CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209521Orig1s000

PRODUCT QUALITY REVIEW(S)

Integrated Quality Assessment (IQA) for NDA 209521

Office of Pharmaceutical Quality (OPQ)

Executive Summary for NDA 209521

Recommendation:

From the OPQ perspective, this 505(b)(1) NDA is recommended for approval.

NDA 209521
Review # 1

Drug Name/Dosage Form	Seysara (sarecycline) tablets
Strength	60 mg, 100 mg, 150 mg tablets
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Allergan, Inc. Jillian McCumber 2525 Dupont Dr. Irvine, CA 92623
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	10-20-2017	All
Amendment	12-22-2017	Drug product, Drug product manufacturing process and Biopharmaceutics
Amendment	01-10-2018	Drug substance and Drug product
Amendment	02-08-2018	Drug substance
Amendment	03-05-2018	Drug product manufacturing process
Amendment	04-05-2018	Drug product and Quality microbiology

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bian	Branch II/Division of New Drug API
Drug Product	Caroline Strasinger	Branch V/Division of New Drug Products II
Process	Jingbo Xiao	Branch V/Division of Process Assessment III
Microbiology	Jingbo Xiao	Branch V/Division of Process Assessment III
Facility	Vidya Pai	Branch III/Division of Inspectional Assessment
Biopharmaceutics	Sandra Suarez	Branch III/Division of Biopharmaceutics
Regulatory Business Process Manager	Bamidele (Florence) Aisida	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type IV		(b) (4)	4	March 20, 2018	Adequate
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
End-of-Phase 2 Meeting Minutes	IND 107645	Discussions of the development plan for sarecycline tablets.
Pre-NDA Meeting Minutes	IND 107645	Discussions of the development plan for sarecycline tablets.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----	N/A	----	----
Pharmacology/Toxicology	----	N/A	----	----
CDRH	----	N/A	----	----
Clinical	----	N/A	----	----
Other	----	N/A	----	----

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility (OPF) has issued an "Acceptable" recommendation for the facilities involved in this application.

The revised Prescribing Information and mock-up container and carton labels are deemed satisfactory from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for approval.

II. Summary of Quality Assessments

A. Product Overview

The NDA of sarecycline tablets is submitted as a 505(b)(1) application by Allergan, Inc. The drug product, sarecycline tablets, are available in the following strengths: 60 mg (equivalent to 64.49 mg sarecycline hydrochloride), 100 mg (equivalent to 107.48 mg sarecycline hydrochloride) and 150 mg (equivalent to 161.22 mg sarecycline hydrochloride) of sarecycline free base.

The indication and recommended dose of the drug product are summarized in the following Table.

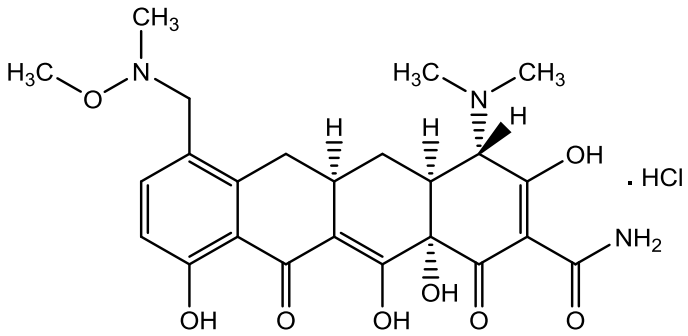
Proposed Indication(s) including Intended Patient Population	The drug product, Seysara (sarecycline) tablets (b) (4) (b) (4)
Duration of Treatment	Up to 12 weeks.
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The active pharmaceutical ingredient (API) in Seysara (sarecycline) tablets is sarecycline hydrochloride, (b) (4)

The chemical name for sarecycline hydrochloride is (4S,4aS,5aR,12aS)-4-(Dimethylamino)-3,10,12,12a-tetrahydroxy-7-[(methoxy-(methyl)-amino)-methyl]-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide monohydrochloride. The chemical structure of sarecycline hydrochloride is:



It has a molecular formula of $C_{24}H_{29}N_3O_8 \cdot HCl$ and a molecular weight of 523.96 g/mol. Sarecycline hydrochloride is a yellow to slightly green powder. It is sparingly soluble in water and methanol, slightly soluble in ethanol, and practically insoluble in acetonitrile. Its aqueous solubility increases with increasing pH (226 mg/mL at pH 8.0). It has pKa values of 2.03, 3.30, 7.60 and 9.92. It is sensitive to light and slightly hygroscopic.

The drug substance manufacturing process has been modified and optimized (b) (4)

(b) (4) The source and fate of potential organic impurities including mutagenic and genotoxic impurities are discussed. The levels of organic and inorganic impurities, and residual solvents are monitored and controlled in the drug substance specification. The identity, purity, strength and quality of the drug substance are adequately assured by the drug substance specification. All non-compendial test methods used for drug substance assay, and its related substances, genotoxic impurities (b) (4)

elemental impurities and residual solvents present in the drug substance were properly validated.

