CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211230Orig1s000
211230Orig2s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 211230
Review #01

Drug Name/Dosage Form	Solriamfetol Tablets
Strength	75 mg, 150 mg (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Jazz Pharmaceuticals Ireland Limited
US agent, if applicable	Jazz Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	20-DEC-2017	*Amendment*	20-JUN-2018
Amendment	13-APR-2018	*Amendment*	05-JUL-2018
Amendment	23-MAY-2018	*Amendment*	19-JUL-2018

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Gene Holbert	Charles Jewell	ONDP
Drug Product	Stephanie Emory	Wendy Wilson-Lee	ONDP
Environmental			
Labeling			
Process	Ziyang Su	Derek Smith	OPF
Microbiology			
Facility	Ziyang Su	Ruth Moore	OPF
Biopharmaceutics	Akm Khairuzzaman	Angelica Dorantes	ONDP
Regulatory Business Process Manager	Teshara Bouie		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	III		(b) (4)	Not reviewed	-	Sufficient information in NDA
	III			Not reviewed	-	Sufficient information in NDA
	III			Not reviewed	-	Sufficient information in NDA
	III			Not reviewed	-	Sufficient information in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		(b) (4)
IND	107203	JZP-110 for treatment of narcolepsy
IND	122590	JZP-110 for treatment of obstructive sleep apnea

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 211230 Solriamfetol Tablets, 75, 150 (b) (4) mg.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Treatment to improve wakefulness and reduce daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea***
Duration of Treatment	***Chronic***
Maximum Daily Dose	(b) (4) ***mg***
Alternative Methods of Administration	***Splitting of the 75 mg tablet is allowed to accommodate a 37.5 mg dose if needed. No other tablet strengths are labeled for splitting***

Jazz Pharmaceutical is seeking approval of solriamfetol tablets for improvement in wakefulness and reduction in excessive sleepiness in adult patients with narcolepsy. Solriamfetol is a new molecular entity (NME) that was granted orphan designation (August 2012). There are currently five FDA-approved treatments for narcolepsy. A public meeting was held in September 2013 as part of the FDA's Patient-Focused Drug Development Initiative with a specific focus on narcolepsy. The most frequently reported patient reported symptom during the meeting was excessive daytime sleepiness.[1] FDA granted BCS Class 1 designation for solriamfetol (February 2017).

OPQ provided guidance on the CMC development program via a CMC-only Type C Written Response meeting (March 2015) and a CMC-only pNDA meeting (August 2017). Topics discussed during these meetings included regulatory starting materials, biowaiver request, drug product stability data package, process validation proposal, requirements for executed batch records, and the dissolution data package.

The drug product is formulated as a rapidly dissolving, immediate-release, scored, film-coated tablet (b) (4). The 75 mg is the only strength intended for splitting to (b) (4) (b) (4) (b) (4) The initial risk assessment identified moderate risk attributes related to tablet splitting such as content

[1] **The Voice of the Patient: Narcolepsy**, FDA Public Meeting Summary Report, June 2014, https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM402907.pdf.

uniformity, friability, in-use stability, loss of mass, and dissolution for the split tablets. Assessment of these attributes, along with the tablet breakability studies, was critical to the evaluation and determination of the overall control strategy for this product. Other key review issues included solid state of the active in the drug product along with the characterization and proposed control strategy for the NME drug substance.

B. Quality Assessment Overview

Solriamfetol (JZP-110) drug substance is prepared (b) (4) (b) (4) (b) (4) The drug substance is a white to off-white solid which is freely soluble in water. The proposed manufacturing process consistently produces (b) (4) crystalline form of the drug substance. No polymorphs have been observed; however, a (b) (4) has been identified which may be distinguished from the (b) (4) form by XRPD and its melting point. The particle size distribution is not critical for drug substance solubility and has been demonstrated to have no impact on the performance of the drug product.

