

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211371Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

**NDA 211371
Review #1**

Drug Name/Dosage Form	Brexanolone Injection
Strength	100 mg/20 ml (5 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sage Therapeutics, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0001	4/19/2018	All
0004	5/29/2018	Microbiology
0010	07/18/2018	Microbiology
0012	7/30/2018	Drug Substance/Drug Product
0014	7/31/2018	Microbiology
0019	8/28/2018	Drug Substance/Drug Product/Micro
0021	9/05/2018	Microbiology

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Raymond Frankewich	Charles Jewell
Drug Product	Andrei Ponta	Wendy Wilson-Lee
Process	Anitha Govada	Derek Smith
Microbiology	Wendy Tan	Brian Riley
Facility	Anitha Govada	Derek Smith
Biopharmaceutics	Qi Zhang	Ta-Chen Wu
Laboratory (OTR)	Cindy Diem Ngo	Hongping Ye
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	David Claffey	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type V		(b) (4)	adequate	7/30/2018	
	Type V		adequate	12/03/2015		
	Type V		adequate	4/25/2017		
	Type III		Adequate			
	Type III		adequate			

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Brexanolone injection

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

Sage Therapeutics developed Zulresso (brexanolone injection) for the treatment of postpartum depression (IND (b) (4)). There are currently no approved drug products for the treatment of postpartum depression. The dose regimen is administered as a continuous intravenous infusion over a total of 60 hours. The drug product is supplied in vials of 100 mg brexanolone in 20 ml of a sterile colorless preservative-free (b) (4) solution (5 mg/mL). The drug product is intended for dilution by a pharmacist prior to administration. The 60-hour infusion begins with a starting dose of 30 mcg/kg/h for 4 hours, which is increased to 60 mcg/kg/h for 20 hours, and further increased to 90 mcg/kg/h for 28 hours. The dose is then ramped down to 60 mcg/kg/h for 4 hours, and finally to 30 mcg/kg/h for the last 4 hours. In-use stability studies found that the diluted solutions can be stored for a maximum of (b) (4) hours in refrigerated conditions followed by 12 hours at room temperature.

Therefore, the infusion bag will have to be changed every 12 hours instead of every (b) (4)

As the drug substance is very water insoluble, a considerable quantity of a cyclodextrin solubilizer is employed, betadex sulfobutyl ether sodium. This is also known as by one of its brand names, Captisol. Each vial contains 5 g of this excipient (250 mg/mL). The diluted drug product was found to be compatible with just one type of infusion tubing (polyolefin, non-DEHP, non-latex IV bag and the PVC, non-DEHP, nonlatex, no filter tubing system). An initial extractable study to on (b) (4) lines found significant levels of extractables. The compatible infusion bag and tubing will require identification in the labeling.

A 36-month drug product expiry period was found acceptable (refrigerated storage). Unused residual brexanolone will need to be discarded each day (should not be used for the next day's doses).

Proposed Indication(s) including Intended Patient Population	Treatment of postpartum depression
Duration of Treatment	60 hours
Maximum Daily Dose	90 mcg/kg/h (2.16 mg/kg/day)
Alternative Methods of Administration	none

B. Quality Assessment Overview

DRUG SUBSTANCE: Brexanolone is a white to off-white crystalline powder. Brexanolone was more widely known by its non-USAN name of allopregnalone – which is an endogenous steroid. Polymorphic (b) (4) was used for this product. During development (b) (4) procedures were used to manufacture brexanolone. Process A was used during early clinical development and for nonclinical studies and Process B1 for the clinical studies and registration stability batches. Process B2 is the proposed commercial process and was used to produce engineering and validation batches. The three processes were determined to be comparable, with most of the differences involving (b) (4). Primary stability data through (b) (4) months storage (b) (4) generated using batches produced using process B1 at the proposed commercial site (b) (4) were found to support the proposed (b) (4) month expiry period. Brexanolone is light-sensitive. The commercial process (b) (4)

These issues are discussed in sections S.3 and S.7 and were found to be adequately controlled. The drug substance specification is typical and adequately controls the drug substance. This includes two specified impurities (b) (4)

DRUG PRODUCT: The drug product is a sterile, clear, colorless, and preservative-free solution. Brexanolone injection is intended for dilution for administration as an intravenous infusion. The drug product vial contains 100 mg of brexanolone in a 20 ml solution (5 mg/mL). As the drug substance is very water insoluble, betadex sulfobutyl ether sodium is employed as a solubilizer. This excipient is also known as Captisol, one of its brand names. Each vial contains 5 g of this excipient (250 mg/mL). Citric acid and sodium citrate as used as (b) (4). Hydrochloric acid and sodium hydroxide are added to adjust the pH of the (b) (4)

(b) (4) The drug product solution is packaged in a 20-mL glass vial with a rubber stopper and aluminum cap. It requires storage under refrigerated conditions. The proposed a 36-month expiry was found acceptable.

