CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211150Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211150
Review #1

Drug Name/Dosage Form	WAKIX (Pitolisant) Tablets
Strengths	4.45 mg, 17.8 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Bioprojet Pharma

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0001	*6/29/2018*	*All CMC*
0005	*12/14/2018*	*All*
0016	*3/1/2019*	*Facilities*
0025	*4/18/2019*	*DS, DP, Process*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Raymond Frankewich	Suong Tran
Drug Product	Rao Kambhampati	Wendy Wilson-Lee
Process	Nathan Davis	Rapti Madurawe
Facility	Nathan Davis	Rapti Madurawe
Biopharmaceutics	Akm Khairuzzaman	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	David Claffey	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status
(b) (4)	Type II	(b) (4)		Adequate
	Type III			Adequate
	Type IV			Adequate

2. **CONSULTS None.**

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend **approval** from a product quality perspective, based on the approval recommendations from each of the OPQ review teams.

II. Summary of Quality Assessments

A. Product Overview

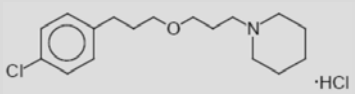
The drug substance, pitolisant hydrochloride is a new molecular entity. It has been marketed in the EU since 2016. Pitolisant hydrochloride is a white or almost white crystalline very water-soluble powder. The drug product is a film-coated round biconvex immediate-release tablet of two strengths, 4.45 mg and 17.8 mg. Tablets used in the Phase III studies were scored or cross-scored but the proposed commercial tablets are not scored but are debossed with "H" or "S" on one side. Dosage strengths are expressed in terms of pitolisant free base. Each tablet contains 5 mg and 20 mg of pitolisant hydrochloride, which is equivalent to 4.45 mg and 17.8 mg of pitolisant free base. The excipients are typical of an immediate release tablet - (b) (4) MCC (b) (4) crospovidone (b) (4) talc (b) (4) magnesium stearate and (b) (4) silicon dioxide (b) (4) . (b) (4) with total tablet weights of 33 and 135 mg and diameters of 3.7 and 7.5 mm, respectively. Tablets are packaged in 30-count 20 mL HDPE bottles and closed with (b) (4) twist-off caps with 2.4 g desiccant.
The drug substance manufacturing process involves several (b) (4) /impurities that have mutagenic structural alerts. However, these are adequately controlled. The drug product is manufactured by (b) (4) Each of the proposed manufacturing and testing sites was found acceptable. Data support the proposed 24-month expiry period at room temperature.

Proposed Indication(s) including Intended Patient Population	1) excessive daytime sleepiness (EDS) in adult patients with narcolepsy; 2) cataplexy in adult patients with narcolepsy.
Duration of Treatment	Chronic
Maximum Daily Dose	35.6 mg

Alternative Methods of Administration	None.

B. Quality Assessment Overview

DRUG SUBSTANCE: The drug substance, pitolisant hydrochloride is a new molecular entity. It is a white or almost white crystalline very water-soluble powder.



One polymorphic form (b) (4) has been found. The manufacturing process involves (b) (4)

(b) (4)

The proposed (b) (4) month retest date was found acceptable. This is supported by stability data collected (b) (4) The manufacturing process for the stability batches differed from the proposed commercial process (b) (4) This approach was found acceptable as the processes at these sites were essentially the same.

Stability data (b) (4) was found adequate to support approval of this NDA.

DRUG PRODUCT: The drug product is a film-coated round biconvex (b) (4) immediate-release tablet of two strengths, 4.45 mg and 17.8 mg. Each tablet contains 5 mg and 20 mg of pitolisant hydrochloride, which is equivalent to 4.45 mg and 17.8 mg of pitolisant free base. The excipients are typical of an immediate release tablet - (b) (4) MCC (b) (4) crospovidone (b) (4) talc (b) (4) magnesium stearate and (b) (4) silicon dioxide (b) (4) total tablet weights of 33 and 135 mg and diameters of 3.7 and 7.5 mm, respectively.

The drug product specification included tests typical of an immediate release tablet. (b) (4) (b) (4) Batch analysis results were provided for developmental and registration lots. All batches complied with the proposed specification. Tablets are packaged in 30-count 20 mL HDPE bottles and closed with (b) (4) twist-off caps with 2.4 g desiccant. Stability data were provided for developmental and registration (b) (4) lots, but since multiple changes were made, only the lots manufactured at the proposed commercial site were considered directly supportive of the proposed expiration period. Several earlier (b) (4) batches contained (b) (4) at some test points but the OPF reviewer stated that they are not a significant safety concern. (b) (4) However, its levels remained within the acceptance criteria, and the applicant provided adequate justification in the 4/18/19 amendment. The pharm/tox reviewer agreed that control of the (b) (4) as a non-mutagenic impurity was acceptable. Real time stability data for tablets manufactured at the proposed commercial site supported an expiry period of 24 months with controlled room temperature storage. Post-approval stability protocol is acceptable.

Biopharmaceutics: The drug product is an immediate release product and the drug substance exhibits a rapid dissolution behavior. The proposed dissolution method and acceptance criteria were found acceptable [USP apparatus II (Paddle) at 75 rpm; 500 mL (4.45 mg strength) and 1000 mL (17.8 mg strength) of 0.1M HCl at 37ºC; Q= (b) (4)% in 30 min] and that no formulation bridging was needed. The attached biopharmaceutics primary review and memoranda document the discussion amongst the biopharmaceutics review team regarding the dissolution testing conditions and acceptance criteria. No formal BCS designation claim was submitted but it appeared that drug belongs to BCS class I.

Manufacturing: (b) (4)

(b) (4)

The application is considered adequate from the Manufacturing perspective.

Facilities: A review of the proposed facilities found the principal drug product manufacturing site (b) (4) has an adequate history as a TCM site and the DFR concurred. The drug substance site has an adequate history as a CSN and was determined to be adequate. After consultation with the drug substance review team, the (b) (4) was classified as CSN and No Evaluation Necessary as the drug substance team determined that inspection was not needed (b) (4) Therefore, the site is treated as a starting material site and not evaluated. (b) (4) is performing labeling/secondary packaging, has approved FACTS profile to perform such activities and is therefore approved. (b) (4) site is performing documentation review only and is profiled as NEC with an NEN outcome. The facility review determined that all the sites were adequate.

Environmental Assessment: The categorical exclusion claim was found acceptable on the basis of EIC (b) (4) ppb and the existence of no extra ordinary circumstances.

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LABELING

NDA 211150

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Wakix (pitolisant)
Dosage form, route of administration	Tablets, oral
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	Yes

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not applicable

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Yes
Strengths: in metric system	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Not usually included in this section
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

4. ***Section 11 Description***

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	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Yes
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not applicable
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Not applicable

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

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

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

The revised Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container (Bottle) Labels***

(b) (4)

2. ***Carton Labels***

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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))	Yes	Yes
Dosage strength	Yes	Yes
Net contents	Yes	Yes
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Yes	Yes
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available		

Reviewer's Assessment of Labels: ***Adequate if the following changes are made on the bottle and carton labels:***

1) **In the name, the established name should be included in a parenthesis.**
2) **Salt-free base equivalency statement should be included**

The labels will comply with all regulatory requirements from a CMC perspective after the above changes are made.