The specification for JZP-110 includes tests and acceptance criteria for appearance, identification (IR, HPLC and presence of (b) (4)), assay (HPLC), related impurities (HPLC), chiral purity [(S)-JZP-110 by HPLC], water content, related solvents, residue on ignition, and microbiological quality (TAMC and TYMC). None of the specified impurities exceeded the qualification limit ((b) (4)%) in any of the batches used in Phase 3 clinical studies. Levels of the potential genotoxic impurities (b) (4) did not exceed (b) (4) (the LOD) in any of the 12 batches studied. Other potential genotoxic impurities were shown to be purged to below (b) (4) in analysis of the DS batches and from spiking experiments. Analytical methods have been validated and deemed adequate for their intended use. No significant changes or trends were observed in appearance, assay, related impurities, chiral purity, water content and or microbial contamination over (b) (4) months storage under long-term storage conditions or at six months storage under the accelerated storage condition. All results comply with the proposed specification. **A retest period of (b) (4) months is granted for the drug substance.** No special storage conditions are necessary.

The product is an immediate release, film-coated tablet (b) (4): 75 mg, 150 mg, (b) (4) The 75 mg tablet has a functional score-line allowing the tablet to be split in half to achieve a 37.5 mg dose (b) (4) (b) (4) (b) (4) Tablets are packaged in 30- and 100-count HDPE bottles for prescription use (b) (4) The application included 18 months' long-term stability data showing no reported impurities and no changes in any parameter. **Based on the provided stability data and in accordance with ICH Q1E, we grant a 30-month shelf-life for the drug product when stored at USP Controlled Room Temperature.** Tablet breakability and split tablet stability were demonstrated per FDA's guidance on scored tablets, as well as tablet breakability on stability. An elemental impurities risk assessment was performed per ICH Q3D. No elemental impurities were detected above the established PDEs, and no additional controls are proposed.

Based on modeled and available data, a low environmental impact risk is expected due to approval of this application. Extraordinary circumstances are not indicated. **The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance is acceptable.**

Solriamfetol is a BCS Class 1 compound. The proposed formulation has (b) (4)% w/w drug load. Unit operations involved in manufacturing the tablet include (b) (4) (b) (4) (b) (4) Multiple commercial-scale batches have been manufactured at the commercial site. Microbial testing has been included in DP release and stability specification.

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent the approval of this application. Based on the firm's inspectional history, EIR reviews and DO recommendation, **the manufacturing facilities listed for NDA 211230 are found to be acceptable.** No inspections were scheduled.

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, 2) Biowaiver request, and 3) bridging of Phase III to Commercial product, and bridging of current to new manufacturing site. Based on the review of the provided information/data, the proposed dissolution method [USP apparatus I (Basket) at 100 rpm; 900 mL of 0.1N HCl at 37°C] and acceptance criterion of Q (b) (4)% at 15 min is acceptable for release and on stability. The proposed drug product was officially designated by FDA as a BCS-Class I, on Sep 26, 2016. The application included a BCS-Class 1 based biowaiver request supporting the bridge between the Phase II to Phase III formulation and dosage form changes (capsules to tablets). **The provided data demonstrated similarity between dissolution profiles of the capsules and tablets; therefore, the Applicant's request is acceptable and the biowaiver is GRANTED.**

The Phase III film-coated tablets were over-encapsulated and back-filled for blinding purposes. The provided dissolution data demonstrated similar dissolution for the un- and over encapsulated Phase III tablets. The bridging is adequate. The formulation of the Phase III film-coated tablets is the same as the to-be-marketed tablets, except for the coating color. The film coating component, (b) (4), used in the Phase III tablets was changed to (b) (4) for the to-be-marketed tablets. The provided dissolution profile comparison data fully support the bridging between Phase III and to-be-marketed drug products. The bridging is acceptable.

The drug product supplies used in the clinical Phase III studies were manufactured at (b) (4) The commercial drug product will be manufactured at (b) (4) There are no significant changes to the overall manufacturing processes used for the clinical supply to those intended for commercial supply. Both manufacturing sites operate to similar procedures and have comparable environmental controls. The provided dissolution profile comparison data support the bridging between the clinical and commercial products manufactured at (b) (4), respectively. Therefore, the proposed site at (b) (4) for the manufacturing of the commercial drug product is acceptable

C. Special Product Quality Labeling Recommendations

None.

D. Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute (CQA)	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Assay	Formulation Container Closure Raw Materials Process/Scale/Equipment Site	**Low**		**Acceptable**	
Solid State		**Medium**	No polymorphs identified; Crystallinity confirmed by XRPD	**Acceptable**	
Content Uniformity	Formulation Raw Materials Process/Scale/Equipment Site	**Medium**	Data demonstrate adequate control of blend uniformity; End product testing	**Acceptable**	
Dissolution	Formulation Container Closure Raw Materials Process/Scale/Equipment Site	**Low**		**Acceptable**	
Microbial Limits		**Low**		**Acceptable**	
Content Uniformity (Split Tablet)	Formulation Process/Scale/Equipment Site	**High**	Development studies demonstrate acceptable tablet breakability	**Acceptable**	
Friability (Split Tablet)	Formulation Container Closure Process/Scale/Equipment Site	**Medium**	Development studies demonstrate acceptable tablet breakability	**Acceptable**	
Dissolution (Split Tablet)		**Medium**		**Acceptable**	
Loss of Mass (Split Tablet)		**Medium**		**Acceptable**	
In-Use Stability (Split Tablet)		**Medium**		**Acceptable**	

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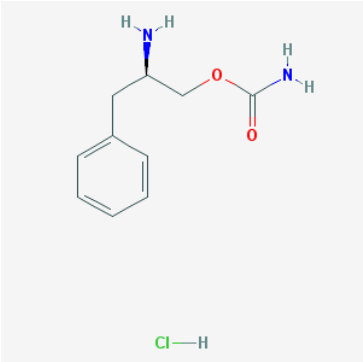
ENVIRONMENTAL

R Regional Information

Environmental Analysis

Application: NDA 211230
API: Drug molecule: solriamfetol
CASRN: 178429-65-7

Canonical Smiles (Pubchem): C1=CC=C(C=C1)CC(COC(=O)N)N



Indication: indicated to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA).

MOA: Solriamfetol is a derivative of the amino acid phenylalanine and is a non-amphetamine wake-promoter. The mechanism(s) by which solriamfetol exerts its wake-promoting effects in humans are presumed to be through its activity as a selective dopamine and norepinephrine reuptake inhibitor (DNRI)

The drug sponsor has submitted a claim of categorical exclusion with supporting information under 21 CFR 25.31(b) including a statement that to "...Jazz Pharmaceuticals' knowledge, no extraordinary circumstances exist including developmental, reproductive, or endocrine effects." Supporting information includes physical and chemical characterization. No data are available for environmental depletion mechanisms or environmental effects.

The drug sponsor correctly estimated an expected introduction concentration (EIC) of (b) (4) ppb (ug/L) for solriamfetol. The EIC is based on the maximum yearly usage during the next five years which equals (b) (4) kg. We determined the "effect ratio", using a fish plasma model (FPM; see references), to be above 1,000, indicating that it is unlikely that solriamfetol will cause effects in fish at the estimated environmental concentration. Additionally, using CERAPP OCHEM and Unistra models, and COMPARA OCHEM

and Unistra models the molecule is not predicted to bind to the estrogen receptor or the androgen receptor.

For aquatic toxicity, a read-across approach was used with the top 3 analogues identified from the Danish QSAR database. The following results were determined:

> Fathead minnow 96h LC_{50} is predicted to be above (b) (4) mg/mL for all analogues.
> Daphnia magna 48h EC_{50} is predicted to be above (b) (4) mg/L.
> Pseudokirchneriella subcapitata 72h EC_{50} is predicted to be above (b) (4) mg/L.

These values are significantly higher than the estimated EIC of (b) (4) ug/L.

Based on the above results, a low risk of environmental impacts to aquatic organisms from patient use and disposal of solriamfetol is anticipated.

References:

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Nallani G, Venables B, Constantine L, Huggett D. 2016. Comparison of measured and predicted bioconcentration estimates of pharmaceuticals in fish plasma and prediction of chronic risk. Bulletin of Environmental Contamination and Toxicology, 96(5):580-584.

Reviewer's Assessment: ***Adequate***

Based on modeled and available data, a low environmental impact risk is expected due to approval of this application. Extraordinary curcumstances are not indicated.

The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance is acceptable.

Primary Environmental Reviewer Name and Date: Raanan A. Bloom, Ph.D.

Secondary Reviewer Name and Date: Scott Furness, Ph.D.

