

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211964Orig1s000

PRODUCT QUALITY REVIEW(S)

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Biopharmaceutics.....	See CMC IQA dated 10 Jul 20 and addendum dated 14 Oct 20
Microbiology.....	N/A

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 211964 Assessment # 2

Drug Product Name	Viloxazine Extended-Release Capsules
Dosage Form	capsules
Strength	100, 150, 200 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Supernus Pharmaceuticals, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 58; eCTD 0058	3 Feb 2021	Drug substance, drug product, facilities
Supporting document 59; eCTD 0059	5 Mar 21	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Grace Chiou	Julia Pinto
Manufacturing	Yongming Lu	Ubrani Venkataram
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Grace Chiou	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval for this application.
Process/facilities recommend approval. Drug substance, drug product and biopharmaceutics recommended approval in the last review cycle and their recommendation remains approval in this review.

The drug product can be granted a 24-month shelf life when stored at 25°C/60%RH.

See also CMC IQA dated 10 Jul 20 and CMC IQA addendum dated 14 Oct 20.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This is the second review of this application. This resubmission is in response to a complete response letter dated 6 Nov 2020. The facilities issues have been resolved in this review cycle.

Viloxazine Extended-Release Capsules, 100, 150 and 200mg (b) (4)
(b) (4)

For the 100 mg capsule, (b) (4)
(b) (4)

For the 150 mg capsule, (b) (4)
(b) (4)

For the 200 mg capsule, (b) (4)
(b) (4)

The drug product can be granted a 24-month shelf life when stored at 25°C/60%RH.

	treatment for pediatric patients 6 to 17 years of age with Attention-Deficit/Hyperactivity Disorder (ADHD)
	chronic
	400 mg according to non-clinical and clinical reviewers (b) (4)
	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The available stability data for three viloxazine hydrochloride drug substance registration stability batches manufactured at (b) (4) support the proposed (b) (4) month retest period when the bulk drug substance is stored at (b) (4).

Drug Product: Adequate

No updated stability information or change to expiry is proposed. It should be noted that it was observed in 3.2.P.8.1. that the specification for total impurities was in conflict with that found in the original review. In eCTD 0058, the specification is listed as, "Report results for information only." However, the specification in 3.2.P.5.1 (in eCTD 0001) is listed as NMT (b) (4) %. Subsequently, an IR was sent to the Applicant who confirmed the total impurities specification is NMT (b) (4) % for the commercial drug product. A separate review was not placed in Panorama.

Labeling: Adequate

See also CMC IQA dated 10 Jul 20 and CMC IQA addendum dated 14 Oct 20.

Manufacturing: Adequate

Withhold decision for Orig-1 was based on a FDASIA 706 record review in lieu of an on-site PAI for Supernus (FEI 3005209462; LCP profile). The PAI could not be performed due to a global travel warning. A withhold recommendation was submitted due to lack of documentation that appropriate re-qualification of analytical instruments was performed and a lack of procedures for handling laboratory records and/or electronic data following the relocation of the laboratory.

In this Resub-58 dated 02/03/2021, Supernus decided to withdraw the facility located at 9715 Key West Ave Rockville, MD from the filing. The testing responsibilities at Supernus (FEI 3005209462; LCP profile) are

covered by Catalent Pharma Solutions, LLC (FEI 1000122400) that is the DP manufacturer and adequate.

Biopharmaceutics: Adequate

See also CMC IQA dated 10 Jul 20 and CMC IQA addendum dated 14 Oct 20.

Microbiology (if applicable): Choose an item.

N/A

Facilities Screenshot showing approval (taken 12 Mar 21)

NON-RESPONSIVE

Search All...

NDA/BLA - NDA 211964

NDA-211964-ORIG-1-RESUB-58

Planned Completion: Apr 3, 2021 | Status: Current | Condition: On Target | Percent Complete: 42.03%

Project Summary | Project Details | Application Life Cycle | Archive | Inspection View | Tasks | More

Inspection View

Inspection View - Overall

Export

Task Number	Task Name	Comments	Assignments	Pin Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Manufacturing Facility Inspection (1)								
60	Overall Manufacturing Inspection Recommendation		J. Yongming Lu	2/3/21	2/26/21	Complete	Go to Form	Approve

Showing all 1 tasks

Inspection View - Facilities

Export

Task Number	Task Name	Multiprofiting Disposition	Comments	Assignments	Pin Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Facility: SUPERNUS PHARMACEUTICALS, INC. FEI: 3005209462 DUNS: 363066452 FACILITY STATUS: WITHDRAWN (1)									
12	Enter Profile Codes			J. Yongming Lu JL ML - Facility Profile Reviewer JL - Facility Profile Reviewer	2/12/21	2/5/21	Complete	Go to Form	FACILITY STATUS: WITHDRAWN



Valerie
Amspacher

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Date: 3/12/2021 09:56:46AM

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/s/

VALERIE R AMSPACHER
03/12/2021 10:07:30 AM

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Drug Substance.....	See CMC IQA dated 10 Jul 20
Drug Product.....	See CMC IQA dated 10 Jul 20
Environmental.....	See CMC IQA dated 10 Jul 20
Labeling.....	See CMC IQA dated 10 Jul 20
Biopharmaceutics.....	See CMC IQA dated 10 Jul 20
Microbiology.....	N/A

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 211964 Assessment 1 Addendum 1

Drug Product Name	Viloxazine Extended-Release Capsules
Dosage Form	capsule
Strength	100, 150, 200 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Supernus Pharmaceuticals, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	8 Nov 20	All, original NDA
Supporting document 11; eCTD 0011	10 Jan 20	Facilities
Supporting document 12; eCTD 0012	14 Jan 20	All; updated DMF references
Supporting document 15; eCTD 0015	31 Jan 20	All; updated DMF references
Supporting document 16; eCTD 0016	10 Feb 20	Facilities
Supporting document 24; eCTD 0024	26 Mar 20	Drug product
Supporting document 26; eCTD 0026	1 Apr 20	Drug substance
Supporting document 27; eCTD 0028	6 Apr 20	Drug substance and Drug product
Supporting document 28; eCTD 0029	6 Apr 20	Biopharm and facilities
Supporting document 33; eCTD 0033	14 May 20	Process
Supporting document 36; eCTD 0036	8 Jun 20	Biopharm

Supporting document 38; eCTD 0038	30 Jun 20	Process and facilities
Supporting document 46; eCTD 0045	2 Sep 20	Biopharm and process and facilities
Supporting document 50; eCTD 0051	23 Sep 20	Facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Grace Chiou	Julia Pinto
Manufacturing	Yongming Lu	Ubrani Venkataram
Microbiology	N/A	N/A
Biopharmaceutics	Leah Falade	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Grace Chiou	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends complete response for this application based on facilities deficiencies. The purpose of this addendum is to include the facilities and process review in the CMC IQA. All other disciplines recommend approval. See original CMC IQA dated 10 Jul 20 in Panorama and DARRTS.

The proposed shelf-life of 24 months, when stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) is acceptable when approved.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Viloxazine Extended-Release Capsules, 100, 150 and 200mg are

(b) (4)

(b) (4)

(b) (4)

For the 100 mg capsule, (b) (4)

For the 150 mg capsule, (b) (4)

For the 200 mg capsule, (b) (4)

The proposed shelf-life of 24 months, when stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) is acceptable when approved.

Proposed Indication(s) including Intended Patient Population	treatment for pediatric patients 6 to 17 years of age with Attention-Deficit/Hyperactivity Disorder (ADHD)
Duration of Treatment	chronic
Maximum Daily Dose	400 mg according to non-clinical and clinical reviewers (b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

See original CMC IQA dated 10 Jul 20 in Panorama and DARRTS.

Drug Product: Adequate

See original CMC IQA dated 10 Jul 20 in Panorama and DARRTS.

Labeling: Adequate

See original CMC IQA dated 10 Jul 20 in Panorama and DARRTS.

Manufacturing: Inadequate

Process: The manufacturing process of Viloxazine Extended-Release Capsules, 100 mg, 150 mg and 200 mg involves following unit operations:

(b) (4)
(b) (4)
(b) (4) All deficiencies have been resolved through the IR process.