The drug substance is packaged [redacted] The proposed retest period of [redacted] months for the drug substance when stored [redacted] is supported by the stability data provided.

The review on the CMC information of the drug substance in the NDA has been conducted by Dr. Sam Bian. The NDA is recommended for **approval** from the drug substance perspective (See **CHAPTER I: Review of Drug Substance**).

Drug Product

The drug product, Seysara (sarecycline) tablets, is available in 3 different strengths, 60 mg, 100 mg, 150 mg. The active pharmaceutical ingredient (API) used in the tablets is sarecycline hydrochloride. The 60 mg tablets are capsule shaped, yellow, film-coated tablets debossed with "S60" on one side and blank on the other side. The 100 mg tablets are capsule shaped, yellow, film-coated tablets debossed with "S100" on one side and blank on the other side. The 150 mg tablets are capsule shaped, yellow, film-coated tablets debossed with "S150" on one side and blank on the other side. The inactive ingredients used in the drug product include: microcrystalline cellulose, povidone, sodium starch glycolate, and sodium stearyl fumarate. The yellow film coating [redacted] contains D&C yellow #10 aluminum lake, iron oxide yellow, methacrylic acid copolymer type C, polyethylene glycol, polyvinyl alcohol, sodium bicarbonate, talc, and titanium dioxide. There are no novel excipients or excipients of human or animal origin. All excipients are commonly used in oral tablet dosage forms.

Thirty tablets (30 tablets) are packaged in 60 cc square HDPE bottle with a 33 mm child resistant [redacted] cap [redacted] Three tablets (3 tablets) of the drug product are packaged 30 cc round white high density polyethylene (HDPE) bottle with a 28 mm child resistant [redacted] cap [redacted]

[redacted] All batches of the drug product met release specification and confirmed batch-to-batch consistency for release testing of the drug product. The drug product specification for Seysara tablets is deemed adequate to ensure the

identity, strength, purity, and quality of the drug product during its expiration dating period.

Stability studies were conducted on nine batches (3 batches for each tablet strength) of the drug product manufactured (b) (4) with the drug substance produced (b) (4) (b) (4) Stability studies were also conducted on three registration batches (one batch for each tablet strength) of the drug product manufactured (b) (4) with the drug substance produced (b) (4) (b) (4) (b) (4) Based on the available stability data of the drug product, a 24-month expiration dating period is recommended for sarecycline tablets, 60 mg, 100 mg, and 150 mg in the commercial packaging configurations when stored at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). The estimated EIC (expected introduction concentration) for the active moiety of the drug substance is (b) (4) ppb. The claim of categorical exclusion is acceptable per 21 CFR 25.31(b).

The drug product is recommended for **approval** from the drug product perspective. The recommended expiration dating period of the drug product is 24 months. The review on the CMC information of the drug product has been conducted by Dr. Caroline Strasinger (See **CHAPTER II: Review of Drug Product**).

Labeling and Labels

The revised Prescribing Information and mock-up container, carton and tray labels are deemed satisfactory from the CMC perspective. The sections of the Prescribing Information related to CMC, and container, carton and tray labels of the drug product of the NDA have been reviewed by Dr. Caroline Strasinger. (See **CHAPTER III: Review of Labeling and Labels**).

Drug Product Manufacturing Process

The proposed drug product, sarecycline tablets, is manufactured by a (b) (4) (b) (4)

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Packaging

(b) (4)

(b) (4) Film-coated tablets are packaged into HDPE bottles.

The batch formula, manufacturing process parameters, and in-process controls are deemed adequate to ensure the robustness of the drug product manufacturing process. The proposed manufacturing process, batch size (b) (4) and facility for intended commercial batches are the same as those used for manufacturing the registration batches of the drug product. The NDA is recommended for **approval** from the perspective of drug product manufacturing process. The review on the drug product manufacturing process has been conducted by Dr. Jingbo Xiao (See **CHAPTER IV: Review of Drug Product Manufacturing Process**).

Biopharmaceutics

The Applicant is seeking approval of Seysara (sarecycline) oral tablets (b) (4)

(b) (4)

The API is a tetracycline-class narrow spectrum antibiotic which exhibits antibacterial activity against clinical isolates of *P. acnes*. The immediate release (IR) film-coated tablets contain 60 mg, 100 mg, or 150 mg of sarecycline (equivalent to 64.5 mg, 107.5 mg, and 161.2 mg sarecycline hydrochloride, respectively). The proposed dose of the drug is (b) (4) once daily. According to the information provided by the Applicant, sarecycline is rapidly absorbed following oral administration of the immediate-release tablet formulation, displays linear and near dose-proportional pharmacokinetics within the range of 60 to 150 mg dosed once daily (QD).

Based on reported permeability and solubility study performed over a physiological pH range, as per Biopharmaceutical Classification System (BCS), sarecycline hydrochloride can be classified as a BCS Class III compound. According to the Applicant, (b) (4)

(b) (4)

The drug product underwent some major CMC changes through the development. Of relevance is a change in formulation from phase 1 (capsules) to phase 2 (film-coated tablets). The change in formulation and dosage form did not affect the in vivo performance of the product as demonstrated by the results of a BE study. The formulation used in the pivotal phase 3 studies is the same as the intended commercial one. No changes in manufacturing site for the drug product occurred from phase 3 to commercial production.

