CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209521
PDUFA Goal Date	October 10, 2018
OSE RCM #	2017-2204
Reviewer Name(s)	Laura Zendel, PharmD
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins Parker
Review Completion Date	July 6, 2018
Subject	Evaluation of the Need for a REMS
Established Name	Sarecycline
Trade Name	Seysara
Name of Applicant	Allergan Inc.
Therapeutic Class	Tetracycline antibiotic
Formulation(s)	Immediate release film coated tablet 60 mg, 100 mg, 150 mg
Dosing Regimen	Once daily with or without food: 60 mg for patients who weigh 33-54 kg 100 mg for patients who weigh 55-84 kg 150 mg for patients who weigh 85-136 kg

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Seysara (sarecycline) is necessary to ensure the benefits outweigh its risks. Allergan, Inc. submitted a New Drug Application (NDA 209521) for sarecycline with the proposed indication for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in patients 9 years or older. The risks associated with sarecycline are generally associated with tetracycline class antibiotics and include gastrointestinal upset, esophageal erosion, fungal infection, increased photosensitivity, and permanent discoloration of teeth and interference with bone growth/formation in children. Sarecycline did not demonstrate in clinical trials, that its adverse effects are worse than other tetracyclines. The applicant did not submit a REMS with this application and did not propose any risk management activities for sarecycline beyond routine pharmacovigilance and labeling.

DRISK and the Division of Dermatology and Dental Products agree that a REMS is not needed to ensure the benefits of sarecycline outweigh its risks. The safety concerns associated with sarecycline are well documented and consistent with known class effects of tetracycline antibiotics that are used for the treatment of acne vulgaris.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Seysara (sarecycline) is necessary to ensure the benefits outweigh its risks. Allergan, Inc. (Allergan) submitted a New Drug Application (NDA) 209521 for sarecycline with the proposed indication for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in patients 9 years or older. This application is under review in the Division of Dermatology and Dental Products (DDDP). The applicant did not submit a REMS with this application and did not propose any risk management activities for sarecycline beyond routine pharmacovigilance and labeling.

2 Background

2.1 PRODUCT INFORMATION

Seysara (sarecycline), a new molecular entity[a], is a novel tetracycline-class narrow spectrum antibiotic proposed for the treatment of acne vulgaris. The tetracycline class of antibiotics work by inhibiting protein synthesis by binding to the 30s subunit of the bacterial ribosome. This class also has notable anti-inflammatory effects, including inhibiting chemotaxis and metalloproteinase activity. The tetracycline class has a well-known adverse event profile including gastrointestinal upset, esophageal erosion, fungal infection, increased photosensitivity, and permanent discoloration of teeth and interference with bone growth/formation in children, but does not carry a boxed warning or a REMS.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

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The exact mechanism of action of sarecycline in treating acne vulgaris is not known. Sarecycline exhibits antibacterial activity against clinical isolates of *Propionibacterium acnes* (*P. acnes*), a Gram-positive anaerobic organism associated with acne vulgaris, including those with high-level resistance to the macrolide erythromycin. Activity was also seen for some other Gram-positive species, but unlike other tetracyclines, sarecycline demonstrated little or no activity for the enteric Gram-negative bacilli *Escherichia coli* (*E. coli*), *Klebsiella pneumonia (K. pneumoniae)*, and *Enterobacter.* Sarecycline's narrow spectrum of activity may result in more limited disturbance of gastrointestinal flora when compared with doxycycline and minocycline, which in contrast are broad-spectrum tetracyclines.