List of Deficiencies:

The following changes are recommended to the proposed bottle and carton labels:

1) ***In the name include "pitolisant" in a parenthesis. For example, Wakix™ (pitolisant) tablets.***

2) ***Include a salt-free base equivalency statement. For example: "Each tablet contains: pitolisant 4.45 (equivalent to 5 mg pitolisant hydrochloride)"***

Overall Assessment and Recommendation: The prescribing information and container and carton labels are acceptable after the recommended changes are made.

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 6/18/19.

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Rao Kambhampati

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Date: 6/18/2019 04:58:55PM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 6/21/2019 10:36:36AM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Wakix® (pitolisant HCl) Tablets
NDA Number	211150
Assessment Cycle Number	0001
Drug Product Name/ Strength	Wakix® (pitolisant HCl) Tablets, 4.45 mg & 17.8 mg
Route of Administration	Oral tablet
Applicant Name	Bioprojet Pharma
Therapeutic Classification/ OND Division	Division of Psychiatry Products
RLD/RS Number	Not Applicable
Proposed Indication	Treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy

Assessment Recommendation[1]: **Adequate**

Assessment Summary:

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the proposed dissolution method and acceptance criteria, and **2)** bridging throughout product development. Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1) ***Dissolution Method and Acceptance Criteria:*** The Applicant's proposed dissolution method [*USP apparatus II (Paddle) at 75 rpm; 500 mL (4.45 mg strength) and 1000 mL (17.8 mg strength) of 0.1M HCl at 37°C*] was validated and is considered acceptable. The proposed acceptance criteria of Q (b) (4)% in 30 min are acceptable for release and on stability.
2) ***Bridging of Formulations:*** The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed.
3) ***Risk Assessment:*** The following table summarize the initial and final risk assessment.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # 0001	Comments
Dissolution	Medium to low	Highly soluble drug, risk is depending on method development and associated PK studies (e.g. bioavailability studies during formulation screening)	Low	Please see overall biopharmaceutics risk assessment under Appendix 1.

[1] Recommendation by the Primary Reviewer. Secondary reviewer, Dr. Angelica Dorantes have different opinion on the method. Please refer to Dr. Angelica's Memo/Secondary review.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001	06/29/2018

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Table 1. Solubility of Pitolisant hydrochloride

Properties	Description		
Solubility (23°C)	Water	< 0.80 mL/g	Very soluble
	Ethanol	< 0.80 mL/g	Very soluble
	Dichloromethane	< 0.82 mL/g	Very soluble
	Cyclohexane	35,000 mL/g	Practically insoluble
Saturation Solubility	Acidic	0.1M HCl	785 mg/mL
	pH 4.5	Phosphate buffer	852 mg/mL
	pH 5.8	Water	981 mg/mL
	Neutral, pH 6.8	Phosphate buffer	1701 mg/mL
	pH 7.5	Phosphate buffer	987 mg/mL
	Alkaline, pH 9.2	Borate buffer	0.3 mg/mL
pH	1% Solution: 5.5 - 6.5		
pKa	9.35 ± 0.02		
Partition Coefficient	0.85 ± 0.18 (Octanol/Water, pH 6.8) $\log P_B = 4.4 \pm 0.3$ (Computer program - Advanced Chemistry Development ACD/Labs Software version 11.02), which reflects the drug substance hydrophobic (lipophilic) character.		

Assessment: Acceptable.

No formal BCS designation claim has been submitted to the FDA. However, the Applicant has submitted a complete report as per the FDA's guidance on BCS class I designation claim. Based on the data it appears that drug belongs to BCS class I.

Solubility: Pitolisant hydrochloride is highly soluble as demonstrated by the solubility data in Table above

Permeability: Pitolisant exhibits high permeability as the A to B Permeability coefficient (Papp) of pitolisant was much greater than that of the co-dosed high permeability internal standard (b) (4)) in a validated Caco-2 cell monolayer (Study # 15BIOPP1GLPS317). The efflux ratios suggest that pitolisant permeates Caco-2 cell monolayers primarily by passive diffusion (refer to Section 2.6.4.3.1.32). In the radiolabeled mass balance study (P15-02), the large majority (approximately 89%) was recovered in the urine and the amount of pitolisant excreted in the feces was low (2.5%), indicating that >90% is absorbed as parent or metabolite (Section 2.7.2.2.1.1.3.3, Table 4)

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Dissolution: The drug product exhibits a rapid dissolution behavior. Please refer to data in later part of the review.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

The dissolution method and dissolution acceptance criteria proposed by the Applicant for the proposed drug product are presented below.

USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Analytical Method	Proposed Acceptance Criteria
II (Paddle)	75	0.1M HCl	500/37 for the 4.45 mg strength 1000/37 for the 17.8 mg strength	HPLC	≥ (b) (4)% Dissolved (Q (b) (4)) in 30 minutes

Applicant also proposed (b) (4)

Dissolution method development[3]: The effect of different dissolution media on the dissolution profile of Pitolisant HCl Tablets was evaluated. (b) (4)

(b) (4)

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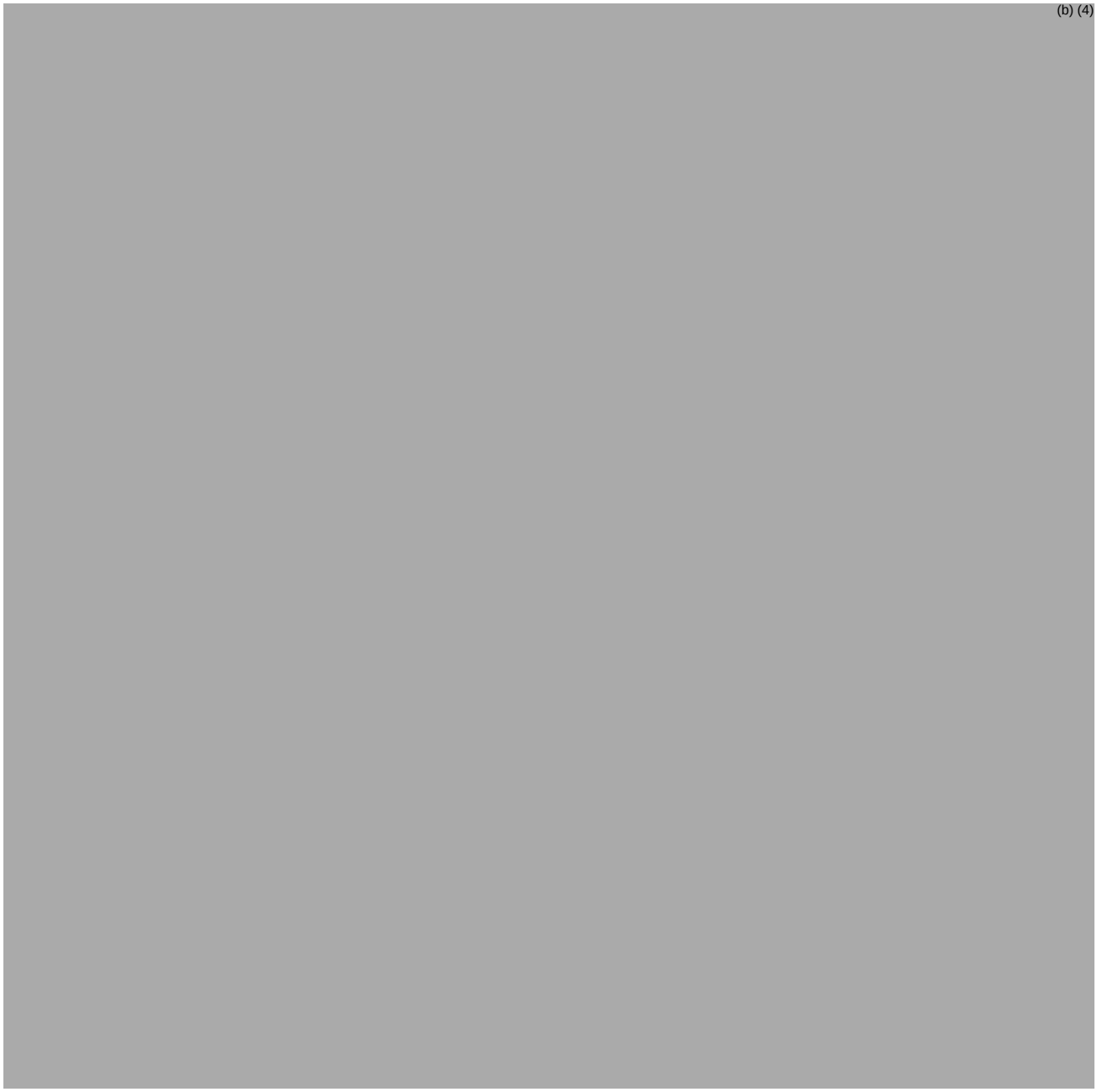