The *in vitro* release test method is summarized in the following Table.

Parameters of Dissolution Test Method

Test Parameter	Setting
Apparatus	USP Apparatus 2 - Paddle
Rotation speed (rpm)	75
Dissolution medium	0.1 N HCl
Medium Volume	500 mL
Medium Temperature	37°C ± 0.5°C

The acceptance criterion of the dissolution test is NLT (b) (4)% (Q) in 15 minutes.

The NDA is recommended for **Approval** from the perspective of Biopharmaceutics. The review on Biopharmaceutics of the drug product of the NDA has been conducted by Dr. Sandra Suarez (See **CHAPTER V: Review of Biopharmaceutics**).

Quality Microbiology

The drug product is immediate release oral tablets. Microbial limit tests, which include tests of total aerobic microbial count (TAMC), total combined yeasts and molds count (TYMC), and the test for *E. coli*, are included in the drug product specification.

Microbial examination was performed on the registration batches of sarecycline tablets as per USP <61> and <62> at release. All tested batches have conformed to the specification limits. (b) (4)

(b) (4)

The NDA is recommended for **Approval** from the perspective of quality microbiology. The review on microbiology controls of the drug product has been conducted by Dr. Jingbo Xiao and is included in his review for drug product manufacturing process (See **CHAPTER IV: Review of Drug Product Manufacturing Process**).

Facilities

The status of the facilities related to the **drug substance** manufacture and testing is summarized in the following Table:

Status of Facilities Related to Drug Substance Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
[redacted]	(b) (4)	Drug substance manufacture, release and stability testing (b) (4)	Acceptable
		Drug substance testing (b) (4) (CTL)	Acceptable

The status of the facilities related to the **drug product** manufacture and testing is summarized in the following Table:

Status of the Facilities Related to the Drug Product Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
(b) (4)		Drug product manufacturing (TCM)	Acceptable
		Drug product packaging (TCM)	Acceptable

All the facilities are deemed acceptable in their identified functions and responsibilities to support the **approval** of NDA 209521. The facility review of the NDA has been conducted by Dr. Vidya Pai (See **CHAPTER VI: Review of Facilities**).

C. Special Product Quality Labeling Recommendations
Protect from moisture and excessive heat.

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies (Attachment II)
None.

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessments - NDA

a) Drug Product

Final Risk Assessment for 209521 (Sarecycline Tablets, 60 mg, 100 mg and 150 mg)

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay and degradation products	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	Both the assay and degradation products of the drug product are quantitated using HPLC methods. All registration and supportive stability batches of sarecycline drug product demonstrated satisfactory chemical stability throughout the long term and accelerated stability studies (b) (4)
Content Uniformity (Uniformity of Dosage Units)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	4	3	24	The test is conducted per USP <905>. The content in each of the test sample is quantitated using an HPLC method. Process parameters (b) (4) (b) (4) (b) (4) are set. Additionally, test (b) (4) (b) (4) is implemented during drug product manufacturing process. All the batches of the drug product comply with USP <905> for the test of uniformity of dosage units.

Mirobial Limits: Total Aerobic Microbial Count (TAMC), Total Combined Yeasts and Molds Count (TYMC) and Test for *E. coli*	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	3	3	18	The microbial limit tests per USP <61 > and <62> are included in the drug product specification. (b) (4) (b) (4) (b) (4) All batches of the drug product tested have conformed to the specification limits for TAMC/TYMC at release and during stability studies.
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	4	2	16	Dissolution test in (b) (4) hydrochloric acid is included in the drug product specification. (b) (4) in dissolution tests at release and during stability studies.
(b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	NMT (b) (4)% (w/w) is proposed for (b) (4) the drug product specification. (b) (4) (b) (4)

FMECA: Failure Mode, Effects and Criticality Analysis

RPN: Risk Priority Number

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{bmatrix} D$$

Low Risk- RPN $\leq$ 25

Moderate Risk - 25 < RPN $\leq$ 60

High Risk - RPN > 60

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead's Assessment and Signature

From the OPQ perspective, the NDA is recommended for approval.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
8/8/2018

Yichun Sun

Digitally signed by Yichun Sun
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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 8/08/2018 04:40:00PM
GUID: 502d0913000029f9798ca689a802fa55

CHAPTER III: Review of Labeling and Labels

LABELING

R. Regional Information

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

SEYSARA™ (sarecycline) tablets for oral use
Initial U.S. Approval: 20XX

2) DOSAGE FORMS AND STRENGTHS

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 60 mg, 100 mg, 150 mg (b) (4) (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Seysara Established Name: (sarecycline) tablets for oral use	Adequate
Dosage form, route of administration	Dosage: Tablet Route: oral use	Adequate
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
Summary of dosage form and strength	Tablet: 60 mg, 100 mg, 150 mg	INADEQUATE preferred format with Dosage Form, colon and strengths

23-APR-2018 Reviewer Assessment: INADEQUATE

Applicant should modify the text of the dosage forms and strengths of the highlights for clarity as noted above. This information was communicated to OND Labeling Team on April 20, 2018.