Sarecycline is proposed as 60 mg, 100 mg, and 150 mg immediate release film-coated tablets to be administered orally once daily. The recommended dosage is 60 mg for patients who weigh 33-54 kg, 100 mg for patients who weigh 55-84 kg, or 150 mg for patients who weigh 85-136 kg orally daily for 12 weeks. If there is no improvement after 12 weeks, treatment with sarecycline should be reassessed[b]. Sarecycline is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 209521 relevant to this review:

- 10/20/2017: NDA 209521[1] submission (b) (4) received
- 03/29/2018: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for sarecycline

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Acne vulgaris is the most common dermatological disorder in the United States, where it is estimated to affect approximately 40 to 50 million people.[2] Acne vulgaris most commonly occurs in adolescents, affecting approximately 80%, but may also occur in 54% of adult women and 40% of adult men.[3] Acne vulgaris is a chronic disease of pilosebaceous follicles that is multifactorial in etiology and is characterized by the formation of two major types of acne lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe cases, nodules/nodulocystic lesions). It can vary in severity according to lesion types, numbers, and extent of involvement. Acne can result in scarring and occurs more frequently on the face, but can occur on non-facial skin (e.g. trunk).

3.2 Description of Current Treatment Options

A number of topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies for acne vulgaris include oral and topical antimicrobials (e.g. erythromycin, clindamycin, benzoyl peroxide), topical retinoids (e.g. tretinoin, tazarotene), and systemic hormonal therapies (e.g.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

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ethinyl estradiol/norgestimate). The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne. Isotretinoin is subject to a REMS, the iPLEDGE REMS Program, to mitigate the risk fetal exposure to isotretinoin by ensuring that no patient starts isotretinoin therapy if pregnant and that no patient on isotretinoin therapy becomes pregnant. The iPLEDGE Program requires certification of prescribers and pharmacies, and enrollment of all patients prescribed isotretinoin. The program is designed to create a verifiable link between the negative pregnancy test and the dispensing of the isotretinoin prescription to patients of reproductive potential.

See Section 10.1, Appendix, for more details about currently available treatments for acne.

4 Benefit Assessment

The efficacy and safety of sarecycline for the treatment of acne vulgaris was demonstrated in two pivotal phase 3 studies (SC1401, NCT02320149 and SC1402, NCT02322866). Supportive evidence and safety evidence was also derived from the Phase 2 dose ranging study (PR-10411, NCT01628549) and the Phase 3 open-label study (SC1403, NCT02413346) which also provided additional evidence of the persistence of efficacy with long-term use. The two pivotal studies, SC1401 and SC1402, were identical in design: multicenter, randomized, double-blind, and placebo-controlled. Each of these studies had the same co-primary efficacy endpoints: absolute change from baseline in inflammatory lesion counts at Week 12 and percentage of subjects with Investigator's Global Assessment (IGA) success. IGA success was defined as at least a 2-point decrease from baseline and clear (0) or almost clear (1) at Week 12. Other efficacy measures included non-inflammatory lesion counts and evaluation of acne on the chest, back, and neck using the IGA. Each study was appropriately powered for analysis of their respective co-primary efficacy endpoints.

The pivotal Phase 3 studies SC1401 and SC1402, enrolled a total of 2002 subjects 9 years of age and older who were equally randomized to sarecycline (n=1002) or placebo (n=1000). A total of 1802 subjects (85%) completed the studies. The sarecycline group demonstrated a -15.3 and -15.5 mean absolute reduction from baseline in inflammatory lesion count in SC1401 and SC1402 respectively compared to -10.2 and -11.1 in the placebo group with a difference of -5.1 ($p<0.0001$) and -4.4 ($p<0.0001$). The sarecycline group demonstrated a 21.9% and 22.6% IGA Success in SC1401 and SC1402 respectively compared to 10.5% and 15.3% in the placebo group with a difference of 11.05% ($p<0.0001$) and 7.3% ($p=0.0038$). Both co-primary endpoints were greater with sarecycline compared with placebo at Week 3 and at subsequent visits for both studies.

The applicant concluded that the results of pivotal Phase 3 studies SC1401 and SC1402 demonstrated that oral sarecycline taken once daily for 12 weeks is an effective treatment for moderate to severe acne vulgaris. The clinical reviewer agrees that the beneficial effects of sarecycline treatment in inflammatory acne have been demonstrated across two pivotal clinical trials.