Facility: Withhold decision is based on a FDASIA 706 record review in lieu of an on-site PAI for Supernus (FEI 3005209462; LCP profile). The PAI could not be performed due to a global travel warning. A withhold recommendation is submitted due to lack of documentation that appropriate re-qualification of analytical instruments was performed and a lack of procedures for handling laboratory records and/or electronic data following the relocation of the laboratory.

Biopharmaceutics: Adequate

See original CMC IQA dated 10 Jul 20 in Panorama and DARRTS.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Controlled by specification	Acceptable	

Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	M	Controlled by specification	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	H	Controlled by specification	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	
Dissolution – BCS Class I	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

“ During a review of records requested under FD&C act section 704(a)(4) provided by Supernus (FEI:3005209462) manufacturing facility the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved.

If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
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(b) (4)	III	(b) (4)	4		
	III		4		
	IV		4		
	III		4		
	III		4		
	III		4		
	III		4		
	IV		4		
	III		4		
	III		4		
	III		4		
	III		4		
	III		4		
	III		4		

Action codes for DMF Table:

1 – DMF Reviewed.

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
IND	(b) (4)	
IND		
IND	108864	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Screenshot of Panorama Inspection View taken 14 Oct 20

Inspection View - Overall

Export

Details Summary

Task Number	Task Name	Comments	Assignments	Pin Comp	Act Comp	Task Status	Actions	Additional Information
14	Enter Application Specific Inspection Criteria		Teshare Boule	11/12/19	11/19/19	Complete	Go to Form	
177	Overall Manufacturing Inspection Recommendation	This decision is based on a FDASIA 706 record review in lieu of an on-site PAI for Supernus (FEI: 3005209462; LCP). The PAI could not be performed due to a global travel warning. A withhold recommendation is submitted due to lack of documentation that appropriate re-qualification of analytical instruments was performed and a lack of procedures for handling laboratory records and/or electronic data following the relocation of the laboratory.	Yongming Lu	11/20/20	7/23/20	Complete	Go to Form	Withhold

Showing all 2 tasks

Inspection View - Facilities

Export

Details Summary

8:14 AM 10/14/2020



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/s/

VALERIE R AMSPACHER
10/14/2020 09:02:40 AM

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Labeling.....	89
Process/Manufacturing.....	pending
Biopharmaceutics.....	105
Microbiology.....	N/A

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 211964 Assessment 1

Drug Product Name	Viloxazine Extended-Release Capsules
Dosage Form	capsule
Strength	100, 150, 200 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Supernus Pharmaceuticals, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	8 Nov 20	All, original NDA
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Supporting document 12; eCTD 0012	14 Jan 20	All; updated DMF references
Supporting document 15; eCTD 0015	31 Jan 20	All; updated DMF references
Supporting document 16; eCTD 0016	10 Feb 20	Facilities
Supporting document 24; eCTD 0024	26 Mar 20	Drug product
Supporting document 26; eCTD 0026	1 Apr 20	Drug substance
Supporting document 27; eCTD 0028	6 Apr 20	Drug substance and Drug product
Supporting document 28; eCTD 0029	6 Apr 20	Biopharm and facilities
Supporting document 33; eCTD 0033	14 May 20	Process
Supporting document 36; eCTD 0036	8 Jun 20	Biopharm

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Grace Chiou	Julia Pinto
Manufacturing	Yongming Lu	Ubrani Venkataram
Microbiology	N/A	N/A
Biopharmaceutics	Leah Falade	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Grace Chiou	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

A CMC recommendation is pending facilities inspection and process review. Based on the review of the information submitted drug product, drug substance and biopharmaceutics recommend approval. Once the process and facility review is complete, an addendum with the final, overall CMC approvability recommendation will be added in Panorama and DARRTS.

The drug product can be granted a 24-month shelf life if approved.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Viloxazine Extended-Release Capsules, 100, 150 and 200mg are (b) (4)

(b) (4)

For the 100 mg capsule, (b) (4)

(b) (4)

For the 150 mg capsule	(b) (4) (b) (4)
For the 200 mg capsule,	(b) (4) (b) (4)
The drug product can be granted a 24-month shelf life if approved.	

	treatment for pediatric patients 6 to 17 years of age with Attention-Deficit/Hyperactivity Disorder (ADHD)
	chronic
	400 mg according to non-clinical and clinical reviewers (b) (4)
	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The synthetic scheme and manufacturing process are adequately detailed. The proposed control of materials (b) (4) are appropriate to ensure the quality of the drug substance. The proposed starting materials (b) (4) Specifications for all materials used in the manufacturing process have been included in the submission. Critical process parameters have been identified. These critical process parameters in the in-process controls, the control strategy for critical process steps and intermediates have proven adequate in minimizing both degradation and impurity formation which further ensures the quality of the drug substance. Process development work has employed methods (b) (4) which has contributed to an improved impurity profile which supports the proposed commercial-scale synthetic scheme, manufacturing scheme, and control strategy. Residual solvents meet the requirements as per ICH Q3C and an Elemental Impurities Risk Assessment (b) (4) is controlled in the specification (b) (4). The drug substance specifications are adequate (consistent with ICH Q3A, Q3C, and Q6A) to

ensure the quality of Viloxazine Hydrochloride as it relates to the safety and efficacy of the eventual drug product.

The stability data for the (b) (4) drug substance registration stability batches have been completed. The stability study was carried out for (b) (4) months under long-term ((b) (4)) and 6-months under accelerated ((b) (4)) conditions (as stability testing is ongoing) in the container closure system consistent with that to be used for the commercial batches, appears to be stable and supports the proposed (b) (4) month retest period for Viloxazine Hydrochloride drug substance.

Drug Product: Adequate

Viloxazine capsules are an extended release drug product available in dosage strengths of 100 mg, 150 mg, and 200 mg. The dosage strengths are distinguished by different colored (b) (4) capsules, intended to provide patients with an oral once a day administration and is dose-proportional. These capsules are (b) (4)

(b) (4)

(b) (4) The specifications contain tests for appearance, identity, assay, impurities, and uniformity of dosage units. Justification for specifications are provided.

The drug product is to be stored at controlled room temperature. The drug product is granted a 24-month shelf life based on a ICH Q1D compliant bracketing strategy.

Labeling: Adequate

Manufacturing: Choose an item.

Process and facility assessment is currently pending. No recommendation is made from process or facilities at this time. Once the process and facility review is complete, an addendum with the final approvability recommendation will be added in Panorama and DARRTS.

Biopharmaceutics: Adequate

From the Biopharmaceutics perspective, NDA-211964-ORIG-1 for Viloxazine Extended-Release Capsules, 100 mg, 150 mg, and 200 mg is recommended for approval.

The Biopharmaceutics review focuses on the evaluation and acceptability of 1) the proposed dissolution method and acceptance criteria, 2) the extended release designation claim, 3) waiver request for the 150 mg strength, 4) the in vitro dose dumping in the presence of alcohol, and 5) the bridging throughout the 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 fully validated dissolution method and acceptance criteria are considered acceptable for the Applicant's Viloxazine Extended-Release Capsules, 100 mg, 150 mg, and 200 mg for batch release and stability testing (see final approved dissolution method and acceptance criteria under Recommendation section). The dissolution method is discriminatory for changes in (b) (4).

2) Extended Release Designation Claim: The Applicant has provided information to fully support the extended release claim for the proposed Viloxazine Extended-Release Capsules.

3) Biowaiver Request: The provided information/data regarding the BA/BE of the 200 mg and 100 mg strengths, formulation proportionality for all proposed strengths, and dissolution profile comparisons (f2 values) are acceptable and fully support the approval of the waiver request for the 150 mg strength. The biowaiver is therefore granted.