Discriminating Capability of the Dissolution Method: The proposed dissolution method was shown to be sensitive (table 3) to the changes of various manufacturing unit operation (b) (4) . However, the changes differences were only observed at early time points such as 5 min and 10 min. But such differences could be due to high % RSD and therefore, it is not conclusive. Additionally the drug is highly soluble in water, therefore irrespective of manufacturing and formulation change the drug release is meeting the acceptance criteria of Q= (b) (4) % in 30 min.

Table 3. Dissolution Results – Mis-Manufacturing Conditions, 17.8 mg Strength

Time (min)	Reference		(b) (4)					
	%Mean	%RSD	%Mean	%RSD	%Mean	%RSD	%Mean	%RSD
50 rpm								
0	0	0	0	0	0	0	0	0
2	30.9	29.9	14.9	22.3	7.1	28.5	7.2	17.1
5	72.6	23.9	39.2	16.7	9.9	27.9	10.1	23.9
7	86.8	11.9	67.9	13.9	19.2	35.4	20.7	35.0
10	91.6	6.7	80.2	7.1	33.9	41.5	36.5	29.6
15	93.7	5.7	83.4	6.7	56.0	35.2	60.2	20.0
20	94.8	5.2	84.9	6.5	78.0	25.0	77.7	10.9
30	96.0	5.0	86.3	6.2	85.8	19.0	83.4	8.3
75 rpm								
0	0	0	0	0	0	0	0	0
2	40.3	23.8	27.0	10.5	10.6	14.5	12.5	21.7
5	82.5	18.3	65.2	8.0	30.8	10.4	37.8	13.7
7	98.8	10.2	91.2	5.6	49.7	7.2	60.7	11.7
10	105.6	2.3	100.4	1.7	75.1	6.1	99.2	3.1
15	106.1	2.2	100.7	1.9	104.9	1.5	102.0	1.7
20	106.3	2.6	101.1	2.1	105.5	1.8	102.4	1.8
30	106.7	2.6	101.6	1.7	106.0	1.8	102.7	1.7
100 rpm								
0	0	0	0	0	0	0	0	0
2	99.3	3.5	75.7	5.0	38.0	5.7	43.8	3.0
5	100.2	3.2	96.4	2.5	79.2	5.5	92.7	3.0
7	100.2	3.4	100.0	1.8	100.0	1.3	100.2	1.3
10	100.4	3.3	100.5	1.6	103.4	0.8	101.1	1.2
15	100.3	3.1	100.3	1.8	103.0	0.7	100.5	1.3
20	100.3	3.3	100.1	1.6	103.0	0.7	100.5	1.2
30	100.1	3.2	100.8	0.8	103.1	0.9	100.2	1.3

Validation of Analytical Method (HPLC) used in the Dissolution Test: Refer to the Drug Product Review, for the evaluation of the adequacy of the validation of the analytical method.

Table 4 summarizes (by the Applicant) all clinical batches dissolution data to support the proposed dissolution limit.

Table 4: Dissolution Data at Release for All the Clinical Batches

Study Number	Lot Number	Description	Dissolution Conditions	%Dissolved – Mean (Min-Max)			
				5 min	10 min	15 min	30 min
P03-01	CPM5292	Swedish Orange capsule size 0	(b) (4)	-	-	-	100
	CPM5107	Swedish Orange capsule, (b) (4) containing one tablet of pitolisant HCl, 20 mg		-	-	-	97.6
P02-02 P03-01 P03-04	CPM5101	White round tablet		-	-	-	99.1 (b) (4)
P07-03 (Harmony I) P07-07 (Harmony II)	3189401	White round scored film-coated tablet with one break mark on one side		-	-	-	103 (b) (4)
P06-10 (Harps I) P06-11 (Harps II) P09-11 (QT interval) P09-12 (Elderly) P09-13 (Renal impairment) P09-14 (Hepatic impairment) P11-03, Part I (Food effect) P11-03, Part II (CYP3A4 inhibition) P11-03, Part III (CYP2D6 inhibition) P11-10 (CYP3A4 induction) P11-11 (Pediatrics) P14-05 (Thorough QT study)	32077V1-2	White round cross-scored film-coated tablet convex on one side with one break mark on the other side		47.9	98.7	98.8	98.9 (b) (4)
P09-10 (Harmony III) P09-15 (Harmony Ibis)	32571V2-3	White round cross-scored film-coated tablet convex on one side with one break mark on the other side		39.0	93.3	101.6	101.7 (b) (4)
P10-01 (Harmony IV) P09-10 (Harmony III) P09-15 (Harmony Ibis)	33315V3-3	White round cross-scored film-coated tablet convex on one side with one break mark on the other side		53.1	98.1	99.9	100 (b) (4)
P09-10 (Harmony III) P11-05 (Harmony CTP)	33614V4-3	White round cross-scored film-coated tablet convex on one side with one break mark on the other side		67.3	105.5	104.8	104.4 (b) (4)
P10-01 (Harmony IV) P11-05 (Harmony CTP) P14-07 (Drug-drug interaction)	3424601	White round cross-scored film-coated tablet convex on one side with one break mark on the other side	75 rpm	37.5	92.4	102.4	102.9 (b) (4)
P15-15 (Drug interaction) P15-02 (Second mass balance study)	35109V1	White, round, biconvex film-coated tablet of 7.5 mm in diameter debossed with 20 on one side	75 rpm	38.3	97.6	98.7	98.0 (b) (4)

Assessment: *Adequate*

Dissolution method was appropriately developed considering all the parameters such as medium composition, volume, pH, speed. The developed method was found to be suitable for routine quality control. Lower rotation speed (50 rpm) and volume (500 ml for higher strength) showed very high variability at 5 min and 10 min time points due to coning effect in the dissolution bath. Applicant's justification for selecting 75 rpm and 1000 ml for the higher strength is therefore acceptable. Since the drug is highly soluble, the method did not show any significant differences in the dissolution as a function of miss-manufacturing condition. Therefore, dissolution is a low risk attribute which is further supported by the bioequivalence demonstration (study #P030013) of two different formulations: tablet vs capsule manufactured by completely two different methods. (b) (4) .