The drug product solution requires dilution prior to The diluted drug product was found to be compatible with just one type of infusion tubing (b) (4) polyolefin, non-DEHP, non-latex IV bag and the PVC, non-DEHP, nonlatex, no filter tubing system). An initial extractable study to on (b) (4) lines found significant levels of extractables. The compatible infusion bag and tubing will need to be identified in the labeling.

The drug product specification is typical for the proposed dosage form. It included limits for the (b) (4) These were found

acceptable in consultation with the pharm/tox review team. (b) (4)

PROCESS: The drug product manufacturing (b) (4)

(b) (4)

FACILITIES: Following a review of the application, inspectional documents, and compliance history of the facilities responsible for the manufacture of the drug product, no pre-approval inspections were warranted. There are no significant, outstanding manufacturing or facility risks that prevent approval of this application. All listed facilities are found to be acceptable for their proposed manufacturing and testing operations.

MICRO: Based on the results of an in-use study which found growth between 16 and 48 hours, the applicant performed an additional study to determine the time at which growth of the gram-negative bacteria has increased. The test organisms *E. coli*, *P. aeruginosa*, and *S. marcescens* were inoculated in both 0.5 mg/mL and 1.5 mg/mL diluted drug product and incubated at room temperature. The results showed that $>0.5 \log_{10}$ growth started around (b) (4) of the diluted drug products when stored at room temperature. Therefore, the applicant proposed to retain the (b) (4) in-use period but changed the storage condition to up to (b) (4) refrigerated (previously (b) (4) and limit room temperature infusion time to 12 hours (previously (b) (4) hours) for the product package insert labeling. The review team was made aware of this change as the infusion bag will now have to be changed every 12 hours instead of every (b) (4). The remainder of the (b) (4) manufacturing process and controls were found adequate from a microbiological perspective.

BIOPHARM: A detailed evaluation was found to be not required as the drug substance is in solution.

ENVIRONMENTAL: The environmental assessment team found the data to be indicative of no significant environmental impact and thus to be adequately supportive of the claim for an exclusion from an EA. The required statement of no extraordinary circumstances also was provided, in accordance with 21 CFR 25.15 and the claim for an exclusion from an EA was found acceptable.

OTR Verification: OTR verified the drug substance and drug product identification, assay and impurity methods and the method for (b) (4) content in the drug substance.

C. Special Product Quality Labeling Recommendations (NDA only)

Ensure that the in-use storage periods are clear and the compatible infusion bags and tubing are used. Ensure that the unused product is discarded at the end of each day.

D. Final Risk Assessment (see Attachment)



David
Claffey

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List of Deficiencies: None.

Primary Drug Substance Reviewer Name and Date:

Raymond P. Frankewich, Ph.D.

August 31, 2018

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

Suong T. Tran, Ph.D.

August 31, 2018



Su (Suong)
Tran

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Raymond
Frankewich

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Andrei
Ponta

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Wendy
Wilson- Lee

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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	ZULRESSO, Brexanolone Injection
Dosage form and route of administration	Injection, IV
Active moiety expression of strength with equivalence statement (if applicable)	NA
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Sulfobutyl ether beta-cyclodextrin (250 mg/mL), sodium citrate (2.57 mg/mL), citric acid (0.265 mg/mL), hydrochloric acid, and sodium hydroxide <i>Reviewer's Note: Applicant will be asked to list the inactive ingredients in alphabetical order and to refer to excipients by nonproprietary name only</i>
Statement of being sterile (if applicable)	Sterile
Pharmacological/ therapeutic class	Positive allosteric modulator of GABAA receptors
Chemical name, structural formula, molecular weight	C ₂₁ H ₃₄ O ₂ , 318.5 Da
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	NA

5. Section 16 How Supplied/Storage and Handling



Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	100 mg/ 20 mL (5 mg/mL)
Available units (e.g., bottles of 100 tablets)	20 mL vial
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<i>Reviewer's Note: Applicant will be asked to include the NDC number</i>
Special handling (e.g., protect from light)	Protect from light
Storage conditions	2°C to 8°C (36°F to 46°F)
Manufacturer/distributor name (21 CFR	Sage Therapeutics



Andrei
Ponta

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Wendy
Wilson- Lee

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List of Deficiencies:

None

Primary Process Reviewer Name and Date: Anitha Palamakula Govada, 8/6/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Derek Smith, 8/22/2018



Anitha
Govada

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Derek
Smith

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Comparability Protocols

Reviewer's Assessment: *None*

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: *None.*

Lifecycle Management Considerations

None

List of Deficiencies: None.

A review of the inspectional documents for the facilities covered in the application indicates there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. Therefore, the manufacturing facilities for NDA 211371 are found to be acceptable.