18-JUL-2018 Reviewer Assessment: ADEQUATE

On 16-JUL-2018 the Applicant submitted revised labeling agreeing to all changes above. The Highlights section is now adequate.

2. "FULL PRESCRIBING INFORMATION

#3: DOSAGE FORM AND STRENGTHS

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	tablets	Adequate
Strengths: in metric system	60 mg, 100 mg, 150 mg	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	(b) (4)	INADEQUATE: Requested to remove (b) (4) (b) (4) by OND. (b) (4) (b) (4) it is deemed acceptable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yellow,capsule shaped, film coated	Adequate

23-APR-2018 Reviewer Assessment: Inadequate

Applicant should modify the text of the dosage forms and strengths for clarity as noted above. This information was communicated to OND Labeling Team on April 20, 2018.

18-JUL-2018 Reviewer Assessment: ADEQUATE

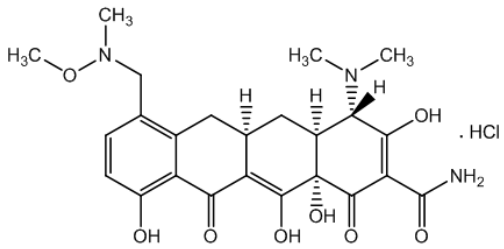
On 16-JUL-2018 the Applicant submitted revised labeling agreeing to all changes above. The Dosage Forms and Strengths section is now adequate.

#11: DESCRIPTION

11 DESCRIPTION

SEYSARA (~~S~~sarecycline) tablets are a tetracycline class drug for oral administration. Sarecycline hydrochloride, (b) (4) is chemically described as (4*S*,4a*S*,5a*R*,12a*S*)-4-(d~~D~~imethylamino)-3,10,12,12a-tetrahydroxy-7-[(methoxy-(methyl)-amino)- methyl]-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide monohydrochloride with an empirical formula of $C_{24}H_{29}N_3O_8$.HCl and a molecular weight of 523.96.

The structural formula is represented below:



SEYSARA tablets (b) (4) contain 64.5 mg, 107.5 mg, and 161.2 mg of sarecycline hydrochloride equivalent to 60 mg, 100 mg, and 150 mg sarecycline respectively. (b) (4)

Inactive ingredients in the tablet formulations are: microcrystalline cellulose (b) (4) povidone, sodium starch glycolate, and sodium stearyl fumarate. The yellow film coating contains D&C yellow #10 aluminium lake, iron oxide yellow, methacrylic acid copolymer type C, polyethylene glycol, polyvinyl alcohol, sodium bicarbonate, talc, and titatnium dioxide. (b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	Seysara (sarecycline)	INADEQUATE add tablets
Dosage form and route of administration	tablets; for oral administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Not provided	INADEQUATE Add contain 64.5 mg, 107.5 mg, and 161.2 mg of sarecycline hydrochloride equivalent to 60 mg, 100 mg, and 150 mg of sarecycline
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Microcrystalline cellulose, sodium stearyl fumarate, povidone, sodium starch glycolate. The film coating is (b) (4) yellow.	INADEQUATE Need to list in alphabetical order and remove (b) (4) and list ingredients instead.
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Not present	INADEQUATE Add tetracycline class
Chemical name, structural formula, molecular weight	Structure, molecular weight, formula presented	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	N/A	

23-APR-2018 Reviewer Assessment: INADEQUATE

Applicant should add therapeutic class, salt equivalency statements, and list the components (b) (4) Additional edits noted above of the Description should be made for clarity. This information was communicated to OND Labeling Team on April 20, 2018.

18-JUL-2018 Reviewer Assessment: ADEQUATE

On 16-JUL-2018 the Applicant submitted revised labeling agreeing to all changes above. The Description section is now adequate.

#16: HOW SUPPLIED/STORAGE AND HANDLING

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

1) **SEYSARA** (sarecycline (b) (4)) tablets, 60 mg are (b) (4) capsule shaped, yellow, film-coated tablets debossed with "S60" on one side and blank on the other side (b) (4) (b) (4)

- Bottles of 30 tablets with child-resistant closure: NDC: 0023-6245-30

2) **SEYSARA** (sarecycline (b) (4)) tablets, 100 mg are (b) (4) capsule shaped, yellow, film-coated tablets debossed with "S100" on one side and blank on the other side (b) (4) (b) (4)

- Bottles of 30 tablets with child-resistant closure: NDC: 0023-6246-30

3) **SEYSARA** (sarecycline (b) (4)) tablets, 150 mg are (b) (4) capsule shaped, yellow, film-coated tablets debossed with "S150" on one side and blank on the other side (b) (4) (b) (4)

- Bottles of 30 tablets with child-resistant closure: NDC: 0023-6247-30

Storage

Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature].