The observed high variability in dissolution when performed using lower volume (500 ml) and lower speed (50 rpm) does not have any clinical significance. However, if the official dissolution method is performed with such dissolution parameter, there is higher risk of f_2 similarity failure at any post approval changes when a dissolution profile comparison will be made to support post approval change management. Additionally, there will be higher risk of stage 1 and 2 dissolution testing leading to possible batch failure. Such outcome is not desirable for a low risk product like this. Therefore, this reviewer agrees with the proposed dissolution method and limit.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: No IVIVC, IVIVR or modeling has been submitted

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: Not Applicable

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: Not Applicable

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: Not Applicable

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS

Assessment: Not Applicable

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS

Assessment: Not Applicable

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS

Assessment: Not Applicable

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: Not Applicable

B.11 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment: Not Applicable

B.12 BRIDGING OF FORMULATIONS

Table 5. Formulation composition at various stages of clinical development

Clinical Phase	First Lot	Description	Composition	Amount per Unit
Early Phase I	CPM5292	Capsule, 20 mg *Swedish Orange capsule size 0*	(b) (4)	
Phase I	CPM5100	Tablet, **10 mg** *White round, **scored** tablet*		
Phase I	CPM5101	Tablet, **20 mg** *White round tablet*		
Phase II	CPM5852	Tablet, 20 mg *White round tablet*		
Phase III	3189401	Tablet, 20 mg *White round scored **film-coated** tablet*		
	32077V1-2	Tablet, 20 mg *White round **cross**-scored film-coated tablet with a cross mark on one side*	As above	As above
Current	35109V1	Tablet, **17.8 mg** strength *White, round, **biconvex** film-coated tablet of 7.5 mm in diameter **debossed with '20'** on one side*	As above	As above
	7W214	Tablet, 17.8 mg strength *White, round, biconvex film-coated tablet of 7.5 mm in diameter debossed with **'H'** on one side*	As above	As above
	5104	Tablet, **4.45 mg** strength *White, round, biconvex film-coated tablet of 3.7 mm in diameter **debossed with '5'** on one side*	Drug substance Microcrystalline cellulose Magnesium Stearate Talc Crospovidone Colloidal Silicon Dioxide (b) (4) **Film-coated Tablet Mass**	5 mg (b) (4) **33.75 mg**
	7W120	Tablet, 4.45 mg strength *White, round, biconvex film-coated tablet of 3.7 mm in diameter debossed with **'S'** on one side*	As above	As above

Assessment: *Adequate*

The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed.

Additionally, according to table above, different formulations of pitolisant HCl tablets were studied at various stages of drug product development as summarized in table 3. Initially, both a hard-shell gelatin capsule and a tablet (b) (4) were manufactured and compared for their in vivo bioavailability[4]. No significant difference was observed (study #P030013). The (b) (4) tablet remained unchanged throughout the entire clinical development. The only formulation change was the introduction of a film-coating for clinical Phase III studies (b) (4) ; however, such formulation was tested in the clinical trial.

[4] BE study #P030013, protocol # P03-01 / BF 2.649 (Phase I stage)

B. 13 BIOWAIVER REQUEST

Assessment: None

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: None

Post-Approval Commitments

Assessment: None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:

Akm Khairuzzaman, PhD, ***6/17/2019***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

APPENDIX 1

OVERALL BIOPHARMACEUTICS RISK ASSESSMENT: Low

Failure mode/Risk Factor		Likelihood to impact Dissolution	Reviewer's Rational
Raw Material Attributes	API PSD & polymorphism	Low	Highly soluble and highly absorbable drug, supported by detailed pH solubility data and in vitro and in vivo permeability data. Therefore, from biopharmaceutics perspective PSD variation is less likely to impact dissolution. (b) (4) .
	Excipient variability	Low	Effect of formulation variability (tablet vs capsules) showed no difference in bioavailability (Study # P030013). Therefore risk of excipient variability is very low.
Manufacturing process parameters from various unit operation	(b) (4)	Low	Does not have any impact on dissolution
		Low	(b) (4)
	Coating	Low	No impact of coating on dissolution within the range established.
Analytical method sensitivity /discriminating capability	Likelihood to release any defective batch by the developed dissolution method is **very low**		Appropriate statistical sampling plan from every batch is in place. (b) (4) (b) (4)

Akm Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 7/02/2019 01:50:01PM
GUID: 502d1ab500002aef5afaa6f74ddf7e69

Paul Seo

Digitally signed by Paul Seo
Date: 7/03/2019 12:10:18PM
GUID: 508da7290002a6c55567e330dad86ffc

DEPARTMENT OF HEALTH & HUMAN SERVICES | Public Health Service
Food and Drug Administration

OFFICE OF NEW DRUG PRODUCTS
Division of Biopharmaceutics/Secondary Review | **Memorandum**

To: Paul Seo, Ph.D.
Division of Biopharmaceutics Director, ONDP/OPQ/CDER

From: Angelica Dorantes, Ph.D.
Biopharmaceutics Branch Chief
Division of Biopharmaceutics-Branch 1, ONDP/OPQ/CDER

Subject: Biopharmaceutics Secondary Review Memo
NDA 211150 for Wakix (pitolisant HCl) Tablets for Oral Use, 4.45 mg and 17.8 mg

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INTRODUCTION

This Memorandum relates to the adequacy and acceptability of the proposed dissolution method, specifically, with regards to the Applicant's selection of: **1)** Apparatus 2/paddle rotation speed and **2)** volume of dissolution medium, for the dissolution test of the proposed product, Wakix (pitolisant HCl) Tablets, 4.45 mg and 17.8 mg under NDA 211150.

I had evaluated the information/data provided in Dr. Akm Khairuzzaman's draft review document for this NDA submission and held follow-up scientific discussion-meetings with Dr. Khairuzzaman (Primary Reviewer) and the Acting Biopharmaceutics Director, Dr. Okpo Eradiri (for Dr. Paul Seo). In these meetings, the scientific, regulatory, and Division's current practice/recommendations for the dissolution test were discussed by the participants. The primary and secondary reviewers' agreements and different views with respect to the issues related to the Applicant's proposed dissolution method testing conditions and the overall data provided to justify/support such conditions, were also discussed.

BACKGROUND

Pitolisant received an Orphan Drug designation for the treatment of narcolepsy, and FDA granted both Fast Track and Breakthrough Therapy designations. FDA agreed on a Rolling Review of the NDA; therefore, NDA 211150-Rolling Review Part 1 of 4 (SDN-001) including the CMC/dissolution Information was submitted on 6/29/2018, and the final Rolling Review Part 4 of 4 (SDN-005) was submitted on 12/14/2018.

In Original NME-NDA 211150 the Applicant is seeking approval of for Wakix® (pitolisant HCL) tablets, 4.45 mg and 17.8 mg, for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy and for the treatment of cataplexy in adult patients with narcolepsy via a 505(b)(1) submission. The proposed product is supplied as an oral film-coated immediate

release tablet debossed with a unique identifier depending on the strength (expressed as mg of pitolisant).