4) In Vitro Alcohol Dose-Dumping: The results of the in vitro alcohol dissolution showed that to 20% and 40% ethanol had faster release profiles compared to 0% ethanol. Because the extended release profile is not maintained in 20% and 40% ethanol, there may be a risk for dose dumping. The Applicant conducted a clinical study to evaluate the effect of alcohol on the bioavailability, assess the safety and tolerability, and evaluate the effect of alcohol on Tmax of a single dose of Viloxazine ER 200 mg capsules when co-administered with 0%, 4%, 20%, and 40% alcohol under fasted conditions. The acceptability of this study is deferred to the Office of Clinical Pharmacology (OCP).

5) Bridging of Formulations: The capsule formulations used in the clinical pivotal studies for the 100mg and 200 mg strengths are identical in composition to the to-be-marketed (TBM) formulations with the exception of the capsule shells. The developmental scale formulations and pivotal clinical batches were manufactured at Supernus in Rockville, MD. The commercial products and primary stability registration batches were manufactured at the intended commercial manufacturing site, Catalent in Winchester, KY. Comparative batch release testing was submitted to support the bridging between the clinical and commercial formulations. The f2 values comparing developmental scale batches to the Phase 3 registration batches are all >50. Therefore, the data bridging the formulations is acceptable.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	M	Controlled by specification	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	H	Controlled by specification	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters	L	Controlled by specification	Acceptable	

	• Scale/equipment • Site				
Dissolution – BCS Class I	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Controlled by specification	Acceptable	

D. List of Deficiencies for Complete Response

- Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

- Drug Substance Deficiencies

- Drug Product Deficiencies

- Labeling Deficiencies

- Manufacturing Deficiencies

- Biopharmaceutics Deficiencies

- Microbiology Deficiencies

- Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	4		
	III			4		
	IV			4		
	III			4		
	III			4		
	III			4		
	III			4		
	IV			4		
	III			4		
	III			4		
	III			4		
	III			4		

(b) (4)	III	(b) (4)	4		
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Action codes for DMF Table:

- 1 – DMF Reviewed.
- 2 –Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
IND	(b) (4)	
IND		
IND	108864	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				



Valerie
Amspacher

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Date: 7/10/2020 02:41:34PM

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing

Information: The PI assessed in this review was submitted on 09 November 2019. Based on the information provided, there are minor edits to be made to the labeling portion of this submission. Please see review below. Overall, the product quality aspects of the labeling will be adequate upon the Applicant's acceptance of the proposed revisions.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor’s Comments
Product Title in Highlights		
Proprietary name	TRADENAME (viloxazine extended-release capsules), for oral use	<i>Inadequate Revise to (viloxazine) extended release capsules, for oral use</i> Note: The proposed tradename is Qelbree; however, the PI has not been updated at the time of review.
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Extended-release capsules: 100 mg, 150 mg and 200 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	NA	NA

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA
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1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

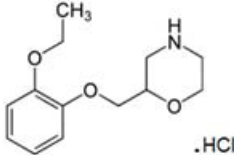
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		<i>Inadequate Revise to include pediatric instruction for use with applesauce</i>

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Extended-release capsules: 100 mg: yellow opaque body and cap (printed "SPN" on the cap, "100" on the body) 150 mg: lavender opaque body and cap (printed "SPN" on the cap, "150" on the body) 200 mg: light green opaque body and cap (printed "SPN" on the cap, "200" on the body)	Adequate
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	<i>Inadequate: Revise to include equivalency statement per FDA guidance as viloxazine HCl is used.</i>
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4) inactive ingredients: Hypromellose, ethylcellulose, talc, titanium dioxide, lactose monohydrate, polyethylene glycol, triacetin, corn starch, sucrose, ammonium hydroxide, medium chain triglycerides, oleic acid, FD&C Yellow #10, FD&C Yellow #6, gelatin, shellac, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide, FD&C Blue #1, FD&C Red #28, FD&C Yellow #5.	<i>Inadequate: Revise to ensure all items are in alphabetical order.</i>
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/therapeutic class	(b) (4)	Adequate
Chemical name, structural formula, molecular weight	Viloxazine is (±)-2-[(2-ethoxyphenoxy)methyl]morpholine hydrochloride, and the structural formula is  Viloxazine hydrochloride is a white to off-white powder. The molecular formula is C₁₃H₂₀NO₃Cl and its molecular weight is 273.8 (HCl salt).	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Viloxazine hydrochloride is soluble in water, 0.1N HCl and aqueous solutions of pH 9.5 and lower. Viloxazine hydrochloride is sparingly soluble in methanol, very slightly soluble in acetonitrile, acetic acid and isopropyl alcohol, and practically insoluble in ethyl acetate.	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	No promotional statements.	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	TRADENAME (viloxazine extended-release) capsules are available in the following strengths and colors: 100mg (yellow capsule printed with "SPN" on capsule cap and "100" on capsule body with edible black ink). Bottles of 100 capsules NDC 17772-131-01 Bottles of 90 capsules NDC 17772-131-90 Bottles of 60 capsules NDC 17772-131-60 Bottles of 30 capsules NDC 17772-131-30 150mg (lavender capsule printed with "SPN" on capsule cap and "150" on capsule body with edible black ink) Bottles of 100 capsules NDC 17772-132-01 Bottles of 90 capsules NDC 17772-132-90 Bottles of 60 capsules NDC 17772-132-60 Bottles of 30 capsules NDC 17772-132-30 200mg (light green capsule printed with "SPN" on capsule cap and "200" on capsule body with edible black ink). Bottles of 100 capsules NDC 17772-133-01 Bottles of 90 capsules NDC 17772-133-90 Bottles of 60 capsules NDC 17772-133-60 Bottles of 30 capsules NDC 17772-133-30	Adequate
Strength(s) in metric system		
Available units (e.g., bottles of 100 tablets)		
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store at 25°C (77°F); excursions permitted between 15°C-30°C (59°F-86°F). (b) (4) (b) (4)	<i>Inadequate</i> <i>Replace "-" with "to" to avoid confusion with minus sign and replace storage temperature with a range rather than a single temperature.</i>
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.		
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	No information included.	Adequate

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	TRADENAME is manufactured by: Catalent Pharma Solutions, LLC, 1100 Enterprise Drive Winchester, KY 40391. Distributed by: Supernus Pharmaceuticals, Inc. Rockville, MD 20850 USA	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): *Inadequate*
Revise Medication Guide language regarding (b) (4) applesauce and to consume within 2 hours of preparation. This is a minor comment.
Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 STRUCTURED PRODUCT LABELING (SPL)

TRADENAME

viloxazine hydrochloride capsule, extended release

Product Information

Product Type

HUMAN PRESCRIPTION DRUG

Item Code (Source)

NDC:1772-131

Route of Administration

ORAL

Active Ingredient/Active Moiety

Ingredient Name

viloxazine hydrochloride (UNII: OQW30I1332) (viloxazine - UNII: S5Y2789ZF)

Basis of Strength

viloxazine hydrochloride

Strength

100 mg

Inactive Ingredients

Ingredient Name

Sucrose (UNII: C151H8M554)

STARCH, CORN (UNII: 0E232NY35J)

HYDROMELLOSE 2910 (5 MPAS) (UNII: R75537TOT4)

TRIACETIN (UNII: XHXC1X673)

POLYETHYLENE GLYCOL 350 (UNII: G2M7P15EP)

LACTOSE MONOHYDRATE (UNII: EWQ57Q815X)

TITANIUM DIOXIDE (UNII: 15FDX9V2JP)

ethylcellulose, unspecified (UNII: 728SPVYZ4B)

WATER (UNII: 059QF8CO8R)

AMMONIA (UNII: 5138Q19F1X)

MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9EL21V7U)

Oleic Acid (UNII: 2UM9U37CP)

TALC (UNII: 78EV74R1U)

D&C YELLOW NO. 10 (UNII: 358W5USQ1G)

FD&C YELLOW NO. 6 (UNII: H77VE91A8)

GELATIN, UNSPECIFIED (UNII: 2G86QN327L)

Shellac (UNII: 46N107B71O)

ALCOHOL (UNII: 3K9958V90M)

ISOPROPYL ALCOHOL (UNII: ND2M416302)

Butyl Alcohol (UNII: 8P361P6TS3)

Propylene Glycol (UNII: 6DC9Q167V3)

FERROSUFERRIC OXIDE (UNII: XM0M87F357)