Raanan Bloom

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Michael Furness

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LABELING

I. Package Insert

1. Documents reviewed (section 1.14.1.3):

- "Draft Labeling Text Word" (submitted 23May2018)
- "Draft Medication Guide - Word" (submitted 19Jul2018)

2. 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	TRADENAME (solriamfetol) tablets, for oral use, C-XX *Reviewer's note: Tradename and controlled substance symbol will be inserted/confirmed during labeling negotiations*
Dosage form, route of administration	
Controlled drug substance symbol	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 75 mg, 150 mg, (b) (4)

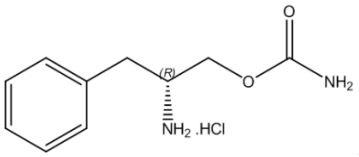
3. Section 2 Dosage and Administration

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)	(b) (4) upon awakening with or without food. 2.4 Dosing in Patients with Renal Impairment • Severe renal impairment (creatinine clearance of 15-29 mL/min): (b) (4) 37.5 mg once daily. (b) (4)

4. 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 **Strengths: in metric system** **Active moiety expression of strength with equivalence statement**	TRADENAME 75 mg – (75 mg solriamfetol equivalent to 89.3 mg of the hydrochloride salt) dark yellow oblong tablet with "75" debossed on one side and a score line on the opposite side. TRADENAME 150 mg – (150 mg solriamfetol equivalent to 178.5 mg of the hydrochloride salt) yellow oblong tablet with "150" debossed on one side.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4)

5. 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	(b) (4) solriamfetol, (b) (4) dopamine and norepinephrine reuptake inhibitor (DNRI). Solriamfetol is (b) (4) phenylalanine derivative with the systematic name (*R*)-2-amino-3-phenylpropylcarbamate hydrochloride.
Dosage form and route of administration	
Active moiety expression of strength with equivalence statement	The molecular formula is $C_{10}H_{15}N_2O_2Cl$, and the molecular weight is 230.69. The chemical structure is: 
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>)	Solriamfetol hydrochloride is a white to off-white solid that is freely soluble in water.
Pharmacological/ therapeutic class	(b) (4) the inactive ingredients hydroxypropyl cellulose and magnesium stearate. In addition, the film coating contains: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and iron oxide yellow.
Chemical name, structural formula, molecular weight	
Other important chemical or physical properties (such as pKa or pH)	*Reviewer's note: Alphabetize inactive ingredients and coating components per USP <1091>. Include quantities of solriamfetol HCl salt form in equivalence statement as required by the USP Salt Policy and FDA's Guidance for Industry "Naming of Drug Products Containing Salt Drug Substances."*

6. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Available units (e.g., bottles of 100 tablets)	TRADENAME (b) (4) packaged in 30-count and 100-count white, high density polyethylene (HDPE) bottles.
Strength of dosage form	TRADENAME tablets, 75 mg - dark yellow oblong tablet with "75" debossed on one side and a score line on the opposite side. NDC 68727-350-01: Bottles of 30 with child-resistant closure NDC 68727-350-02: Bottles of 100 with child-resistant closure TRADENAME tablets, 150 mg - yellow oblong tablet with "150" debossed on one side. NDC 68727-351-01: Bottles of 30 with child-resistant closure NDC 68727-351-02: Bottles of 100 with child-resistant closure
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)
Special handling (e.g., protect from light)	none
Storage conditions	Store TRADENAME at 20°to 25°C (68°to 77°F); excursions permitted between 15°to 30°C (59°to 86°F) (see USP controlled room temperature).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Distributed by: Jazz Pharmaceuticals, Inc. Palo Alto, CA 94304

7. Section 17 Patient Counseling Information

Item	Information Provided in NDA
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	None.

8. Medication Guide

Item	Information Provided in NDA
Proprietary name and established name	SUNOSI™ (suh-NOH-see) (solriamfetol) Tablets, for oral use, C-XX *Reviewer's note: Controlled substance symbol will be inserted/confirmed during labeling negotiations*
Dosage form and route of administration	
Controlled drug substance symbol	
Storage information	Store SUNOSI at room temperature between 68° to 77°F (20° to 25° C)
Active ingredient	solriamfetol
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>)	hydroxypropyl cellulose and magnesium stearate. In addition, the film coating contains: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxide yellow. *Reviewer's note: Alphabetize inactive ingredients and coating components per USP <1091>.*

Reviewer's Assessment of Package Insert: ***Adequate, pending applicant's acceptance of the above proposed revisions.***

The Prescribing Information & Medication Guide comply with all regulatory requirements from a CMC perspective.

