR 25.31 (d). **The claim of categorical exclusion is acceptable.**

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment (see Attachment I)

ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – NDA 206709 Stiripentol Capsules, 250 mg and 500 mg

From Initial Risk Identification			Review Assessment		
Critical Quality Attributes	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Assay	Formulation Container closure Raw materials Process Parameters Scale/equipment/site	**Low**	Highly stable drug substance; End product testing	**Acceptable**	
Content Uniformity	Formulation Raw materials Process Parameters Scale/equipment/site	**Low**	(b) (4)	**Acceptable**	
Dissolution		**Medium**		**Acceptable**	
Microbial Contamination		**Low**		**Acceptable**	
Physical State		**Medium**		**Acceptable**	
Moisture Content	Formulation Container closure Raw materials Process Parameters Scale/equipment/site	**Low**		**Acceptable**	

40 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

ENVIRONMENTAL ANALYSIS

R Regional Information

Environmental Analysis (Seq. #0012)

The applicant claims a categorical exclusion from the requirements of an environmental impact analysis statement under 21 CFR § 25.31(b).

The applicant also stated that in accordance with 21 CFR 25.31 (d), to the applicant's knowledge, no extraordinary circumstances exist.

Reviewer's Assessment: Adequate.

Thomas Wong

Digitally signed by Thomas Wong
Date: 5/18/2018 06:31:57AM
GUID: 508da7230002a25bbe89865c0c14bc44

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 5/18/2018 09:28:51AM
GUID: 50816dbc000085595ca3284bbca465a8