Potassium Hydroxide (UNII: WZHU448M4T)

Product Characteristics

Color

YELLOW

Score

no score

Shape

CAPSULE

Size

19mm

Flavor

Imprint Code

SPN:100

Contains

Packaging

#

Item Code

Package Description

Marketing Start Date

Marketing End Date

1

NDC:1772-131-30

30 in 1 BOTTLE, Type 0: Not a Combination Product

10/25/2019

2

NDC:1772-131-40

60 in 1 BOTTLE, Type 0: Not a Combination Product

10/25/2019

3

NDC:1772-131-90

90 in 1 BOTTLE, Type 0: Not a Combination Product

10/25/2019

4

NDC:1772-131-01

100 in 1 BOTTLE, Type 0: Not a Combination Product

10/25/2019

Marketing Information

Marketing Category

NDA

Application Number or Monograph Citation

NDA211964

Marketing Start Date

10/25/2019

Marketing End Date

TRADENAME			
viloxazine hydrochloride capsule, extended release			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:1772-132
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
viloxazine hydrochloride (UNII: OQW30I1332) (viloxazine - UNII: S5Y2789ZF)		viloxazine hydrochloride	150 mg
Inactive Ingredients			
Ingredient Name			Strength
Sucrose (UNII: C151H8M554)			
STARCH, CORN (UNII: 0E232NY35J)			
HYDROMELLOSE 2910 (5 MPAS) (UNII: R75537TOT4)			
TRIACETIN (UNII: XHXC1X673)			
POLYETHYLENE GLYCOL 350 (UNII: G2M7P15EP)			
LACTOSE MONOHYDRATE (UNII: EWQ57Q815X)			
TITANIUM DIOXIDE (UNII: 15FDX9V2JP)			
ethylcellulose, unspecified (UNII: 728SPVYZ4B)			
WATER (UNII: 059QF8CO8R)			
AMMONIA (UNII: 5138Q19F1X)			
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9EL21V7U)			
Oleic Acid (UNII: 2UM9U37CP)			
TALC (UNII: 78EV74R1U)			
FD&C BLUE NO. 1 (UNII: H3R47K1TBD)			
D&C RED NO. 28 (UNII: 767P0Y5NH)			
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)			
Shellac (UNII: 46N107B71O)			
ALCOHOL (UNII: 3K9958V90M)			
ISOPROPYL ALCOHOL (UNII: ND2M416302)			
Butyl Alcohol (UNII: 8P361P6TS3)			
Propylene Glycol (UNII: 6DC9Q167V3)			
FERROSOFERRIC OXIDE (UNII: XM0M87F357)			
Potassium Hydroxide (UNII: WZHU448M4T)			

Product Characteristics				
Color	PURPLE	Score	no score	
Shape	CAPSULE	Size	24mm	
Flavor		Imprint Code	SPN;150	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC-17772-132-30	30 in 1 BOTTLE, Type 0: Not a Combination Product	10/25/2019	
2	NDC-17772-132-60	60 in 1 BOTTLE, Type 0: Not a Combination Product	10/25/2019	
3	NDC-17772-132-90	90 in 1 BOTTLE, Type 0: Not a Combination Product	10/25/2019	
4	NDC-17772-132-01	100 in 1 BOTTLE, Type 0: Not a Combination Product	10/25/2019	
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA211964	10/25/2019	

TRADENAME

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4.0 CARTON AND CONTAINER LABELING

4.1 Container Label

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Qelbree (viloxazine extended-release capsules)	Adequate
Dosage strength	100 mg	Adequate
Route of administration	Swallow capsule whole or sprinkle on (b) (4)	<i>Inadequate</i> <i>Revise to include instruction for use with applesauce (b) (4)</i>
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		Inadequate: Include equivalency statement per USP Salt Policy
Net contents (e.g. tablet count)	100 capsules	Adequate
"Rx only" displayed on the principal display	"Rx only" displayed	Adequate
NDC number	NDC 17772-131-01	
Lot number and expiration date	GTIN XXXXXXXXXXXXX LOT XXXXXXX EXP DDMMYY S/N XXXXXXXXXXX	Adequate The Applicant has stated in the cover letter to eCTD 0031 that the format for the lot and expiration will be displayed as shown here.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store (b) (4) (b) (4) (b) (4) [25°C (77°F); excursions 15°C-30°C (59°F-86°F)]. (b) (4) (b) (4)	<i>Inadequate</i> <i>Replace "- " with "to" to avoid confusion with minus sign</i>
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Bar code		Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4) Manufactured for Supernus Pharmaceuticals, Inc. Rockville, MD 20850 USA	Adequate
Medication Guide (if applicable)	Attention Pharmacist: Dispense the Accompanying Medication Guide to Each Patient	Adequate
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: Adequate

The container labeling assessed in this review was submitted 28April2020. There are minor edits; however, the labeling is adequate pending the Applicant's acceptance of the revisions. The Applicant confirmed via email to the RPM there is no carton or carton label intended for the drug product. As it is stated in 3.2.P.7.1. that there is no secondary packaging configuration, a formal submission was not provided. This is acceptable.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Adequate, pending the Applicant's acceptance of the revisions noted above in red.

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes have been made to the label.



Grace
Chiou

Digitally signed by Grace Chiou
Date: 6/18/2020 03:16:08PM
GUID: 5c5df155002b1863abe42e6c00c2780f



Julia
Pinto

Digitally signed by Julia Pinto
Date: 6/21/2020 03:33:17PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

CHAPTER VI: BIOPHARMACEUTICS

[IQA NDA Assessment Guide Reference](#)

NDA Number	211964
Drug Product Name/ Strength	Viloxazine Extended-Release Capsules/100 mg, 150 mg, and 200 mg
Route of Administration	Oral
Applicant Name	Supernus Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Division of Psychiatry
Proposed Indication	For the treatment of attention deficit/hyperactivity disorder (ADHD) in pediatric patients ages 6 to 17 years.
Submission Date	11/08/2019
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: Adequate

Background:

Supernus Pharmaceuticals Inc. is seeking approval for its Viloxazine Extended-Release Capsules (SPN-812V), 100 mg, 150 mg, and 200 mg to be administered orally for the treatment of attention deficit/hyperactivity disorder (ADHD) in children ages 6-17. The proposed drug product is an encapsulated (b) (4) formulation containing (b) (4)

(b) (4) The drug product is intended to deliver viloxazine at a sustained rate to allow for once-daily administration.

Viloxazine is a new chemical entity in which the Applicant has submitted this NDA under 505 (b)(1) to the Division of Psychiatry. The clinical package in support of this NDA includes 17 studies evaluating safety and 4 pivotal phase 3 efficacy studies. Study 812P310 in an ongoing, long-term, Open-Label Extension (OLE) safety study with safety as primary and efficacy as secondary endpoints. Four PK studies were conducted in healthy adults to establish bioavailability.

Assessment Summary:

The Biopharmaceutics review focuses on the evaluation and acceptability of 1) the proposed dissolution method and acceptance criteria, 2) the extended release designation claim, 3) waiver request for the 150 mg strength, 4) the in

vitro dose dumping in the presence of alcohol, and 5) the bridging throughout the 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 fully validated dissolution method and acceptance criteria are considered acceptable for the Applicant's Viloxazine Extended-Release Capsules, 100 mg, 150 mg, and 200 mg for batch release and stability testing (see final approved dissolution method and acceptance criteria under Recommendation section). The dissolution method is discriminatory for changes in (b) (4) and (b) (4) durations.
- 2) Extended Release Designation Claim:** The Applicant has provided information to fully support the extended release claim for the proposed Viloxazine Extended-Release Capsules.
- 3) Biowaiver Request:** The provided information/data regarding the BA/BE of the 200 mg and 100 mg strengths, formulation proportionality for all proposed strengths, and dissolution profile comparisons (f2 values) are acceptable and fully support the approval of the waiver request for the 150 mg strength. The biowaiver is therefore granted.
- 4) In Vitro Alcohol Dose-Dumping:** The results of the in vitro alcohol dissolution showed that to 20% and 40% ethanol had faster release profiles compared to 0% ethanol. Because the extended release profile is not maintained in 20% and 40% ethanol, there may be a risk for dose dumping. The Applicant conducted a clinical study to evaluate the effect of alcohol on the bioavailability, assess the safety and tolerability, and evaluate the effect of alcohol on Tmax of a single dose of Viloxazine ER 200 mg capsules when co-administered with 0%, 4%, 20%, and 40% alcohol under fasted conditions. The acceptability of this study is deferred to the Office of Clinical Pharmacology (OCP).
- 5) Bridging of Formulations:** The capsule formulations used in the clinical pivotal studies for the 100mg and 200 mg strengths are identical in composition to the to-be-marketed (TBM) formulations with the exception of the capsule shells. The developmental scale formulations and pivotal clinical batches were manufactured at Supernus in Rockville, MD. The commercial products and primary stability registration batches were manufactured at the intended commercial manufacturing site, Catalent in Winchester, KY. Comparative batch release testing was submitted to support the bridging between the clinical and commercial formulations. The f2 values comparing developmental scale batches to the Phase 3

registration bathes are all >50. Therefore, the data bridging the formulations is acceptable.