Handling

(b) (4) Protect from moisture and excessive heat. (b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	60, 100, 150 mg (b) (4) (b) (4)	INADEQUATE remove (b) (4) (b) (4)
Available units (e.g., bottles of 100 tablets)	Bottles of 30 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Capsule shaped, yellow film coated with imprint	Adequate
Special handling (e.g., Dispense in tight and light resisteant container as defined in USP)	Protect from moisture and excessive heat; (b) (4)	INADEQUATE Per best labeling practices (b) (4) statements should be removed from handling
Storage conditions	Store at 20ºC – 25ºC (68ºF – 77ºF); excursions permitted to 15ºC-30ºC (59ºF-86ºF) [See USP Controlled Room Temperature]	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Distributed by Allergan USA, Inc. Irvine, CA 92612, USA	Adequate

23-APR-2018 Reviewer Assessment: INADEQUATE

Applicant should remove (b) (4) (b) (4)

(b) (4) **The Applicant should also modify the text of the How Supplied/Storage and Handling for clarity as noted above. This information was communicated to OND Labeling Team on April 20, 2018.**

18-JUL-2018 Reviewer Assessment: ADEQUATE

On 16-JUL-2018 the Applicant submitted revised labeling agreeing to all changes above. The How Supplied/Storage and Handeling section is now adequate.

II. Labels (Provided October 20, 2017)

1. IMMEDIATE CONTAINER LABEL

The immediate container labels includes a 3 count label and a 30 count label for each strength. The comments below are applicable to all presentations and strengths. A single 3 and 30 count representation of the lable provided in the original submission have been provided for reference.

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Seysera (sarecycline) tablets	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	Not Present	INADEQUATE Remove (b) (4) On side panel include equivalency for each strength
Net contents	3 tablets; 30 tablets	Adequate
"Rx only" displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Present	Adequate
Lot number and expiration date (21 CFR 201.17)	Not present	INADEQUATE Confirm location of lot number and expiration date location
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20ºC – 25ºC (68ºF – 77ºF); excursions permitted to 15ºC-30ºC (59ºF-86ºF) [See USP Controlled Room Temperature]	Adequate
Bar code (21CFR 201.25)	Included	Adequate
Name of manufacturer/distributor	Present	Adequate
And others, if space is available		

23-APR-2018 Reviewer Assessment: INADEQUATE

The following should be communicated to the Applicant with respect to the 3 and 30 count container label for each strength.

- Remove (b) (4)
- Confirm location of lot number and expiration date
- Edit side panel to read the below. Adjust equivalency for each strength.
  Each tablet contains:
  sarecycline…….....60 mg
  (equivalent to 64.5 mg of sarecycline hydrochloride)

Inactive ingredients microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, and yellow film coating.

27-JUL-2018 Reviewer Assessment: ADEQUATE

On 27-JUL-2018 the Applicant submitted a revised label agreeing to all changes above. The immediate container label is now adequate. A revised 30 count has been provided for reference.

(b) (4)

2. CARTON LABELS:

The carton labels includes a 3 count label and a 30 count label for each strength. The comments below are applicable to all presentations and strengths.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Seysera (sarecycline) tablets	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	Not Present	INADEQUATE Remove (b) (4) On side panel include equivalency for each strength
Net quantity of dosage form	3 tablets and 30 tablets	Adequate
"Rx only" displayed prominently on the main panel	Displayed on multiple panels	Adequate
Lot number and expiration date	Not present	INADEQUATE Confirm location of lot number and expiration date
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20ºC – 25ºC (68ºF – 77ºF); excursions permitted to 15ºC-30ºC (59ºF-86ºF) [See USP Controlled Room Temperature]	Adequate
Bar code (21CFR 201.25)	Bottom panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Multiple panels	Adequate
Manufacturer/distributor's name	Back panel	Adequate
Quantitative ingredient information (injectables)	Listed in alphabetical order	Adequate
Statement of being sterile (if applicable)	NA	Adequate
"See package insert for dosage information"	Back Panel.	Adequate
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Back Panel	Adequate

23-APR-2018 Reviewer Assessment: INADEQUATE

The following should be communicated to the Applicant with respect to the 3 and 30 count carton label for each strength.

- Remove (b) (4)
- Confirm location of lot number and expiration date
- Edit side panel to read the below. Adjust equivalency for each strength.
  Each tablet contains:
  sarecycline……..60 mg
  (equivalent to 64.5 mg of sarecycline hydrochloride)
  Inactive ingredients microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, and yellow film coating.

27-JUL-2018 Reviewer Assessment: ADEQUATE

On 27-JUL-2018 the Applicant submitted a revised label agreeing to all changes above. The carton label is now adequate. A revised 3 count has been provided for reference.

III. LIST OF DEFICIENCIES:

There are no remaining Label or Labeling deficiencies. On July 16, 2018 and July 27, 2018, the Applicant submitted revised labeling and labels, respectively, agreeing to all previous deficiencies communicated during this review cycle.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

On July 16, 2018 and July 27, 2018, the Applicant submitted revised labeling and labels, respectively, agreeing to all deficiencies noted above in the review. The Label and Labeling of NDA 209521 is now adequate.

The NDA is recommending for approval from the Label and Labeling Perspective.