REVIEW ISSUES:

The current Secondary Review Memo was written because this Secondary Reviewer did not agree with the "Adequate" recommendation given by the Primary Reviewer, Dr. Khairuzzaman, for the proposed dissolution method. Specifically, the Secondary Reviewer did not agree with the following 2 issues:

1. Acceptability of the proposed higher paddle rotation speed of 75 rpm (Apparatus 2) without adequate supportive data justifying the implementation of a higher speed.
2. Acceptability of using different volumes of the dissolution medium for the dissolution testing of the lower and higher proposed strengths without adequate supportive data justifying the implementation of different volumes.

The Applicant states that their decision for selecting a higher paddle rotation speed and different dissolution-medium volumes for the testing of each strength, was because of the high variability at the initial 5-, 10-, and 15-minute sampling time points.

SECONDARY REVIEWER ASSESSMENT:

BCS-Class: Although the Applicant did not request an official BCS-Class 1 designation for their proposed drug product, the solubility (*solubility of pitolisant in 0.1M HCl, phosphate buffer pH 4.5 and buffer pH 6.8 are 785 mg/mL, 852 mg/mL and 1701 mg/mL, respectively*) and permeability (*in vitro Caco 2 Cell study and in vivo-mass balance study*) information provided in the submission indicates that, if requested, this drug product could be officially designed as a BCS-Class 1 drug substance/drug Product.

Dissolution Test: The Applicant's proposed dissolution method and acceptance criterion are described below in Table 1.

TABLE 1. Applicant's Proposed Dissolution Method and Acceptance Criterion

USP Apparatus	Speed (rpm)	Medium/Temp	Volume (ml)	Proposed Acceptance Criterion
II (Paddle)	75	0.1M HCL/ 37°C ± 2°C	4.45 mg strength: 500 ml 17.8 mg strength: 1000ml	Q= (b) (4) in 30 minutes

Selection of Dissolution Medium Volume: The provided mean dissolution profile data for the proposed higher 17,8 mg strength are presented in table 2. It is noted that the paddle rotation speed used to generate these data was not mentioned in the submission. It can be assumed that the speed is 75 rpm.

TABLE 2. Mean Dissolution Data for 17.8 mg Strength (App 2, 0.1M HCl)

Time (min)	500 mL		1000 mL	
	%Dissolved	%RSD	%Dissolved	%RSD
5	45	57.0	49	10.9
10	68	24.2	68	5.7
15	97	6.2	98	1.7
20	102	1.3	102	1.6
30	102	1.7	101	1.6
45	101	1.6	101	1.5
60	102	3.0	100	1.7

Secondary Reviewer Comments and Recommendation:

As expected with immediate release oral dosage forms, the variability at earlier time points is generally high. However, the key question is if the observed variability is relevant or not to control the product's quality and clinical performance. For this drug product the provided data clearly show that the observed high variability in 500 ml dissolution medium at the earlier 5- and 10-minute sampling time points is NOT relevant. Specifically, the above Table 2 shows that at the 15-minute time point, >95% of drug is dissolved with a low 6.2 %RSD for the 500 ml volume. At the 20- and 30-minute time points, the %RSD is very low (1.3-1.7 %RSD) for both the 500 ml and 1000 ml dissolution volumes. Therefore, the Applicant's justification for the selection of different dissolution medium-volumes for the testing of the lower and higher strengths is not supported by the dissolution data at the relevant sampling time points and is not acceptable.

Overall, the provided data show that the Applicant's claim of high variability using 500 ml dissolution medium is not supported. Also, the information suggests that the proposed drug product is a BCS-Class 1 and therefore, as per the recommendations provided in the FDA's 2017-BCS and 2018-Dissolution Guidances, as well as the Division of Biopharmaceutics' current review practices, which are critical to maintain consistency in our assessment and recommendations, the implementation of the same 500 ml dissolution volume for the dissolution testing of both strengths of the proposed product is recommended.

Selection of Paddle Rotation Speed: Using USP Apparatus 2 (paddle) and 1000 ml 0.1 M HCl dissolution medium, the Applicant investigated the paddle rotation speed with the higher 17.8 mg strength of the proposed product. The results are presented in Table 3 below.

TABLE 3. Mean Dissolution Data for 17.8 mg Strength at Different Rotation Speeds

	50 rpm		75 rpm		100 rpm	
Time (min)	%Mean	%RSD	%Mean	%RSD	%Mean	%RSD
0	0	0	0	0	0	0
5	23	**18.0**	46	11.8	49	10.9
10	45	**31.6**	68	6.7	68	5.7
15	74	**14.7**	98	1.8	98	1.7
20	94	5.8	101	1.1	102	1.6
30	100	1.4	101	1.1	101	1.6
45	100	1.7	101	1.1	101	1.5
60	100	1.6	100	1.2	100	1.7

Secondary Reviewer Comments:

1. *The Applicant claims* [redacted] (b) (4) *Therefore, they selected 75 rpm as the paddle rotation speed for the dissolution testing of both strengths of their proposed drug product.*

   It is noted that the proposed sampling time point for the acceptance criterion is 30 min. Therefore, the observed variability at 15 minutes is not clinically relevant. It also noted that variability due to coning can be reduced with the use of USP Apparatus 1 (basket) at 100 rpm; therefore, in general when coning is reported, it is recommended to conduct dissolution testing with Apparatus 1, instead of increasing the paddle rotation speed with Apparatus 2.

   For this drug product, the dissolution data presented in Table 3 clearly show that independently of the paddle rotation speed used in the dissolution testing, almost complete dissolution (>90%) is achieved in 20 minutes with low %RSD values. Also, Table 3 shows that when 50 rpm rotation speed is used, 100% dissolution is achieved with very low variability (1.4 %RSD) at the proposed 30-minute acceptance criterion time point. Therefore, the Applicant's justification for selecting a 75-rpm paddle rotation speed due to high variability is not supported by the dissolution data at the relevant acceptance criterion sampling time point and is NOT acceptable.

2. *Additionally, it is noted that the Applicant provided dissolution data from batches using mis-manufacturing conditions. The mis-manufactured batches were for the 17.8 mg strength and were produced either by* [redacted] (b) (4) *. These mis-manufactured batches were tested for dissolution at various paddle rotation speeds (50, 75 and 100 rpm) in comparison to a batch of the 17.8 mg strength made by the standard process (reference). The dissolution data were generated using 1000 ml 0.1 M dissolution medium. The results are summarized in Table 4 below and presented in Figure 1.*

TABLE 4. Mean Dissolution Data for 17.8 mg Strength at Different Rotation Speeds for Standard Manufacturing (Reference) and Mis-Manufacturing Conditions