Recommendation

From the Biopharmaceutics perspective, NDA-211964-ORIG-1 for Viloxazine Extended-Release Capsules, 100 mg, 150 mg, and 200 mg is recommended for approval.

FDA-Approved Dissolution Method and Acceptance Criteria for Viloxazine Extended-Release Capsules, 100 mg, 150 mg, and 200 mg

Apparatus	Speed	Medium/Temperature	Volume	Dissolution Acceptance Criteria
2 (Paddles) with sinkers	50 rpm	50 mM potassium phosphate buffer, pH 6.8/37°C	900 mL	1 hr: (b) (4) % 4 hr: (b) (4) % 12 hr: NLT (b) (4) %

List Submissions being assessed:

Document(s) Assessed	Date Received
Application 211964 - Sequence 0001 - 0001 (1) 11/08/2019 ORIG-1 /Multiple Categories/Subcategories	11/08/2019
Application 211964 - Sequence 0029 - 0029 (28) 04/06/2020 ORIG-1 /Multiple Categories/Subcategories	04/06/2020
Application 211964 - Sequence 0036 - 0036 (36) 06/08/2020 ORIG-1 /Quality/Response To Information Request	06/08/2020

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):

This is the first review cycle.

B.1 BCS DESIGNATION

Assessment:

The Applicant submitted solubility and permeability data. Based on the data, the API has high solubility and high permeability and would be classified as BCS I. There is no BCS claim submitted by the Applicant.

Solubility:

The solubility of viloxazine at 37°C and room temperature was shown not to be pH dependent from pH 1.2 to 7.5 as presented in Table 1. At the highest proposed dose of 200 mg and the lowest solubility of 65 mg/mL at 37°C, pH 1.2, the amount of solvent required to dissolve the API is 3.08 mL which is <250 mL. Therefore, viloxazine can be classified as highly soluble as per the BCS Guidance.

Table 1. Solubility Profile of Viloxazine over the Physiological pH Range

Media Description	Solubility at Ambient Temperature (mg/mL) ^a
Deionized Water	43
USP Buffer pH 1.2	35
USP Buffer pH 4.5	44
USP Buffer pH 6.8	45
USP Buffer pH 7.5	52
USP Buffer pH 9.5	53
Media Description	Solubility at 37°C (mg/mL) ^a
Deionized Water	78
USP Buffer pH 1.2	65
USP Buffer pH 4.5	79
USP Buffer pH 6.8	85
USP Buffer pH 7.5	87

^a Mean solubility value for three drug substance batches

Permeability:

The Applicant submitted a permeability study of viloxazine in Caco-2 cells and found that the mean monolayer permeability is 5.04E-5 cm/s. The results indicate that viloxazine is a high permeability compound.

Dissolution: See the assessment below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

Dissolution Method

(b) (4)



Acceptance Criteria

The acceptance criteria were proposed based on the data from 2 batches used in the pivotal clinical studies (100 mg, lot #1634350 and 200 mg, lot#1634203) and 6 primary registration batches of 100 mg and 200 mg capsules (3 batches per strength). The reviewer averaged the dissolution data from the Applicant's submission (Table 7). The pull times were selected to define early, middle, and late stages (1, 4, and 12 hours) of the release profile as per SUPAC-MR Guidance and Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations Guidance.

Drug product packaged in 100-count bottles, 30-count bottles, and 7-count bottles had satisfactory stability and met stability specifications at 25°C/60%RH through 24 months. A slight increase in dissolution rate was observed on stability of drug product in the proposed commercial packaging configurations at the 40°C/75%RH condition through 6 months and at the 30°C/65%RH condition through 12 months. Due to the slight increase observed under extreme and intermediate conditions (40°C/75%RH and 30°C/65%RH, respectively), the specification range at 4-hr (b) (4)

(b) (4) The reviewer finds the proposed acceptance criterion for the 4-hr time-point acceptable as the range is still (b) (4) %.

Table 7. Dissolution Data of Viloxazine ER Capsules, 100 mg and 200 mg

Time (hr)	1	2	4	6	8	10	12	14	16	20	24
Mean	22	31	52	68	81	90	97	98	100	101	103
Min	(b) (4)										
Max	(b) (4)										



Figure 9. Mean batch release dissolution profiles for pivotal clinical and primary registration stability batches of SPN-812V ER capsules, 100 mg and 200 mg

Based on the dissolution data, the Applicant's proposed acceptance criteria are acceptable:

1 hr: (b) (4) %

4 hr: (b) (4) %

12 hr: NLT (b) (4) %

B.3 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: *Adequate*

The Applicant performed dissolution studies on the 100 mg and 200 mg strengths in the compendial medium (phosphate buffer, pH 6.8) and 0.1 N HCl containing 0%, 5%, 10%, 20%, and 40% ethanol.

Exposure to 5% and 10% ethanol in pH 6.8 buffer showed no change in modified release characteristics, especially in the first 2 hours, as the profiles were similar to 0% ethanol. Exposure to 20% and 40% ethanol showed faster release profiles compared to 0% ethanol. For the 100 mg strength, the f2 values are <50 in 20% and 40% ethanol, while the 200 mg strength had an f2 value <50 only in 40% ethanol. The f2 values and dissolution profiles are presented in Tables 8 and 9 and Figures 10 and 11 below.

Table 8. Mean Dissolution Results for SPN-812V ER Capsules, 100 mg (50 mM Potassium Phosphate Buffer, pH 6.8 with Different Ethanol Levels)

Dissolution Media:	Time (hours)										Similarity Factor, f2
% Ethanol	0.5	1	2	4	6	8	10	14	16	20	
0% (Sample ID 33013)	20	22	30	49	62	74	82	93	97	100	
5% (Sample ID 33069)	19	22	31	52	67	79	89	98	101	104	69
10% (Sample ID 33070)	20	22	32	56	70	83	93	103	105	107	57
20% (Sample ID 33071)	20	26	41	68	84	94	100	105	106	107	41
40% (Sample ID 32960)	74	103	106	106	107	107	107	108	108	109	14