Primary Facilities Reviewer Name and Date: Anitha Palamakula Govada, 8/27/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Derek Smith 8/27/2018



Anitha
Govada

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Derek
Smith

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BIOPHARMACEUTICS**NDA: 211371****Submission Type: 505b(1) Type 1-NME****Drug Product Name / Strength: ZULRESSO™ (brexanolone injection), 5 mg/ 1 mL****Route of Administration: Intravenous****Dosage Form: Injection, Solution****Applicant Name: Sage Therapeutics, Inc.****Intended for Use: Treatment of postpartum depression****Submit date: 4/19/2018****REVIEW SUMMARY**

Brexanolone Injection 5 mg/mL is a sterile, clear, colorless solution intended for dilution followed by intravenous infusion. The drug product contains brexanolone, Captisol® as a solubilizer, citric acid and sodium citrate as (b) (4) and water for injection, USP.

Early clinical studies (PPD-201, (b) (4) and CLP-101) were conducted with (b) (4)

(b) (4) he final formulation used in all the subsequent Phase 1 PK characterization and Phase 2 (547-PPD-202A) and Phase 3 studies (547-PPD-202B and 547-PPD-202C). The (b) (4) formulation used in clinical studies is the same as the proposed commercial drug product formulation. The manufacturing site of the clinical batches is also the proposed commercial site. Therefore, bridging between the clinical and the proposed commercial drug products is not needed.

Conclusion and Recommendation:

A detailed review by the Division of Biopharmaceutics is not needed for this NDA regarding ZULRESSO (brexanolone injection), 5 mg/ 1 mL, considering the proposed dosage form and no relevant Biopharmaceutics issues that need to be addressed.

Primary Biopharmaceutics Reviewer Name and Date:**Qi Zhang, PhD 9/4/2018****Secondary Reviewer Name and Date:****Ta-Chen Wu, PhD 9/4/2018**



Qi
Zhang

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Ta-Chen
Wu

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MICROBIOLOGY

Product Background

NDA: 211371

Drug Product Name / Strength: Zulresso, (b) (4) solution for infusion, 5 mg/mL

Route of Administration: Intravenous Infusion

Applicant Name: Sage Therapeutics, Inc., 215 First Street, Ste 220, Cambridge, MA 02142

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Theme (ANDA only): Product sterility assurance

Justification (ANDA only): N/A

Review Summary:

- The submission is **recommended** for approval on the basis of sterility assurance.
- The product is (b) (4). There are no deficiencies identified based on the information submitted.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
04/19/2018	04/19/2018	N/A	04/26/2018
05/29/2018	05/29/2018	N/A	05/30/2018
07/18/2018	07/18/2018	N/A	07/19/2018
08/28/2018	08/28/2018	N/A	08/29/2018
09/05/2018	09/05/2018	N/A	09/06/2018

Highlight Key Outstanding Issues from Last Cycle: N/A – this is the first cycle review

Remarks:

- This application is designated “breakthrough Therapy” and “Fast Track” status.
- Information requests and responses from 07/18/2018, 08/28/2018, and 09/05/2018 are included in this review.

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

- Type V DMF# (b) (4) owned by (b) (4) for their (b) (4)

- DMF (b) (4) microbiology review (b) (4) dated 7/30/2018 (adequate)
- Type V DMF# (b) (4) owned b (b) (4)
- Type V DMF # (b) (4) owned by (b) (4)
- Microbiology review (b) (4) .doc dated 7/16/2015 (inadequate); (b) (4) dated 11/02/2015 (inadequate); (b) (4) dated 12/03/2015 (adequate); (b) (4) dated 08/04/2017 (adequate)
- Microbiology review (b) (4) dated 2/3/2017; and (b) (4) dated 4/25/2017 (adequate)

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

Reviewer's Assessment:

The drug substance is (b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – A sterile, clear, colorless solution intended for dilution followed by intravenous infusion. Indicated for the treatment of postpartum depression.
- **Drug product composition – (P.3.2.)**

Ingredient	Function	Content (mg/mL)
Brexanolone (Allopregnanalone), in-house	API	5.0
Sulfobutyl ether beta-cyclodextrin (SBECD), USP/NF	Solubilizing Agent	250.0
Sodium citrate, dihydrate, USP/Ph. Eur.	(b) (4)	2.57
Citric acid monohydrate, USP/Ph. Eur.	(b) (4)	0.265
Hydrochloric Acid, NF/Ph. Eur.	pH adjustment	(b) (4)
Sodium Hydroxide, NF/Ph. Eur.	pH adjustment	(b) (4)
WFI, USP/Ph. Eur.	(b) (4)	(b) (4)