II. Labels (Section 1.14.1.1, all labels submitted 20Dec2017)

1. Bottle Labels

The bottle labels for all tablet strengths (75 mg, 150 mg, (b) (4)) and bottle counts (30 and 100) are equivalent. The label for the 30-count bottle of 75 mg tablets is shown below

(b) (4)

2. (b) (4)

(b) (4)

(b) (4)

Item	Information provided in the labels
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	See representative labels above *Reviewer's note: Tradename and controlled substance symbol will be inserted/confirmed during labeling negotiations*
Dosage strength	
Net contents	
"Rx only" displayed prominently on the main panel	
NDC number (21 CFR 207.35(b)(3)(i))	
Lot number and expiration date (21 CFR 201.17)	
Equivalence statement	
Storage conditions	
Bar code (21CFR 201.25)	
Name of manufacturer/distributor	
Controlled drug substance symbol	

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

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

List of Deficiencies: ***None***

Overall Assessment and Recommendation: ***Adequate, pending acceptance of PI revisions described above***

Stephanie Emory

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

NDA: 211230 - Original submission dated 12/20/2017
Drug Product Name/Strength: Sunosi (solriamfetol) Tablets, 75 mg, 150 mg, (b) (4)
(Drug product is referred as Jazz-110 during drug product development)
Route of Administration: Oral
Applicant Name: Jazz Pharmaceuticals

Submission: Jazz Pharmaceuticals, Inc. is seeking approval for Sunosi (solriamfetol) Tablets, 75 mg, 150 mg, (b) (4) Tablets under the 505 (b)(1) path. The drug product (previously called JZP-110) is to be administered orally for the treatment of excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea. The proposed drug product is a film coated immediate release tablet.

This 505(b)(1) NDA relies in part on findings of safety, efficacy and pharmacokinetics from 9 studies conducted in healthy volunteers and special populations, 3 studies conducted in subjects with major depressive disorder (undertaken by a previous sponsor), and 6 studies conducted in subjects with narcolepsy.

REVIEW 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, **2)** Biowaiver request, and **3)** bridging of Phase III to Commercial product, and bridging of current to new manufacturing site.

Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1) DISSOLUTION TEST:
Dissolution Method and Acceptance Criteria: The Applicant's proposed dissolution method [*USP apparatus I (Basket) at 100 rpm; 900 mL of 0.1N HCl at 37°C*] and acceptance criterion of Q(b) (4)% at 15 min are **acceptable** for release and on stability.

2) BIOWAIVER REQUEST:
The proposed drug product was officially designed by FDA as a BCS-Class I, on Sep 26, 2016 [1]. The application included a BCS-Class 1 based biowaiver request supporting the bridge between the Phase II to Phase III formulation and dosage form changes (capsules to tablets). The provided data demonstrated similarity between dissolution profiles of the capsules and tablets; therefore, the Applicant's request is acceptable and the biowaiver is **GRANTED**.

[1] https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80405577&showAsPdf=true

3) **BRIDGING**

Bridging of Clinical Tablets to Over-Encapsulated Clinical Tablets: The Phase III film-coated tablets were over-encapsulated and back-filled with microcrystalline cellulose for blinding purposes. The provided dissolution data demonstrated similar dissolution for the un- and over-encapsulated Phase III tablets. The bridging is ***Adequate.***

Bridging of Clinical to to-be-marketed Drug Product: The formulation of the Phase III-film coated tablets is the same as the to-be-marketed tablets, except for the coating color. The film coating component, (b) (4), used in the Phase III tablets was changed to (b) (4) for the to-be-marketed tablets. The provided dissolution profile comparison data fully support the bridging between Phase III and to-be-marketed drug products. The bridging is ***Acceptable.***

Bridging of Manufacturing Sites for Clinical Supplies and Commercial Drug Product: The drug product supplies used in the clinical Phase III studies were manufactured at (b) (4) The commercial drug product will be manufactured at (b) (4) There are no significant changes to the overall manufacturing processes used for the clinical supply to those intended for commercial supply. Both manufacturing sites operate to similar procedures and have comparable environmental controls. The provided dissolution profile comparison data support the bridging between the clinical and commercial products manufactured at (b) (4) respectively. Therefore, the proposed site at (b) (4) for the manufacturing of the commercial drug product is ***Acceptable***