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5 Risk Assessment & Safe-Use Conditions

The evidence of safety supporting the use of sarecycline for the target indication is based on pooled safety data from the safety populations from the following 4 studies: Phase 2 Study PR-10411, pivotal Phase 3 Studies SC1401 and SC1402, and long-term Phase 3 Study SC1403 (extension study for SC1401 and SC1402). The populations defined for the pooled safety analyses were as follows: the pooled double-blind safety population included patients who received sarecycline 1.5 mg/kg/day or placebo in the Phase 2 or Phase 3 double-blind 12-week studies (n=2133; sarecycline: 1064 subjects, placebo: 1069 subjects) while the pooled sarecycline 1.5 mg/kg/day safety population included subjects who received sarecycline in any of the four studies (n=1300).

In the double blind safety population, the most common treatment emergent adverse events (TEAEs) with none reaching greater than 3.1% incidence were headache, nasopharyngitis, nausea, upper respiratory tract infection, and blood creatinine phosphokinase (CPK) increase. The only TEAE meeting the adverse drug reaction (ADR) criteria[c] was nausea, occurring at a 1.1% higher incidence rate in the sarecycline group than in the placebo group.

The incidences of treatment-emergent serious adverse events[d] (SAEs) were similar in the sarecycline and placebo groups (0.7% and 0.6%, respectively). The 9 SAEs reported for 7 subjects in the sarecycline group were ALT increased, AST increased, and gamma-glutamyltransferase (GGT) increased (1 subject), DKA, nephrolithiasis, Crohn's disease, tonsillitis, depression, and abortion which was reported as elective termination of pregnancy. The 7 SAES reported for 6 subject in the placebo group were appendicitis, miscarriage of partner, abortion spontaneous (2 subjects), cellulitis and suicide attempt (1 subject), and oppositional defiant disorder.

5.1 Tetracycline Class Effects

Known adverse effects of the tetracycline class of antibiotics include gastrointestinal upset, esophageal erosion, fungal infection, increased photosensitivity, and permanent discoloration of teeth and interference with bone growth/formation in children. Teratogenic effects were noted in the embryofetal toxicity study in rats, which are considered class effects of tetracyclines. Tetracyclines as a class are contraindicated in pregnancy and breastfeeding and should not be given to children 8 years of age or younger. Additional adverse effects associated with tetracyclines include dizziness, lightheadedness,

[c] TEAEs occurring at a $\geq$ 1% overall incidence rate and at a $\geq$ 1% higher incidence rate in the sarecycline group than in the placebo group were considered ADRs. In addition, TEAEs not meeting these ADR criteria, but with clinical presentations (frequency, location, temporal relationship, etc.) that may represent potential ADRs were also considered for inclusion as ADRs.

[d] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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vertigo, ataxia, tinnitus, brown discoloration of sclera and nails, blue or black discoloration of sclera or gingiva, pseutotumor cerebri, autoimmune hepatitis, risk for serum sickness reactions, hypersensitivity reactions, and drug-induced lupus. The proposed Warnings and Precautions include similar risk messaging to other tetracycline antibiotics including teratogenic effects, *Clostridium difficile* associated diarrhea (CDAD), central nervous system effects, intracranial hypertension, photosensitivity, development of drug resistant bacteria, and superinfection/potential for antimicrobial overgrowth. In addition to the Warnings and Precautions, information on the potential for fetal harm, permanent discoloration of teeth, and reversible inhibition of bone growth when administered during pregnancy is included in the Use In Specific Populations section of the label.

The applicant concluded and the clinical reviewer concurs[4] that clinical safety data consistently demonstrate sarecycline to be safe and well-tolerated for the overall populations enrolled in the studies and for all evaluated demographic subgroups. In addition, sarecycline exhibits a narrower spectrum of activity relative to doxycycline and minocycline, including less activity against Gram-negative bacteria, which may translate to a reduced propensity to disrupt or exert selective pressure on normal gastrointestinal flora.