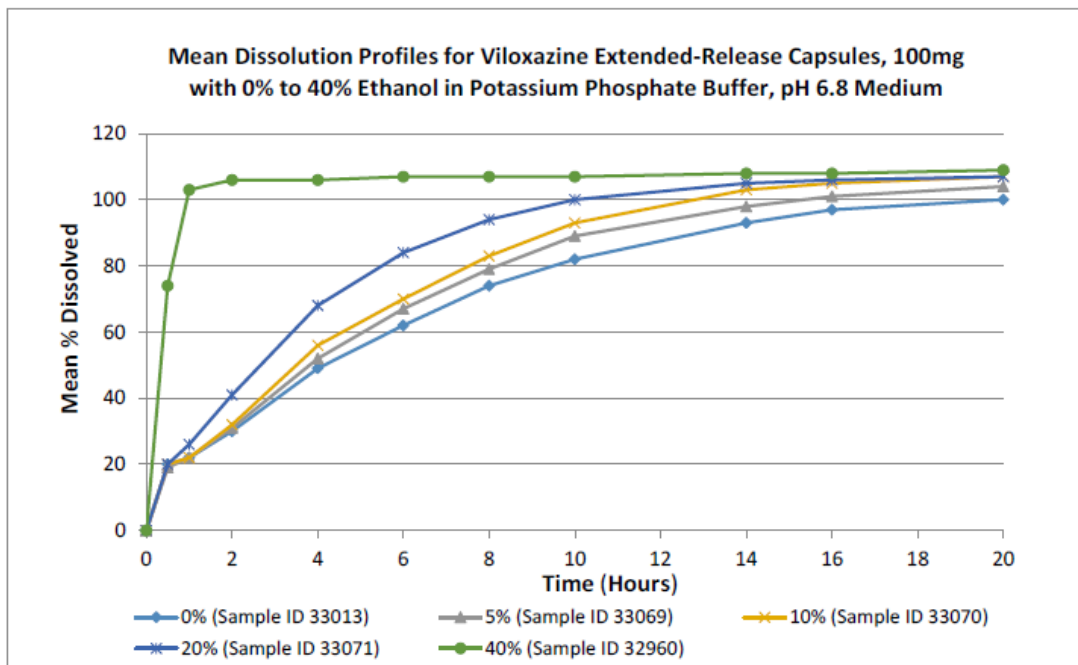


Figure 10. Mean dissolution profiles for SPN-812V ER capsules, 100 mg (50 mM potassium phosphate buffer, pH 6.8 with different ethanol levels)

Table 9. Mean Dissolution Results for SPN-812V ER Capsules, 200 mg (50 mM Potassium Phosphate Buffer, pH 6.8 with Different Ethanol Levels)

Dissolution Medium:	Time (hours)										Similarity Factor, f2
% Ethanol	0.5	1	2	4	6	8	10	14	16	20	
0% (Sample ID 33014)	19	21	28	47	62	76	86	96	98	101	
5% (Sample ID 33072)	18	21	31	52	69	83	93	102	104	107	64
10% (Sample ID 33073)	18	21	34	57	73	87	96	104	106	107	54
20% (Sample ID 33074)	18	21	31	53	69	82	92	103	105	108	65
40% (Sample ID 32962)	56	97	104	105	105	105	106	106	106	106	14

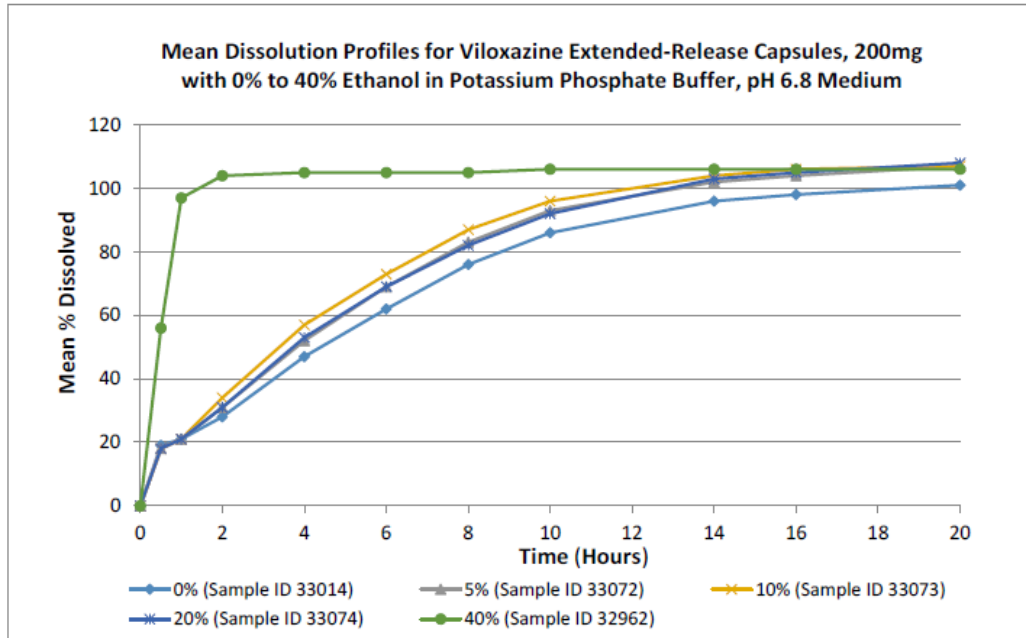


Figure 11. Mean dissolution profiles for SPN-812V ER capsules, 200 mg (50 mM potassium phosphate buffer, pH 6.8 with different ethanol levels)

In 0.1 N HCl, a similar trend was observed where the f2 values for both strengths are <50 in 20% and 40% ethanol. The f2 values and dissolution profiles are presented in Tables 10 and 11 and Figures 12 and 13 below.

Table 10. Mean Dissolution Results for SPN-812V ER Capsules, 100 mg (0.1 N HCl, pH 1.1 with Different Ethanol Levels)

Dissolution Media:	Time (hours)										Similarity Factor, f2
% Ethanol	0.5	1	2	4	6	8	10	14	16	20	
0% (Sample ID 33081)	20	22	27	43	54	64	72	84	89	95	
5% (Sample ID 33082)	20	22	26	46	57	66	75	88	92	98	78
10% (Sample ID 33083)	19	21	26	47	59	68	76	89	94	101	71
20% (Sample ID 33084)	20	23	38	64	78	89	97	106	108	110	36
40% (Sample ID 33080)	36	77	101	107	108	109	110	112	112	113	16

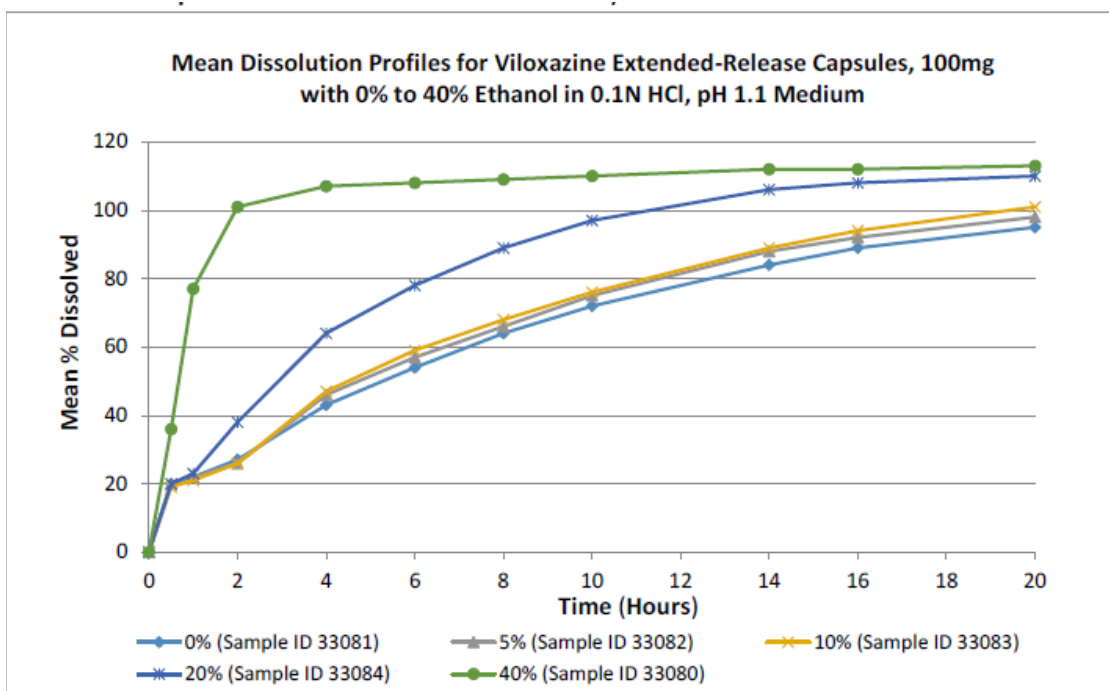


Figure 12. Mean dissolution results for SPN-812V ER capsules, 100 mg (0.1 H HCl, pH 1.1 with different ethanol levels)