Time (min)	Reference		(b) (4)					
	%Mean	%RSD	%Mean	%RSD	%Mean	%RSD	%Mean	%RSD
50 rpm								
0	0	0	0	0	0	0	0	0
2	30.9	29.9	14.9	22.3	7.1	28.5	7.2	17.1
5	72.6	23.9	39.2	16.7	9.9	27.9	10.1	23.9
7	86.8	11.9	67.9	13.9	19.2	35.4	20.7	35.0
10	91.6	6.7	80.2	7.1	33.9	41.5	36.5	29.6
15	93.7	5.7	83.4	6.7	56.0	35.2	60.2	20.0
20	94.8	5.2	84.9	6.5	78.0	25.0	77.7	10.9
30	96.0	5.0	86.3	6.2	85.8	19.0	83.4	8.3
75 rpm								
0	0	0	0	0	0	0	0	0
2	40.3	23.8	27.0	10.5	10.6	14.5	12.5	21.7
5	82.5	18.3	65.2	8.0	30.8	10.4	37.8	13.7
7	98.8	10.2	91.2	5.6	49.7	7.2	60.7	11.7
10	105.6	2.3	100.4	1.7	75.1	6.1	99.2	3.1
15	106.1	2.2	100.7	1.9	104.9	1.5	102.0	1.7
20	106.3	2.6	101.1	2.1	105.5	1.8	102.4	1.8
30	106.7	2.6	101.6	1.7	106.0	1.8	102.7	1.7
100 rpm								
0	0	0	0	0	0	0	0	0
2	99.3	3.5	75.7	5.0	38.0	5.7	43.8	3.0
5	100.2	3.2	96.4	2.5	79.2	5.5	92.7	3.0
7	100.2	3.4	100.0	1.8	100.0	1.3	100.2	1.3
10	100.4	3.3	100.5	1.6	103.4	0.8	101.1	1.2
15	100.3	3.1	100.3	1.8	103.0	0.7	100.5	1.3
20	100.3	3.3	100.1	1.6	103.0	0.7	100.5	1.2
30	100.1	3.2	100.8	0.8	103.1	0.9	100.2	1.3

Figure 1. Mean Dissolution Profiles for 17.8 mg Strength at Different Paddle Rotation Speeds for Standard Manufacturing (Reference) and Mis-Manufacturing Conditions

The dissolution data collected from the mis-manufactured batches clearly show that the selected 75 rpm paddle speed does not have the ability to discriminate/reject mis-manufactured batches at the 15-, 20-, and 30-minute sampling time points. It is noted that the dissolution data provided in Table 4 using 50 rpm rotation speed at the 10- and 15-minutes sampling timepoints show >90% drug dissolved and very low variability. These data further confirm that 50 rpm paddle rotation speed is the most appropriate speed for the dissolution testing of both strengths of the proposed product.

3. (b) (4)

However, the above dissolution data indicate that the selection of 30 minutes as the dissolution acceptance criterion timepoint is less than optimal for the proposed product because all mis-manufactured batches will easily pass this time point when a 75 rpm is used. Based on these data, 15 minutes is the appropriate sampling timepoint for the dissolution acceptance criterion of the proposed drug product, when 50 rpm paddle rotation speed is used.

CONCLUSIONS:

I have a thorough understanding of the dissolution data available for Pitolisant Tablets, as well as strong knowledge of the FDA's regulatory policy and Guidances, and the Division of Biopharmaceutics' internal regulatory policy, general recommendations, and processes that should be followed to achieve consistency and quality in the regulatory reviews among primary and secondary reviewers in regard to the assessment of the dissolution information/data provided in submissions, as well as the regulatory recommendations given to the Sponsors/Applicants on the development and validation of optimal dissolution methods and setting of adequate dissolution acceptance criteria/criteria for the proposed drug products.

This Secondary Reviewer does not agree with the "ADEQUATE" recommendation given by the Primary Reviewer, Dr. Akm Khairuzzaman, for the dissolution method with respect to the Applicant's proposed **1)** paddle rotation speed of 75 rpm, and **2)** use of a different higher 1000 ml dissolution medium volume for the 17.8 mg strength. The overall dissolution data clearly show that the Applicant's justifications for the selection of these dissolution testing conditions are no supported by the provided data, and they are NOT acceptable. Therefore, the Applicant will be requested to revise their product's dissolution method and implement a paddle rotation speed of 50 rpm and a volume of 500 ml for both strengths of their proposed product.

With respect to the proposed dissolution acceptance criterion of Q=(b) (4)% at 30 minutes, the provided data indicate that setting a tighter Q(b) (4)% at 15 minutes acceptance criterion would be more appropriate for the proposed product. However, taking into account that the provided information seems to indicate that proposed product is a BCS-Class 1 drug product with a highly soluble/highly permeable drug substance and the overall risk on the product's quality and clinical performance in selecting 30 minutes instead of 15 minutes is very low, I am willing to compromise and accept the proposed dissolution acceptance criterion of Q=(b) (4) at 30 minutes for the dissolution test of the proposed drug product, provided the recommended changes to the dissolution method are implemented.

RECOMMENDATION:

Based on the review of the overall dissolution information/data, the Applicant's provided justifications for the selection of a higher 75 rpm paddle rotation speed and different 1000 ml medium-volume for the 17.8 mg strength are not acceptable. It is recommended that the following dissolution method and acceptance criterion be implemented for the dissolution test of the proposed drug product, Wakix® (pitolisant HCl) Tablets, 4.45 mg and 17.8 mg at release and on stability.

USP Apparatus	Speed (rpm)	Volume/Medium/Temp	Proposed Acceptance Criterion
II (Paddle)	50	500 ml of 0.1M HCL @ 37°C ± 2°C	Q=(b) (4)% in 30 minutes

Secondary Reviewer Name and Review Date:

Angelica Dorantes, Ph.D. June 28, 2019
Biopharmaceutics Branch Chief
Office of New Drug Products, OPQ, CDER

Angelica Dorantes

Digitally signed by Angelica Dorantes
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DEPARTMENT OF HEALTH & HUMAN SERVICES | Public Health Service
Food and Drug Administration

OFFICE OF NEW DRUG PRODUCTS
Division of Biopharmaceutics/Secondary Review

Memorandum

To: Memorandum to Administrative File

CC: Giuseppe Randazzo, MS, ONDP Acting Director
Tom Oliver, Ph.D., DNDPI Division Director

From: Paul Seo, Ph.D.
Director
Division of Biopharmaceutics, ONDP/OPQ/CDER

Subject: Biopharmaceutics Tertiary Review Memo
NDA 211150 for Wakix (pitolisant HCl) Tablets for Oral Use, 4.45 mg and 17.8 mg
Bioprojet Pharma

INTRODUCTION

This Memorandum relates to the adequacy and acceptability of the proposed dissolution method, specifically, with regards to the Applicant's selection of: **1)** Apparatus 2/paddle rotation speed and **2)** volume of dissolution medium, for the dissolution test of the proposed product, Wakix (pitolisant HCl) Tablets, 4.45 mg and 17.8 mg under NDA 211150, and provides recommendations of the next highest management official as outlined in CDER MAPP 4151.1 Rev. 1 (Scientific / Regulatory Dispute Resolution for Individuals Within a Management Chain)

Based on the holistic assessment of application data, primary draft review document by Dr. Akm Khairuzzaman, secondary review memo by Dr. Angelica Dorantes, related clarifying discussions (as referenced in Dr. Dorantes' memo and this memo), and considering the unmet medical need of this drug product (as evidenced by both the Orphan Drug and Breakthrough Therapy designations) for this NDA submission, the proposed dissolution method and acceptance criteria outlined in Dr. Khairuzzaman's draft review are adequately justified from a regulatory and scientific perspective.