6 Expected Postmarket Use

Sarecycline is expected to be prescribed by various prescribers including but not limited to primary care physicians, dermatologists, and other specialists involved in the treatment of acne. It is likely to be used by patients in an outpatient setting. Patients and their caregivers should be informed about the possibility of fetal harm when sarecycline, like other tetracyclines, is administered to a pregnant woman.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for sarecycline beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of sarecycline on the basis of the efficacy and safety information currently available.

Sarecycline is a novel tetracycline-class narrow spectrum antibiotic with antibacterial activity against clinical isolates of P. acnes, including isolates with high-level resistance to the macrolide erythromycin. In common with other tetracyclines, the antimicrobial action of sarecycline is mediated via inhibition of protein synthesis. The benefits of treatment with sarecycline were demonstrated by meeting the co-primary endpoints of the clinical trials. Based on these results, sarecycline was found to be efficacious with an acceptable safety profile (b) (4)

Acne vulgaris is the most common dermatological disorder in the US. Acne vulgaris is a chronic disease of sebaceous follicles that is multifactorial in etiology. It can vary in severity according to lesion types, numbers, and extent of involvement and can result in scarring. There are a number of topical and systemic products approved for treatment of acne vulgaris. Combination therapy utilizing agents with complementary mechanisms such as an antimicrobial and a topical retinoid is often prescribed in the management of acne vulgaris, since most anti-acne medications do not act against all of the major pathophysiologic processes or types of lesions of acne vulgaris.

The safety profile of sarecycline is consistent with known class effects of tetracycline antibiotics that are used for the treatment of acne vulgaris. The most common treatment emergent adverse events included headache, nasopharyngitis, nausa, upper respiratory tract infection, and increased blood creatinine phosphokinase. Teratogenic effects were noted in the embryofetal toxicity study in rats, which are considered class effects of tetracyclines. The Warnings and Precautions section of the labeling will contain similar risk information including teratogenic effects, *Clostridium difficile* associated diarrhea, intracranial hypertension, central nervous system effects, photosensitivity, development of drug resistant bacteria, and superinfection or potential for microbial overgrowth. Adverse event profiles of other tetracyclines are well established, and do not require a REMS. The clinical reviewer concluded that sarecycline's risks can be managed with labeling and routine pharmacovigilance[5].

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with sarecycline use are well documented and similar to other tetracycline antibiotics. Sarecycline did not demonstrate in clinical trials that its adverse effects are worse than other tetracyclines. Labeling is sufficient to manage risks associated with sarecycline.

Should DDDP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 Currently Available Treatments for Acne

Categories	Drug Products	Risk Management Approach
Topical		
Salicylic acid	Multiple products	Over the counter (OTC) warnings
Benzoyl peroxide	Multiple products	OTC warnings
Sulfa products	Sulfacetamide, Sulfur	OTC warnings
Azelaic acid	Multiple products	Warnings and Precautions (W&P): skin irritation, hypopigmentation