Primary Labeling Reviewer Name and Date:

Caroline Strasinger, PhD 27-JUL-2018
OPQ, ONDP, DNDP II, BV

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

I agree with Dr. Strasinger's assessment on the labeling and labels and concur with her recommendation that this application is ready for approval as of this review.

Moo-Jhong Rhee, Ph.D. 27-JUL-2018
Chief, Branch V
DNDP II/ONDP

Caroline Strasinger

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Moo Jhong Rhee

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CHAPTER V: Review of Biopharmaceutics

BIOPHARMACEUTICS

Product Background:

NDA: 209521 ORIG-1

Drug Product Name / Strength: Seysara™ (sarecycline) Oral Tablets, 60 mg, 100 mg, 150 mg.

Route of Administration: Oral

Applicant Name: Allergan

The Applicant is seeking approval of Seysara™ (sarecycline) Oral Tablets (b) (4) (b) (4) The drug product is a novel tetracycline-class narrow spectrum antibiotic that exhibits antibacterial activity against clinical isolates of P. acnes. The proposed dosage is once daily (b) (4) Seysara is an immediate release (IR) film-coated tablet containing 60 mg, 100 mg, or 150 mg of sarecycline (equivalent to 64.5 mg, 107.5 mg, and 161.2 mg sarecycline hydrochloride, respectively. (b) (4)
According to the Applicant, Sarecycline is rapidly absorbed following oral administration of the immediate-release tablet formulation, displays linear and near dose-proportional pharmacokinetics within the range of 60 to 150 mg dosed once daily (QD) (PK study SCR-PK-06).

This application was filed as a 505(b)(1). The drug product development program for this drug product consist of 18 completed clinical studies, including 14 Phase 1 studies (3 bioavailability/bioequivalence studies and 11 clinical pharmacology studies), as well as a Phase 2 dose-ranging study, 2 pivotal Phase 3 studies, and a long-term extension safety study in subjects with moderate to severe acne vulgaris. The sarecycline tablet formulation investigated in the Phase 3 studies (Studies SC1401, SC1402, and SC1403) is identical to the to-be-marketed formulation.

Review Summary:
Seysara™ (sarecycline) Oral Tablets is an IR formulation (b) (4) The drug product is provided in three strengths, 60 mg. 100 mg and 150 mg, (b) (4) An in vivo PK dose-proportionality was included in the submission in support of their approval. The qualification of this study is under the purview of OCP.

The drug product underwent some manufacturing changes through the phases of development, which are considered major. Of relevance is a change in formulation from phase 1 (capsule) to phase 2 (film-coated table) which did not affect the in vivo performance of the product as demonstrated by the results of a BE study. The final formulation was used in the pivotal phase 3

studies and this formulation is the same as the intended commercial formulation. No changes in manufacturing site for the drug product occurred from phase 3 to commercial drug product.

The following in vitro release method and acceptance criterion were agreed upon (refer to submission dated Dec 22, 2017):

DISSOLUTION METHOD AND ACCEPTANCE CRITERION	
Description	**Parameter**
Apparatus	USP Apparatus 2-Paddles
Revolutions	75 rpm
Dissolution media	0.1 N HCl
Media Volume	500 mL
Media Temperature	37°C ± 0.5°C
Acceptance criterion	NLT (b)(4)% (Q) in 15 min

The proposed control strategy for this drug product (with rapid dissolution characteristics and high soluble API) is acceptable from biopharmaceutics perspective to assure product quality and performance and hence is adequate for lifecycle management of the product for changes within process/formulation ranges tested.

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
10/20/17	0000
12/22/17	0003

Concise Description Outstanding Issues Remaining: NONE

From Biopharmaceutics perspective, NDA 209521 for **Seysara™ (sarecycline) Oral Tablets, 60 mg, 100 mg, 150 mg** *is recommended for* ***Approval***.

Drug Product

The drug product consists of a yellow film-coated immediate release oral tablet formulation. The three commercial strengths of drug product are 60 mg, 100 mg, and 150 mg sarecycline free-base (equivalent to 64.5 mg, 107.5 mg, and 161.2 mg sarecycline hydrochloride, respectively). The drug product is manufactured (b) (4)
(b) (4)

(b) (4)

(Table 1).

Table 1. Components and composition of Seysara™ (sarecycline) Oral Tablets, 60 mg, 100 mg, 150 mg.

Excipient	Quality Standard	Function	60mg		100 mg		150 mg		IIG Limits
			mg/tab	%w/w	mg/tab	%w/w	mg/tab	%w/w	(mg/unit)
(b) (4)									
Sarecycline Hydrochloride	In-house	Active Ingredient	64.49[1]	(b) (4)	107.48[1]	(b) (4)	161.22[1]	(b) (4)	NA
Microcrystalline Cellulose	USP/NF								(b) (4)
Povidone	USP/NF								
(b) (4)									
Sodium Starch Glycolate	USP/NF								
Sodium Stearyl Fumarate	USP/NF								
(b) (4)									

[1]Equivalent to 60 mg, 100 mg, and 150 mg sarecycline (free-base), respectively

Drug Substance

BCS Designation

The pH solubility profile of Sarecycline Hydrochloride is shown in Table 2.