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 211230 for Sunosi (solriamfetol) Tablets, 75 mg, 150 mg, (b) (4), is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Akm Khairuzzaman, PhD ***7/30/2017***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Angelica Dorantes, PhD **8/3/2017**
Branch Chief,
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT[2]

- **OVERALL BIOPHARMACEUTICS RISK ASSESSMENT: Low**

Failure mode/Risk Factor		Likelihood to impact Dissolution	Reviewer's Rational
Raw Material Attributes	API PSD	Low	BCS-Class I drug (Approved designation)
	API polymorphism	Low	BCS-Class I drug, it exists as a single crystalline form
	Excipient variability	Low	BCS-Class I drug (designation approved by FDA), changes in excipient did not show any difference in dissolution.
Manufacturing process parameters from various unit operation	(b) (4)	Low	(b) (4)
	(b) (4)	Low	Does not have any impact on dissolution
		Low	(b) (4)

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	Coating	Low	No impact on coating within the range established. (b) (4)

- **DRUG PRODUCT:**

The proposed drug product is a film coated immediate release tablet. The formulations of all strengths (b) (4) containing the active ingredient, Solriamfetol HCL. Inactive ingredients are hydrxypropyl cellulose, magnesium stearate and film coating color components. The manufacturing process utilizes (b) (4)

- ***BCS DESIGNATION***

The drug, Solriamfetol HCL is a **BCS-Class I** compound. The official BCS-Class 1 designation for the drug substance/drug product was approved by FDA on Sep 26, 2016. For details please refer to (V:\DIVISION\BIO\BCS\BCS Drug Lists: BCS Committee Reviewed Products; Last updated on 4/18/2017.

- ***DISSOLUTION INFORMATION:***

Proposed Dissolution Method and Acceptance Criteria: The dissolution method and dissolution acceptance criterion 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
I (Basket)	100	0.1N HCl	900/37	On-Line UV	Q= (b) (4)% at 15 min

- ***DISSOLUTION METHOD DEVELOPMENT***

(b) (4)

Refer to the Drug Product Review, for the evaluation of the adequacy of the validation of the analytical method used to assay the dissolution samples.

- ***DISSOLUTION ACCEPTANCE CRITERIA***

Based on the dissolution profile data of pivotal clinical batches, stability data, and manufacturing experience, the Applicant proposed Q= (b) (4)% at 15 min, as the dissolution acceptance criterion for batch release and stability testing.

Reviewer's Assessment: **ADEQUATE**
The evaluation on the Applicant's proposed acceptance criterion was based on the provided dissolution data from all clinical trials (Table 6, Table 8-10, table 9, figure 1-5, module 3.2.P.2.2), batch release data from registration lots, and stability data. A total of 281 number of dissolution analyses (b) (4) were conducted and the lowest dissolution data observed was (b) (4)% in 15 min. The dissolution acceptance criterion for the drug product used in Phase III studies (film coated tablets and over-encapsulated film-coated tablets) and the commercial film-coated tablets, was met at > 85% of label claim in 15 minutes. Based on the data analyses, the proposed limit appears to be slightly lower than that of the observed value. However, due to the nature of BCS class 1 of this drug, the proposed criterion limit is **acceptable**.

Additionally, it is noted that the Applicant has (b) (4) in place with a limit of NMT (b) (4) min. The (b) (4) assures an acceptable dissolution value for the finished drug product.

- ***TABLET SCORING***

The commercial 75 mg (b) (4) a score line to permit patients to split tablets into equal doses. As described in the pre-NDA briefing package, a scored 75 mg tablet will allow for a dose of 37.5 mg, (b) (4)

Reviewer's Assessment: ***ADEQUATE***
Testing was carried out in line with "*FDA Guidance for Industry – Tablet Scoring, Nomenclature, Labeling, and Data for Evaluation*". Dissolution data on split tablets met the finished product dissolution release requirement (refer to table 18-21, module 3.2.P.2.2).

- ***BIOWAIVER REQUEST:***

Different formulations of solriamfetol were studied at the various stages of product's development, as follows:

Formulation 1 Used in Phase I & II studies: Drug substance in capsule, with or without excipients.
Formulation 2 Used in Phase III studies – Film coated Tablets (in the clinical studies the tablets were encapsulated to enable blinding)
Formulation 3 Commercial Product – Same Phase III Film coated Tablets (except for the coating color). The film coating component ((b) (4) was changed to (b) (4) .