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Antibiotics	Clindamycin	W&P: diarrhea, Clostridium difficile-associated diarrhea (CDAD)
	Erythromycin	W&P: pseudomembranous colitis
	Metronidazole	W&P: avoid contact with eyes, local skin irritation
	Dapsone	W&P: Methemoglobinemia, hemolysis
Retinoids	Tretinoin	W&P: flammable, avoid contact with eyes, may cause sensitivity to sun
	Tazarotene	W&P: Embryofetal toxicity, local irritation and hypersensitivity reactions, photosensitivity and risk for sunburn
	Adapalene	W&P: local irritation and hypersensitivity reactions
Systemic		
Antibiotics	Erythromycin	W&P: hepatotoxicity, QT prolongation, CDAD
	Tetracycline	W&P: teratogenic effects, photosensitivity
	Doxycycline	W&P: teratogenic effects, CDAD, intracranial hypertension/pseudotumor cerebri, photosensitivity
	Minocycline	W&P: teratogenic effects, photosensitivity, CNS effects, intracranial hypertension/pseudotumor cerebri, superinfection, development of drug resistant bacteria
	Azithromycin	W&P: hypersensitivity, hepatotoxicity, infantile hypertrophic pyloric stenosis, QT prolongation, CDAD, exacerbation of myasthenia gravis, development of drug resistant bacteria
	Trimethoprim	W&P: hypersensitivity reactions, caution in folate deficiency, caution in impaired renal or hepatic function
	Trimethoprim/ sulfamethoxazole	W&P: embryofetal toxicity, hypersensitivity, thrombocytopenia, CDAD, development of drug resistant bacteria, caution in folate deficiency, hemolysis in glucose-6-phosphate dehydrogenase deficiency, hypoglycemia
Retinoids	Isotretinoin	REMS: iPLEDGE, teratogenicity Medication Guide Boxed Warning: teratogenicity W&P: psychiatric disorders, pseutotumor cerebri, serious skin reactions, pancreatitis, elevated triglycerides, hearing impairment, hepatotoxicity, inflammatory bowel disease
Hormonal	Ethinyl estradiol/	Boxed Warning: cigarette smoking and serious cardiovascular events

Therapies	norgestimate	W&P: thromboembolic disorders and other vascular problems, liver disease, risk of liver enzyme elevations with concomitant hepatitis C treatment, high blood pressure, gallbladder disease, carbohydrate and lipid metabolic effects, headache, bleeding irregularities and amenorrhea, depression, carcinoma of breast and cervix, increased serum concentration on binding globulins, hereditary angioedema exacerbation, chloasma
	Ethinyl estradiol/ Norethindrone	Boxed Warning: cigarette smoking and serious cardiovascular events W&P: thromboembolic disorders and other vascular problems, carcinoma of the reproductive organs, hepatic neoplasia, liver enzyme elevations with concomitant hepatitis C treatment, ocular lesions, gallbladder disease, carbohydrate and lipid metabolic effects, elevated blood pressure, headache, bleeding irregularities
	Ethinyl estradiol/ Drospirenone	Boxed Warning: cigarette smoking and serious cardiovascular events W&P: thromboembolic disorders and other vascular problems, hyperkalemia, carcinoma of the breasts and reproductive organs, liver disease, risk of liver enzyme elevations with concomitant hepatitis C treatment, high blood pressure, gallbladder disease, carbohydrate and lipid metabolic effects, headache, bleeding irregularities, depression, interference with laboratory tests, angioedema, chloasma
Anti-androgen	Spironolactone	Boxed Warning: tumorigen, should only be used in those conditions described under indications and usage. W&P: fluid or electryolyte imbalance (hyperkalemia, hypomagnesemia, hyponatremia, hypochloremic alkalosis), gynecomastia, somnolence and dizziness
Corticosteroids	Prednisone	W&P: may mask signs of infection, posterior subcapsular cataracts, glaucoma, elevated blood pressure, psychiatric disorders, kaposi's sarcoma, convulsions

10.2 REFERENCES

[1] Allergan, Inc. Orig 1. NDA 209521 Sarecycline, Dated 10/20/2017

[2] Bhate K, Williams HC. Epidemiology of acne vulgaris. Br J Dermatol. 2013;168(3):474-85

[3] Ramos-e-Silva M, Carneiro SC. Acne vulgaris: review and guidelines. Dermatol Nurs. 2009;21;63-68

[4] Chiang, G. DDDP. Sarecycline Midcycle Slides, Dated 3/27/2018

[5] Chiang, G. DDDP. Email correspondence, Dated 3/8/2018

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/s/

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