Table 2. pH solubility profile for Sarecycline Hydrochloride

Media	Solubility (mg/mL) (37°C)
pH 1.2 buffer	14
pH 4.5 buffer	35
pH 6.8 buffer	43
pH 8.0 buffer	226

Based on the pH solubility profile table for Sarecycline Hydrochloride, the highest strength (150 mg) / Lowest solubility (14 mg/mL) = 10 mL which is much less than 250 mL. Therefore, Sarecycline Hydrochloride can be considered to have high solubility. Based on reported

permeability and solubility study performed over a physiological pH range, as per Biopharmaceutical Classification System (BCS), Sarecycline Hydrochloride can be considered a BCS Class III compound.

Polymorphism

According to the Applicant, (b) (4)

Dissolution Method and Acceptance Criterion

Dissolution Method

The following method is being proposed for QC purposes (product release and stability testing):

PROPOSED DISSOLUTION METHOD	
Description	**Parameter**
Apparatus	USP Apparatus 2-Paddles
Revolutions	75 rpm
Dissolution media	0.1 N HCl
Media Volume	500 mL
Media Temperature	37°C ± 0.5°C
Sampling Time Point	15, 30,45 minutes

Dissolution method development

(b) (4)

Selection of Paddle Speed

(b) (4)

(b) (4) A paddle speed of 75 rpm provided adequate dissolution profile for this drug product.

Method Discriminating Ability

The discriminating ability of the method was evaluated (b) (4)

(b) (4)

(b) (4)

Dissolution Acceptance Criteria

The following acceptance criterion was originally proposed for the drug product under review. According to the Applicant, the data supporting these criteria are shown in Figure 2.

Time Point	Acceptance Criterion
	(b) (4)

Figure 2: Typical dissolution profiles for clinical pivotal batches.

Reviewer's comments

The ***originally*** proposed dissolution acceptance criterion (b) (4) ***is not acceptable.*** Based on the data provided, the proposed criterion is not adequate to ensure similar in vitro performance and in vivo performance (e.g. BE) to the clinical batch. Although the Applicant is not formally classifying Sarecycline Hydrochloride as a BCS class 3 drug substance and no biowaiver request has been submitted, this drug product contains a highly soluble drug substance and it dissolves rapidly (i.e., within 15 min). Thus, the following acceptance criterion recommendation is given in consistency with the dissolution guidance (Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs):

NLT (b) (4) % (Q) of the labeled amount of Sarecycline Hydrochloride is dissolved in 15 minutes

The Applicant agreed with the above recommendation on a submission dated Dec 22, 2017. This acceptance criterion covers all strengths.

Reviewer's Assessment: ADEQUATE
The data provided demonstrated that the dissolution method along with the recommended acceptance criterion are discriminating against critical quality attributes (b) (4) and will ensure consistent in vitro and in vivo performance of the drug product throughout its life cycle.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: ADEQUATE
There were no data linking the CQA to dissolution and systemic exposure, and thus, IVIVR/IVIVC is not available. Nevertheless, given the nature of the drug substance/drug product, it is likely that the dissolution specifications (method and acceptance criterion) being approved under this NDA are clinically relevant as they are also set based on the performance of the clinical batches.

Application of Dissolution/IVIVC in QbD
The identified CQAs are listed in table below.

CQAs	Justification
Identification	**Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact drug substance identity**
Assay	**Variability in assay may affect safety and efficacy**
Content Uniformity	**Variability in content uniformity may affect safety and efficacy**
Degradation products	**Limits on degradation products are critical for drug safety and are as per ICH Q3(B)**
Dissolution	**Drug dissolution is an important characteristic of an IR dosage form impacting drug release from the dosage form**
(b) (4)	**The specification of NMT (b) (4) % (b) (4) is based on the results from batch analyses and registration stability studies**
Microbiological Examination	**Non-compliance with microbial examination tests may impact patient safety**

Based on scientific understanding and prior knowledge of the process, an initial risk assessment was completed to evaluate the potential impact of the raw material attributes on the drug product CQAs. Based on this assessment, it was concluded (b) (4)

(b) (4)

Reviewer's Assessment: ADEQUATE

The reviewer agrees with the Applicant's the risk assessment. (b) (4)

Bridging of Formulations throughout the Phases of Drug Product Development

The batch history of the drug product formulations used during the clinical development of the sarecycline drug product is summarized in Table 3. No changes in formulation composition are proposed for the intended commercial formulation relative to the phase 3 clinical trial formulation.