During the clinical development program, two JZP-110 formulations types were used. The first formulation was used in the previous Sponsors' Phase I and Phase II studies and comprised of a capsule filled with drug substance, with or without excipients. These capsules were produced at strengths of 21 mg, 84 mg, and 150 mg JZP-110. The second formulation was used in the Phase 3 studies. It was manufactured by Jazz Pharmaceuticals and comprised of film-coated. Four film-coated tablet strengths were produced (37.5 mg, 75 mg, 150 mg, and 300 mg). All the strengths were used in PK and Phase III clinical studies.

This application included BCS-Class 1 based waiver requests to provide comparative bioequivalence studies in support of a change in drug product formulation from Phase II (drug substance-in-capsule) to Phase III (over-encapsulated film-coated tablets), and from Phase III clinical trial product to the commercial formulation-product (film-coated tablets). Therefore, this NDA does not include comparative bioavailability/bioequivalence clinical studies.

Reviewer's Assessment: **ADEQUATE**
Because of the high permeability, high solubility, GI stability, and rapid dissolution of the proposed drug product, it was officially designed by FDA as a BCS-Class I, on Sep 26, 2016.

This application included a BCS-Class 1 based biowaiver request supporting the bridge between the Phase II to Phase III formulation and dosage form changes (capsules to tablets). The provided dissolution profile comparison data in 3 pH media demonstrated similarity between dissolution profiles of the capsules and tablets and the changes in the product's formulation and dosage should not have any impact on the bioavailability of the drug product in patients. The similarity, f2 values were not calculated because dissolution was >85% in 15 minutes. Based on the overall data, the Applicant's request for a BCS-Class 1 based biowaiver request is acceptable and the biowaiver is **GRANTED**.

Although the Applicant requested biowaivers to support bridging throughout product's development, it is noted that a BA/BE study is not needed to support the bridging of, **1)** Phase III tablets to over-encapsulated tablets used in the phase III-clinical studies, **2)** clinical-Phase III to commercial tablets, and **3)** clinical to commercial manufacturing sites because the bridging of the before- and after-changes do not require in vivo BE data and all these changes can be supported with only in vitro dissolution profile comparison data. Therefore, if in vivo BA/BE studies are not needed for these changes, biowaivers are not needed.

- **BRIDGING**

✓ ***Bridging of Clinical Tablets to Over-Encapsulated Clinical Tablets:*** The Phase III film-coated tablets were over-encapsulated and back-filled with microcrystalline cellulose for blinding purposes in the clinical Phase III studies. Figure 1 presents the dissolution profiles of over-encapsulated Phase III tables in different pH media.

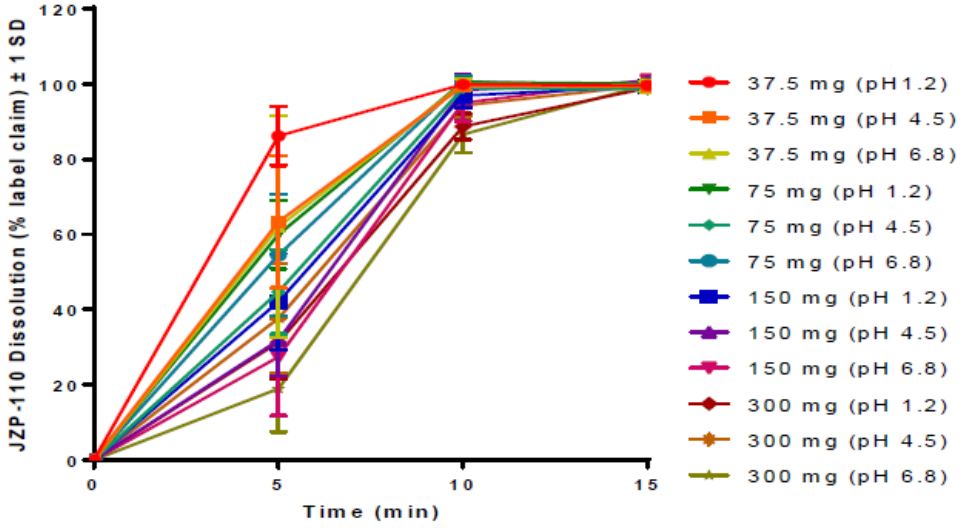

Fig 1. Dissolution Profile in various pH media of the Phase III Over-Encapsulated Tablets

Reviewer's Assessment: ADEQUATE
The provided dissolution profile data for the over-encapsulated tablets show fast dissolution and similar dissolution profiles between the Phase III tablets and the over-encapsulated Phase III tablets. The bridging is ***Acceptable***.