BACKGROUND

Pitolisant received an Orphan Drug designation for the treatment of narcolepsy, and FDA granted both Fast Track and Breakthrough Therapy designations. FDA agreed on a Rolling Review of the NDA; therefore, NDA 211150-Rolling Review Part 1 of 4 (SDN-001) including the CMC/dissolution Information was submitted on 6/29/2018, and the final Rolling Review Part 4 of 4 (SDN-005) was submitted on 12/14/2018.

In Original NME-NDA 211150 the Applicant is seeking approval of for Wakix® (pitolisant HCL) tablets, 4.45 mg and 17.8 mg, for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy and for the treatment of cataplexy in adult patients with narcolepsy via a 505(b)(1) submission. The proposed product is supplied as an oral film-coated immediate release tablet debossed with a unique identifier depending on the strength (expressed as mg of pitolisant).

REVIEW ISSUES:

A Secondary Review Memo was written and submitted to the Director (via email on July 1, 2019) because the Secondary Reviewer, Dr. Angelica Dorantes, did not agree with the "Adequate" recommendation given by the Primary Reviewer, Dr. Akm Khairuzzaman, for the proposed dissolution method. Specifically, Dr. Dorantes and Dr. Khairuzzaman could not reach alignment as defined in CDER MAPP 4151.1 Rev. 1, with regard to the following 2 issues:

1. Acceptability of the proposed higher paddle rotation speed of 75 rpm (Apparatus 2) without adequate supportive data justifying the implementation of a higher speed.
2. Acceptability of using different volumes of the dissolution medium for the dissolution testing of the lower and higher proposed strengths without adequate supportive data justifying the implementation of different volumes.

It should be noted that the Applicant attempts to justify selection of a higher paddle rotation speed and different dissolution-medium volumes for the testing of each strength, attributing the need for increased dissolution speed and higher media volume to the fact that there was observed high variability at the initial 5-, 10-, and 15-minute sampling time points. It should also be noted that the applicant attempted multiple variations in dissolution testing and provided that data to help justify the proposed dissolution medium volume.

SECONDARY REVIEWER ASSESSMENT:

BCS-Class: Although the Applicant did not request an official BCS-Class 1 designation for their proposed drug product, the solubility (*solubility of pitolisant in 0.1M HCl, phosphate buffer pH 4.5 and buffer pH 6.8 are 785 mg/mL, 852 mg/mL and 1701 mg/mL, respectively*) and permeability (*in vitro Caco 2 Cell study and in vivo-mass balance study*) information provided in the submission indicates that, if requested, this drug product could potentially be designated as a BCS-Class 1 drug substance/drug Product.

Dissolution Test: The Applicant's proposed dissolution method and acceptance criterion are described below in Table 1.

TABLE 1. Applicant's Proposed Dissolution Method and Acceptance Criterion

USP Apparatus	Speed (rpm)	Medium/Temp	Volume (ml)	Proposed Acceptance Criterion
II (Paddle)	75	0.1M HCL/ 37°C ± 2°C	4.45 mg strength: 500 ml 17.8 mg strength: 1000ml	Q= (b) (4) % in 30 minutes

Selection of Dissolution Medium Volume: The provided mean dissolution profile data for the proposed higher 17.8 mg strength are presented in table 2. It is noted that the paddle rotation

speed used to generate these data was not mentioned in the submission. It can be assumed that the speed is 75 rpm.

TABLE 2. Mean Dissolution Data for 17.8 mg Strength (App 2, 0.1M HCl)

	500 mL		1000 mL	
Time (min)	%Dissolved	%RSD	%Dissolved	%RSD
5	45	57.0	49	10.9
10	68	24.2	68	5.7
15	97	6.2	98	1.7
20	102	1.3	102	1.6
30	102	1.7	101	1.6
45	101	1.6	101	1.5
60	102	3.0	100	1.7

Secondary Reviewer Comments and Recommendation:

As expected with immediate release oral dosage forms, the variability at earlier time points is generally high. However, the key question is if the observed variability is relevant or not to control the product's quality and clinical performance. For this drug product the provided data clearly show that the observed high variability in 500 ml dissolution medium at the earlier 5- and 10-minute sampling time points is NOT relevant. Specifically, the above Table 2 shows that at the 15-minute time point, >95% of drug is dissolved with a low 6.2 %RSD for the 500 ml volume. At the 20- and 30-minute time points, the %RSD is very low (1.3-1.7 %RSD) for both the 500 ml and 1000 ml dissolution volumes. Therefore, the Applicant's justification for the selection of different dissolution medium-volumes for the testing of the lower and higher strengths is not supported by the dissolution data at the relevant sampling time points and is not acceptable.

Overall, the provided data show that the Applicant's claim of high variability using 500 ml dissolution medium is not supported. Also, the information suggests that the proposed drug product is a BCS-Class 1 and therefore, as per the recommendations provided in the FDA's 2017-BCS and 2018-Dissolution Guidances, as well as the Division of Biopharmaceutics' current review practices, which are critical to maintain consistency in our assessment and recommendations, the implementation of the same 500 ml dissolution volume for the dissolution testing of both strengths of the proposed product is recommended.

Tertiary Reviewer Comments and Recommendation:

Although Dr. Dorantes' observations and inferences are reasonable, as stated in her response above, the early time point variability is not relevant in the justification of use of 1000mL media volume. However, the applicant put forth due diligence to address this justification and ultimately, the use of 1000 mL as QC media poses little risk to the patient due to the low risk nature of the drug product/substance (i.e. potential BCS 1 candidate). As per a discussion with both Dr. Khairuzzaman and Dr. Dorantes on 7/2/2019, the variability is primarily a concern when accounting for future post approval manufacturing changes where the variability could impact

comparability failures and result in a potential lack of product on market. When considering the patient benefit of the drug product and inherent low risk of using the higher volume as QC media, as well as the previously discussed data, use of 1000 mL should be considered acceptable.

Selection of Paddle Rotation Speed: Using USP Apparatus 2 (paddle) and 1000 ml 0.1 M HCl dissolution medium, the Applicant investigated the paddle rotation speed with the higher 17.8 mg strength of the proposed product. The results are presented in Table 3 below.

TABLE 3. Mean Dissolution Data for 17.8 mg Strength at Different Rotation Speeds

	50 rpm		75 rpm		100 rpm	
Time (min)	%Mean	%RSD	%Mean	%RSD	%Mean	%RSD
0	0	0	0	0	0	0
5	23	**18.0**	46	11.8	49	10.9
10	45	**31.6**	68	6.7	68	5.7
15	74	**14.7**	98	1.8	98	1.7
20	94	5.8	101	1.1	102	1.6
30	100	1.4	101	1.1	101	1.6
45	100	1.7	101	1.1	101	1.5
60	100	1.6	100	1.2	100	1.7

Secondary Reviewer Comments:

1. *The Applicant claims that Q=* (b) (4) *Therefore, they selected 75 rpm as the paddle rotation speed for the dissolution testing of both strengths of their proposed drug product.*

   It is noted that the proposed sampling time point for the acceptance criterion is 30 min. Therefore, the observed variability at 15 minutes is not clinically relevant. It also noted that variability due to coning can be reduced with the use of USP Apparatus 1 (basket) at 100 rpm; therefore, in general when coning is reported, it is recommended to conduct dissolution testing with Apparatus 1, instead of increasing the paddle rotation speed with Apparatus 2.