Table 11. Mean Dissolution Results for SPN-812V ER Capsules, 200 mg (0.1 N HCl, pH 1.1 with Different Ethanol Levels)

Dissolution Media:	Time Points (hours)										Similarity Factor, f ₂
% Ethanol	0.5	1	2	4	6	8	10	14	16	20	
0% (Sample ID 33076)	18	21	27	43	55	64	73	85	90	95	
5% (Sample ID 33077)	18	21	26	46	57	67	76	89	94	99	79
10% (Sample ID 33078)	18	21	25	44	55	63	70	84	89	97	88
20% (Sample ID 33079)	17	21	45	72	85	93	99	104	105	106	33
40% (Sample ID 33075)	38	79	102	105	106	106	107	108	108	109	15

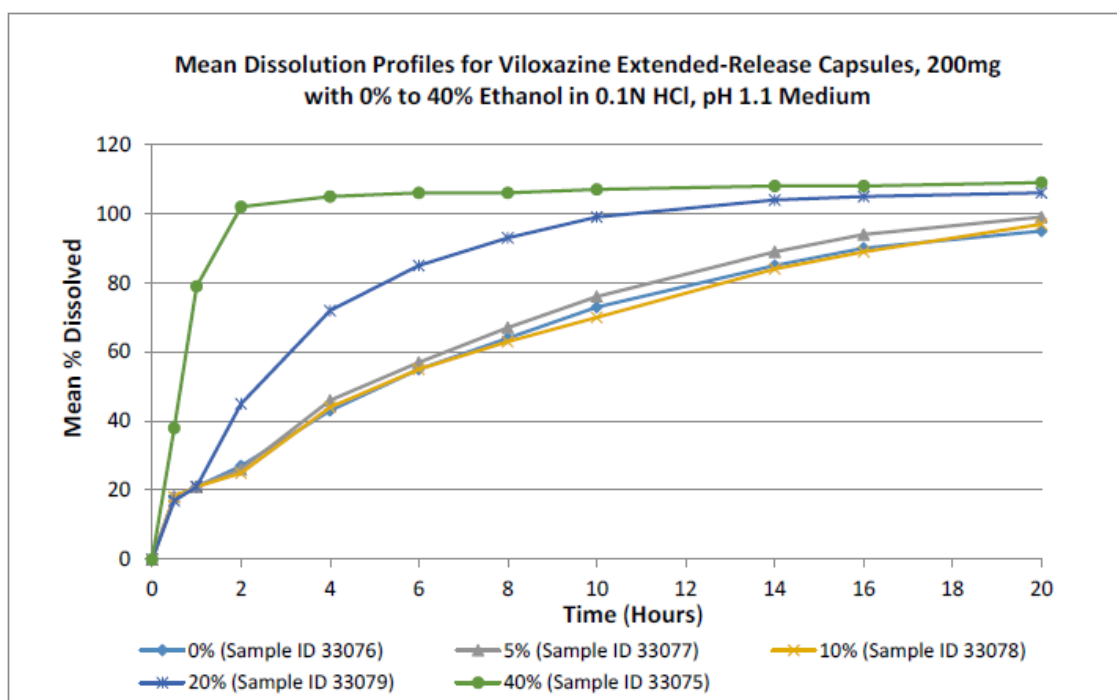


Figure 13. Mean dissolution results for SPN-812V ER capsules, 200 mg (0.1 H HCl, pH 1.1 with different ethanol levels)

Because the extended release profile is not maintained in 20% and 40% ethanol, there may be a risk for dose dumping. The Applicant conducted Study #812P115 “Effect of Alcohol on the Bioavailability of SPN-812 ER Capsules in Healthy Adult Males” to evaluate the effect of alcohol on the bioavailability, assess the safety and tolerability, and evaluate the effect of alcohol on Tmax of a single dose of SPN-812 ER 200 mg capsules when co-administered with 0%, 4%, 20%, and 40% alcohol under fasted conditions. The acceptability of this study is deferred to OCP.

B.4 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: Adequate

Dissolution testing of the contents of Viloxazine ER Capsules, 200 mg was conducted in the compendial medium after exposure to applesauce. The contents were exposed to applesauce (~15 g) for 5 minutes prior to dissolution testing. The dissolution profiles (Figure 14) of the capsule contents exposed to

applesauce and unexposed were similar ($f_2=64$). Therefore, exposure to applesauce does not affect the drug release profile in pH 6.8 phosphate buffer.

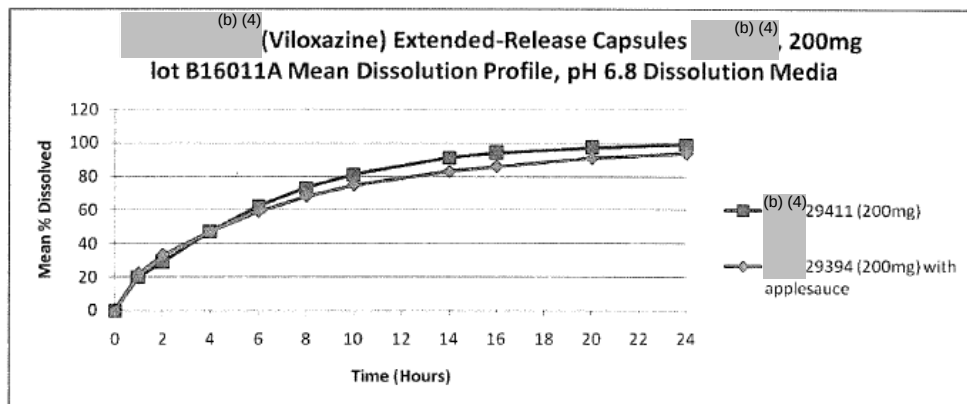


Figure 14. Comparison of mean dissolution profiles for (b) (4) (Viloxazine) extended-release capsules (b) (4), 200 mg lot B16011A (from bulk lot B16011) (contents exposed to applesauce vs. intact capsules)

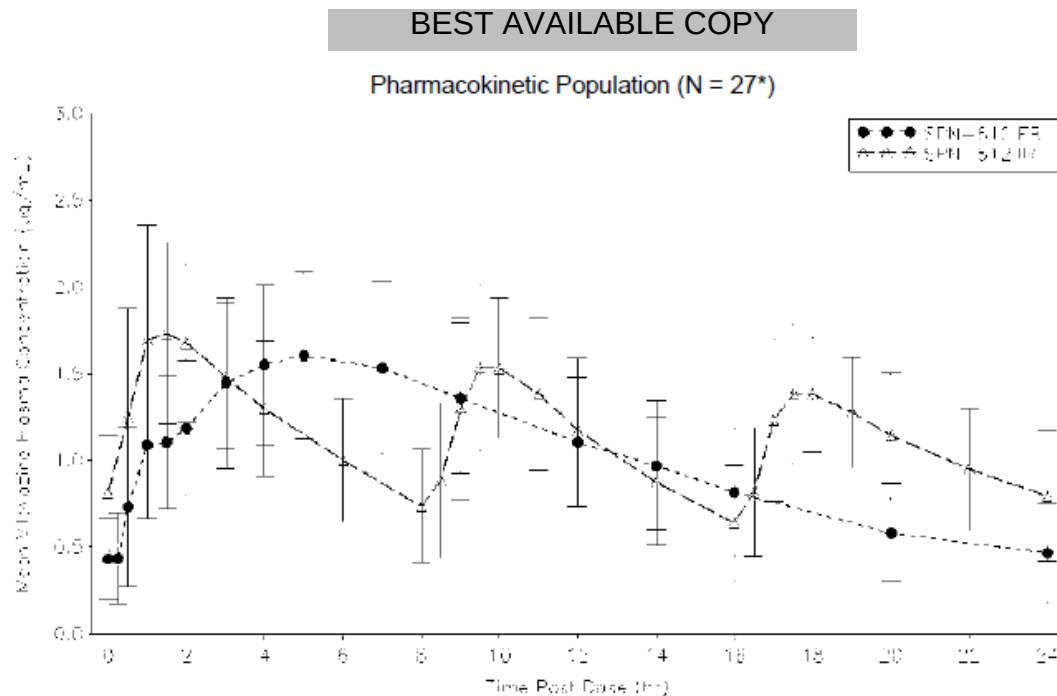
B.5 EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim Assessment: Adequate

The Applicant has submitted the following information to support the extended release designation claim:

- The Dosage and Administration section of the proposed labeling indicates once daily dosing;
- The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a non-controlled release comparator drug product;
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;

Data from Study #812P103 showed that the SPN-812 ER product's steady state performance is comparable to the SPN-812 IR product over the course of 4 days of dosing. The % Fluctuation for the ER product qd was 124.9% while the IR product q8h had 119.0% fluctuation (Figure 15 and Table 12). The overall systemic exposure was also comparable between the ER and IR products with

AUC₀₋₂₄ being 24.7 hr ug/mL for the ER product qd and 27.3 hr ug/mL for the IR product q8h.