✓ ***Bridging of Clinical product to Commercial product:*** The intended commercial drug product differs from the Phase III film-coated table only in color of the cosmetic film-coat. The following table presents the difference in formulation composition between the phase III and Commercial products.

		Phase 3 Formulation[a]	Commercial Formulation[b]
Component	**Function**	**Composition (% w/w)**	
JZP-110 (as HCl salt)	Active	(b) (4)	
Hydroxypropyl Cellulose (HPC)			
Magnesium Stearate			
(b) (4)			

Figure 2 shows representative dissolution profiles using the proposed testing conditions (USP App1 @100 rpm in 900 ml of HCl 0.1 N) for solriamfetol Phase III clinical film-coated tablets product in various pH media.

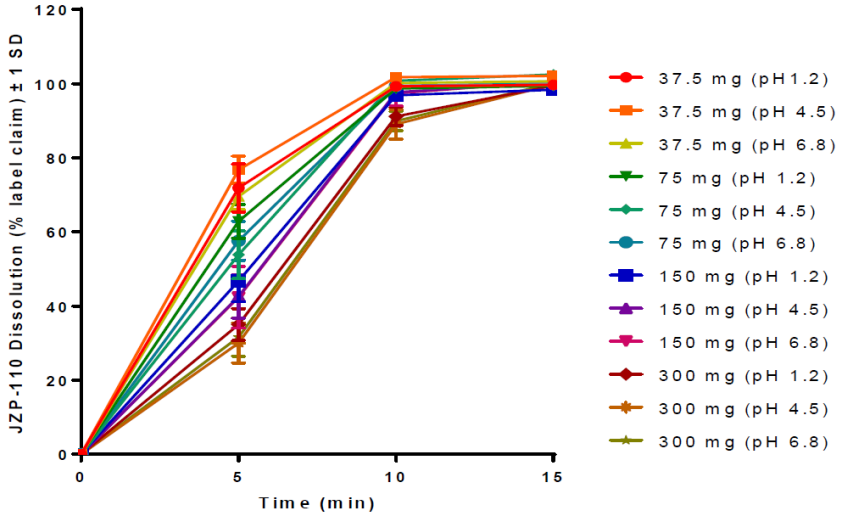

Fig 2. Dissolution Profile in various pH media of the Phase III Solriamfetol (JZP-110) Tablets

The formulation of the Phase III-film coated tablets is the same as the commercial tablets, except for the coating color. The film coating component, [redacted](b) (4), used in the Phase III tablets was changed to [redacted](b) (4) for the Commercial tablets.

Reviewer's Assessment: ADEQUATE
The provided dissolution profile comparison data fully support the bridging between clinical-Phase III and commercial products. The bridging is ***Acceptable***.

✓ ***Bridging of Manufacturing Sites for Clinical and Commercial Products:*** The drug product supplies used in the clinical Phase III studies were manufactured at [redacted](b) (4). The commercial drug product will be manufactured at [redacted](b) (4). There are no significant changes to the overall manufacturing processes used for the clinical supply to those intended for commercial supply. Both manufacturing sites operate to similar procedures and have comparable environmental controls.

Reviewer's Assessment: ADEQUATE
The provided dissolution profile comparison data support the bridging between the clinical and commercial products manufactured at [redacted](b) (4), respectively. Therefore, the proposed site at [redacted](b) (4) for the manufacturing of the commercial drug product is ***Acceptable***

➢ **OVERALL RECOMMENDATION:**

From a Biopharmaceutics perspective, NDA 211230 for Sunosi (solriamfetol) Tablets, 75 mg, 150 mg, [redacted](b) (4), is recommended for **APPROVAL**.

Akm Khairuzzaman

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Wendy
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