   For this drug product, the dissolution data presented in Table 3 clearly show that independently of the paddle rotation speed used in the dissolution testing, almost complete dissolution (>90%) is achieved in 20 minutes with low %RSD values. Also, Table 3 shows that when 50 rpm rotation speed is used, 100% dissolution is achieved with very low variability (1.4 %RSD) at the proposed 30-minute acceptance criterion time point. Therefore, the Applicant's justification for selecting a 75-rpm paddle rotation speed due to high variability is not supported by the dissolution data at the relevant acceptance criterion sampling time point and is NOT acceptable.

2. *Additionally, it is noted that the Applicant provided dissolution data from batches using mis-manufacturing conditions. The mis-manufactured batches were for the 17.8 mg strength and were produced either by* (b) (4) *These mis-manufactured batches were tested for dissolution at various paddle rotation speeds (50, 75 and 100 rpm) in comparison to a batch of the 17.8 mg strength made by the standard process (reference). The dissolution data were generated using 1000 ml 0.1 M dissolution medium. The results are summarized in Table 4 below and presented in Figure 1.*

TABLE 4. Mean Dissolution Data for 17.8 mg Strength at Different Rotation Speeds for Standard Manufacturing (Reference) and Mis-Manufacturing Conditions

Time (min)	Reference		(b) (4)					
	%Mean	%RSD	%Mean	%RSD	%Mean	%RSD	%Mean	%RSD
50 rpm								
0	0	0	0	0	0	0	0	0
2	30.9	29.9	14.9	22.3	7.1	28.5	7.2	17.1
5	72.6	23.9	39.2	16.7	9.9	27.9	10.1	23.9
7	86.8	11.9	67.9	13.9	19.2	35.4	20.7	35.0
10	91.6	6.7	80.2	7.1	33.9	41.5	36.5	29.6
15	93.7	5.7	83.4	6.7	56.0	35.2	60.2	20.0
20	94.8	5.2	84.9	6.5	78.0	25.0	77.7	10.9
30	96.0	5.0	86.3	6.2	85.8	19.0	83.4	8.3
75 rpm								
0	0	0	0	0	0	0	0	0
2	40.3	23.8	27.0	10.5	10.6	14.5	12.5	21.7
5	82.5	18.3	65.2	8.0	30.8	10.4	37.8	13.7
7	98.8	10.2	91.2	5.6	49.7	7.2	60.7	11.7
10	105.6	2.3	100.4	1.7	75.1	6.1	99.2	3.1
15	106.1	2.2	100.7	1.9	104.9	1.5	102.0	1.7
20	106.3	2.6	101.1	2.1	105.5	1.8	102.4	1.8
30	106.7	2.6	101.6	1.7	106.0	1.8	102.7	1.7
100 rpm								
0	0	0	0	0	0	0	0	0
2	99.3	3.5	75.7	5.0	38.0	5.7	43.8	3.0
5	100.2	3.2	96.4	2.5	79.2	5.5	92.7	3.0
7	100.2	3.4	100.0	1.8	100.0	1.3	100.2	1.3
10	100.4	3.3	100.5	1.6	103.4	0.8	101.1	1.2
15	100.3	3.1	100.3	1.8	103.0	0.7	100.5	1.3
20	100.3	3.3	100.1	1.6	103.0	0.7	100.5	1.2
30	100.1	3.2	100.8	0.8	103.1	0.9	100.2	1.3

Figure 1. Mean Dissolution Profiles for 17.8 mg Strength at Different Paddle Rotation Speeds for Standard Manufacturing (Reference) and Mis-Manufacturing Conditions

The dissolution data collected from the mis-manufactured batches clearly show that the selected 75 rpm paddle speed does not have the ability to discriminate/reject mis-manufactured batches at the 15-, 20-, and 30-minute sampling time points. It is noted that the dissolution data provided in Table 4 using 50 rpm rotation speed at the 10- and 15-minutes sampling timepoints show >90% drug dissolved and very low variability. These data further confirm that 50 rpm paddle rotation speed is the most appropriate speed for the dissolution testing of both strengths of the proposed product.

3. (b) (4)

However, the above dissolution data indicate that the selection of 30 minutes as the dissolution acceptance criterion timepoint is less than optimal for the proposed product because all mis-manufactured batches will easily pass this time point when a 75 rpm is used. Based on these data, 15 minutes is the appropriate sampling timepoint for the dissolution acceptance criterion of the proposed drug product, when 50 rpm paddle rotation speed is used.

Tertiary Reviewer Comments:

The intention of the 2018 dissolution guidance is to ensure all drug substance is presented to the GI tract for optimal absorption time and let biological physiology control absorption mechanics

by way of ensuring enough drug substance is solubilized and available for absorption (which would then be primarily controlled by gastric emptying time). This is evident from the fact there is a single generally recommended dissolution acceptance criterion irrespective of product formulation. In this case, discriminating ability of the dissolution method becomes not only irrelevant, but the ability to detect the "mis-manufactured" batches is also less of a concern as there are other CMC controls/specifications in place to detect gross/negligent changes (b) (4) *as studied in the applicant's dissolution method development. Overall, the risk to the patient remains low when increasing the paddle speed from 50 to 75. Furthermore, justification (data) is provided by the applicant and additional data driven justification would prove difficult for a high solubility compound.*

CONCLUSIONS:

Although both the primary and secondary reviewers were unable to reach alignment, both their scientific judgment are sound and reasonable. However, in this assessment for Wakix Tablets, the dispute revolves more around regulatory discretion with regards to justification of various dissolution methodologies. Based on the holistic assessment of all data and viewpoints, the unmet medical need for this drug product, and the high benefit/low risk to the patient, the higher management official concurs with Dr. Khairuzzaman's assessment of using the Applicant's proposed **1)** paddle rotation speed of 75 rpm, and **2)** use of a different higher 1000 ml dissolution medium volume for the 17.8 mg strength.

With respect to the proposed dissolution acceptance criterion of Q= (b) (4) at 30 minutes, the acceptance criterion follows current regulatory guidance and internal practices and therefore is considered acceptable. More specifically, a Q= (b) (4)% at 30 minutes would ensure a gastric emptying controlled absorption and minimize formulation/process risk.

RECOMMENDATION:

Based on the review of the overall dissolution information/data, the Applicant's provided justifications for the selection of a higher 75 rpm paddle rotation speed and different 1000 ml medium-volume for the 17.8 mg strength are acceptable. It is recommended that the following dissolution method and acceptance criterion be implemented for the dissolution test of the proposed drug product, Wakix® (pitolisant HCl) Tablets, 4.45 mg and 17.8 mg at release and on stability.

USP Apparatus	Speed (rpm)	Medium/Temp	Volume (ml)	Proposed Acceptance Criterion
II (Paddle)	75	0.1M HCL/ 37°C ± 2°C	4.45 mg strength: 500 ml 17.8 mg strength: 1000ml	Q= (b) (4)% in 30 minutes

It should be noted that editorial/grammatical edits made by Dr. Dorantes should still be implemented in the final draft review document.

Tertiary Reviewer Name and Memo Date:

Paul Seo, Ph.D. July 2, 2019
Director
Division of Biopharmaceutics, Office of New Drug Products, OPQ, CDER

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