*ER treatment data for one subject were excluded due to emesis within 24 hr of dosing.

Figure 15. Plot of mean ($\pm$ SD) viloxazine plasma concentrations versus time by treatment after multiple dose on a linear scale

Table 12. Statistical Analysis of Viloxazine Steady-State Relative Bioavailability Following Administration of SPN-812 ER to SPN-812 IR

PK Parameter (units)	Geometric LS Mean		LS Mean Ratio (Test/Ref) (%)	CV%	90% CI (%)
	SPN-812 ER (Test)	SPN-812 IR (Ref)			
C _{max,ss} (µg/mL)	1.593	1.844	86.4	15.7	(80.3, 92.9)
C _{avg} (h*µg/mL)	0.981	1.071	91.6	12.5	(86.4, 97.1)
AUC ₀₋₂₄ (h*µg/mL)	23.5	25.7	91.6	12.5	(86.4, 97.1)
C _{min,ss} (µg/mL)	0.320	0.534	60.0	41.3	(49.9, 72.1)
%FL (%)	124.9	119.0	105.0	16.4	(97.3, 113.2)

CI = confidence interval; CV = coefficient of variation; ER = extended release; IR = immediate release; LS = least square.

The data support the extended-release claim for the proposed product and is acceptable.

B.6 BRIDGING OF FORMULATIONS

Assessment: Adequate

Following the completion of Phase 1 study #812P103, the formulations (b) (4) for the to-be-marketed (TBM) commercial drug product. The bulk capsule formulation for the 100 mg and 200 mg strengths are identical in composition to the TBM formulation with the exception of the capsule shells. The developmental scale formulations and pivotal clinical batches were manufactured at Supernus in Rockville, MD. The commercial products and primary stability registration batches were manufactured at the intended commercial manufacturing site, Catalent in Winchester, KY.

In support of bridging the development scale batches manufactured at Supernus to the TBM commercial scale batches manufactured at Catalent, comparative batch release analysis was performed. The f2 values comparing the Phase 3 and Registration batches to the Phase I developmental batch are all >50. The formulation bridging is therefore adequate.

B. 7 BIOWAIVER REQUEST

Assessment: Adequate

The 100 mg and 200 mg strengths were developed during the clinical development program. The proposed 150 mg strength was introduced to the drug product line after the registration activities for the 100 mg and 200 mg strengths. In support of the waiver request for the 150 mg strength, the Applicant has submitted comparative dissolution data and formulation comparison. The 150 mg strength uses the same (b) (4) as the 100 mg and 200 mg strengths (b) (4). Overall, the 150 mg strength capsules are proportional to the 100 mg and 200 mg strength. The formulations are presented in Table 13.

Table 13. Formulation Proportionality of the Overall Composition of Viloxazine Extended-Release Capsules, 100 mg, 150 mg, and 200 mg Produced at Catalent

Component	Reference to Quality Standard	Function	100mg Capsule		150mg Capsule		200mg Capsule	
			Theoretical Amount per Capsule (%)	Theoretical Amount per Capsule (mg/capsule) ^a	Theoretical Amount per Capsule (%)	Theoretical Amount per Capsule (mg/capsule) ^a	Theoretical Amount per Capsule (%)	Theoretical Amount per Capsule (mg/capsule) ^a
Viloxazine Hydrochloride ^a	Supernus in-house standard	Active ingredient	41.95	115.5	41.95	173.23	41.95	231.0
(b) (4)								
Total capsule weight				351		520		681
(b) (4)								

The dissolution profile for 1 batch of the 150 mg strength (batch #3828169) was compared to 3 primary registration batches and the phase 3 clinical batches of the 100 mg and 200 mg strengths. The dissolution profiles were found to be similar with f2>50 (Table 14 and Figure 16).

Table 14. Dissolution Similarity Factor (f₂) for Viloxazine Extended-Release Capsules, 150 mg Compared with 100 mg and 200 mg

Dissolution Timepoint (hours)	Mean Percent Dissolved ^a					
	150mg capsules (batch 3828169)	100mg capsules (primary registration batches 1668200, 1668201, 1668202)	100mg capsules (Phase 3 clinical batch 1634350)	200mg capsules (primary registration batches 1668203, 1668204, 1668205)	200mg capsules (Phase 3 clinical batch 1634203)	200mg capsules (812P103 clinical batch B15014B) ^b
1	20	22	21	22	22	21
2	28	34	29	30	30	30
4	49	55	51	49	49	47
6	66	72	68	62	62	61
8	80	85	82	75	73	72
10	89	93	90	84	83	81
12	94	98	96	N/A	N/A	N/A
14	98	100	99	96	94	92
16	99	102	100	99	97	96
20	N/A	N/A	N/A	102	101	100
24	N/A	N/A	N/A	103	103	102
Dissolution Similarity Factor (f₂) ^c	N/A	64	86	72	68	64

^a N/A indicates not applicable.

^b Tested as primary packaged batch B15014A.

^c Calculated using mean results at time points 1, 2, 4, 6, 8, and 10 hours; f₂ value ≥ 50 indicates similar dissolution profiles.

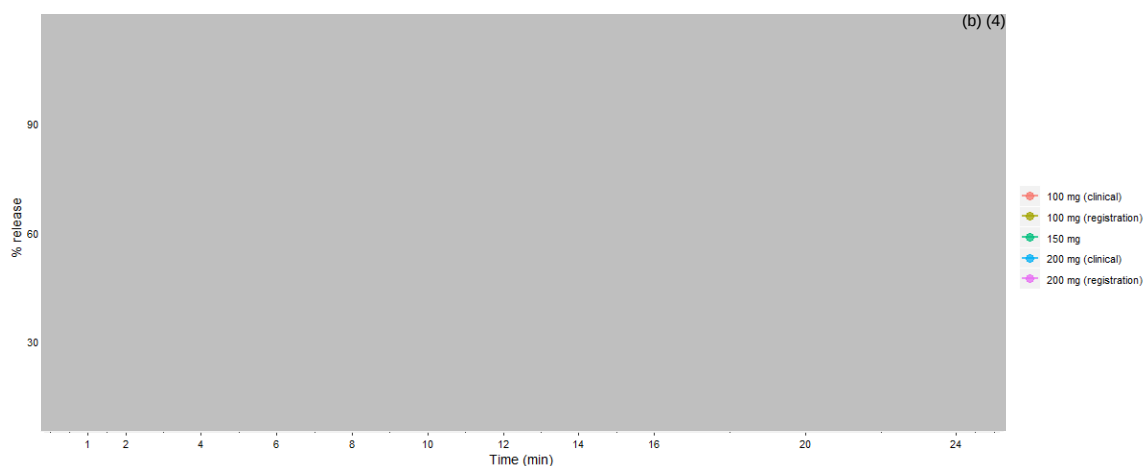


Figure 16. Comparison of mean dissolution profiles for SPN-812V ER Capsules 150 mg to 100 mg and 200 mg registration and clinical batches

Based on the formulation proportionality and dissolution similarity, the waiver for the 150 mg strength of Viloxazine ER Capsules is granted provided OCP finds the pivotal clinical studies acceptable.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None



Ta-Chen
Wu

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