- **Description of container closure system – (P.2.3, P.3.2)**

Configuration	Component	Description	Manufacturer
5 mg/mL, 20 mL fill	Glass Vial	Type ^{(b) (4)} clear ^{(b) (4)} glass vial, 20 mm	^{(b) (4)}
	Stopper	20 mm ^{(b) (4)} rubber stopper	
	Aluminum cap	20 mm flip-off blue seal, aluminum cap	

Exhibit Batch: Executed batch record for Lot B170524 is provided in the submission. The lot is a pre-validation scale up for ^{(b) (4)} theoretical yield of ^{(b) (4)} vials.
 Proposed Commercial Batch Size: ^{(b) (4)} vials)

Reviewer's Assessment: Adequate

Information provided for the drug product composition and container closure system is adequate.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes



^{(b) (4)}

List of Deficiencies: NDA 211371

There are currently no deficiencies identified based on the information submitted.

Primary Microbiology Reviewer Name and Date:

Wendy Tan, Ph.D.

Microbiologist

CDER/OPQ/OPF/DMA/BII

September 7, 2018

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

Bryan S. Riley, Ph.D.

Branch Chief

CDER/OPQ/OPF/DMA/BII

September 7, 2018



Wendy
Tan

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Bryan
Riley

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**METHOD VERIFICATION
REPORT SUMMARY**

Date: August 30, 2018

To: Andrei Ponta, Drug Product Reviewer
Raymond Frankewich, Drug Substance Reviewer
Teshara Bouie, Project Manager

Through: Hongping Ye, Acting Lab Chief Branch I, OPQ/OTR/DPA

From: Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPA
Cynthia Sommers, MVP Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 211371: Brexanolone Solution for Infusion
5 mg/mL

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. 3.2.P.5.2 Control of Drug Product: Identification, Assay and Degradation Products of Brexanolone Injection 5mg/mL, Intravenous Infusion using HPLC-UV at 205 nm.
2. 3.2.S.4.2 Control of Drug substance: Assay, Impurities and Identification of Brexanolone in the Drug substance (Brexanolone, [REDACTED] (b) (4))
3. 3.2.S.4.2 Control of Drug substance: [REDACTED] (b) (4)

Original analyst worksheets can be viewed using this ECMS link:
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f881bae411>

Summary of Analysis

1. 3.2.P.5.2 Control of Drug Product: Identification, Assay and Degradation Products:

Assay: % LC of brexanolone injection 5 mg/mL is 100.4 %, Specification (b) (4) %, pass

% Degradation products:

Name	Average (n=3 vials)	Specifications
Unknown	(b) (4) %	NMT (b) (4) %, pass
(b) (4)	(b) (4) %	NMT (b) (4) %, pass
(b) (4)	(b) (4) %	NMT (b) (4) %, pass
(b) (4)	(b) (4) %	NMT (b) (4) %, pass
Total % Degradation products	(b) (4) %	NMT (b) (4) %, pass

Identification by Retention time: The retention time of the main peak in the sample chromatogram matches the average retention time of the brexanolone peak in the standard injections within (b) (4) %.

Identification by UV: The UV spectrum of the main peak in sample chromatogram is consistent with the UV spectrum of the brexanolone peak in the standard injection.

2. 3.2.S.4.2 Control of Drug substance: Assay, Impurities and Identification of Brexanolone in the Drug substance (b) (4)

Assay: % brexanolone in drug substance is 100.1 %, Specification (b) (4) %, pass

% Impurities:

Name	Average (n=3)	Specifications
(b) (4)	(b) (4) %	NMT (b) (4) %, pass
(b) (4)	(b) (4) %	NMT (b) (4) %, pass
Each unspecified and identified	(b) (4) %	NMT (b) (4) % % each, pass
Each unspecified and un-identified	(b) (4) %	NMT (b) (4) % % each, pass
Total % Impurities	(b) (4) %	NMT (b) (4) %, pass

ND: Not Detected

Identification by Retention time: The retention time of the main peak in sample chromatogram matches the retention time of the brexanolone peak in the standard injections within (b) (4) of the standard.

Identification by UV: The UV spectrum of the main peak in sample chromatogram is consistent with the UV spectrum of the brexanolone peak in the standard injection.

3. 3.2.S.4.2 Control of Drug substance: (b) (4)

(b) (4)

ATTACHMENT I: Final Risk Assessments

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability (impurities/ degradation products)		L	(b) (4)	Acceptable	
Uniformity of Dose		L		Acceptable	
Reconstituti on Time		L		Acceptable	
Physical Stability		M		Acceptable	
Endotoxins		H		Acceptable	
Sterility		H		Acceptable	Ensure that any labelign changes are supported by micro studies
Particulate Matter		M		Acceptable	
Extractables and Leachables	Captisol and tubing composition, in- use storage time and conditions	H		Acceptable	See drug product review. Evidence that certain infusion bags/lines can leach because of captisol excipient



David
Claffey

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