Table 3. Batch history during the clinical development

Clinical Phase	Study Protocol	Use	Dosage Form and Strength	Bulk Drug Product Batch	Drug Substance Batch	Drug Substance Manufacturer
Phase 1	PR-01010	Human PK Single-Ascending Dose Study	Capsules 20 mg 160 mg	 10L0003 10L0004	 AA-023655 AA-023655	(b) (4)
	PR-05011	Human PK Multiple-Ascending Dose Study	Capsules 20 mg 80 mg 160 mg	 10L0003 0000506604 10L0004	 AA-023655 340001N10 AA-023655	
	SRC-PK-06	Single and Multiple Dose PK Characterization Study	Tablets 60 mg 100 mg 150 mg	 009311 009343 009347	 36 (31, 32, 26) (32,33)	
	SRC-PK-03	Hepatic Impairment PK Study	Tablet 150 mg	 009347	 (32,33)	
	SRC-PK-04	Renal Impairment PK Study	Tablet 150 mg	 009347	 (32, 33)	
	SCR-PK-07	Digoxin Drug Drug Interaction Study	Tablet 150 mg	 009347	 (32,33)	
	SRC-PK-08	Oral Contraceptive Drug Drug Interaction Study	Tablet 150 mg	 009347	 (32,33)	
	PR-07112	Thorough QT Study	Capsules 100 mg	 0000510905	 340002N11	
	PR-07811	Phototoxicity Study	Capsules 80 mg	 XD11D001	 340001N10	
	PR-07711	Multiple-dose Tolerability Study	Capsules 40 mg 80 mg	 XD11D002 XD11G002	 340001N10	
Phase 2	PR-10411	Phase 2 Efficacy	Capsules 50 mg 100 mg	 0000510904 0000510905	 340002N11 340002N11	

Clinical Phase	Study Protocol	Use	Dosage Form and Strength	Bulk Drug Product Batch	Drug Substance Batch	Drug Substance Manufacturer
Phase 1	PR-10711	Food Effect	Capsule 80 mg	 XD11D001	 340001N10	(b) (4)
	PR-11914	Food Effect	Tablet 150 mg	 009347	 (32,33)	
	PR-12014	Capsule vs Tablet Bioequivalency	Capsule 100 mg Tablet 100 mg	 0000527852 009343	 20 (31, 32, 36)	
Phase 3	SC1401	Pivotal Phase 3	Tablets 60 mg 100 mg 150 mg	 009311 009343 and 009344 009347	 36 (31, 32, 36) and (33, 34) (32, 33)	
	SC1402	Pivotal Phase 3	Tablets 60 mg, 100 mg 150 mg	 009311 009343 and 009344 009347	 36 (31, 32, 36) and (33, 34) (32, 33)	
	SC1403	Long-term Safety	Tablets 60 mg 100 mg 150 mg	 009311 009344 and 009345 009348	 36 (33, 34) and (38) (31, 37)	

Figure 4 summarizes the main changes implemented to the drug product under phases of development. The changes implemented from phase 1 to phase 2 were major; however, given that the product dissolves within 15 min and the API has high solubility, it is expected that the changes did not impact the in vivo performance. Additional changes were implemented to the phase 2 formulation. Based upon the results of the phase 2 clinical study, 60 mg, 100 mg and 150 mg dosage strengths of sarecycline were selected for further clinical development. Formulation and dosage form optimization focused on producing an immediate release film-coated tablet. A BE study was conducted to bridge the capsule and tablet formulations. This study (PR-12014) demonstrated the bioequivalence of sarecycline when administered as either a capsule or tablet (Table 5). The tablet formulation is the same as used in phase 3 clinical and registration stability studies. There were no changes in the drug product manufacturing site. (b) (4) is the proposed manufacturing site for the commercial drug product.

Figure 4. Schematic overview of formulation development.

Reviewer's Assessment: ADEQUATE
The Applicant provided adequate information to bridge across phases of development. The final formulation was used in the pivotal phase 3 studies and this formulation is the same as the intended commercial formulation. No changes in manufacturing site for the drug product occurred from phase 3 to commercial drug product.

Data Available Supporting the Approval of Lower Strengths
Reviewer's Assessment: NA

(b) (4) Sarecycline is rapidly absorbed following oral administration of the immediate-release tablet formulation, appears to display linear and near dose-proportional pharmacokinetics within the range of 60 to 150 mg dosed once daily (QD) (PK study SCR-PK-06, this study is under the purview of OCP).

In addition, all strengths dissolved within 15 min suggesting similar in vivo performance in dose-proportional PK.

Lifecycle Management Considerations

The proposed control strategy is acceptable from biopharmaceutics perspective to assure product quality and performance and hence is adequate for lifecycle management of the product for changes within process/formulation ranges tested. However, during the lifecycle, if the changes are proposed beyond the ranges tested, depending on the criticality of the changes and its effect on drug product CQA and hence on product quality and performance, it would indicate a need of in vitro BE testing (e.g., SUPAC Level 3 process change).

List of Deficiencies: NONE pending.

Primary Biopharmaceutics Reviewer Name and Date:

Sandra Suarez Sharp, Ph.D. (Branch 2\DB\ONDP\OPQ), 07/10/18

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Vidula Kolhatkar, Ph.D., Acting Team Lead (Branch 2\DB\ONDP\OPQ), July 16, 2018

Vidula Kolhatkar

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Sandra Suarez

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CHAPTER VI: Review of Quality Microbiology

Note: The review of quality microbiology of the drug product is included in Chapter IV: Review of Drug Product Manufacturing Process.

Vidya Pai

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Michael Klapal

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