Brand Name[1]: Seysara
Generic Name[1]: sarecycline
Manufacturer[2]: Paratek Pharmaceuticals
Drug Class[1,2,3]: Antiacne Antibacterial, tetracycline derivative

Uses:

Labeled Uses[1,2]: Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 9 years of age.

Unlabeled Uses[1,2]: No current unlabeled uses for sarecycline.

Mechanism of Action[1]: Sarecycline inhibits synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s) of susceptible bacteria.

Pharmacokinetics: Absorption[1,2,3]:

T_{max}	1.5 - 2 hours after oral digestion
V_d	91.4 - 97 L
$t_{1/2}$	21 - 22 hours
Clearance	3L/hour
Protein binding	62.4% - 74.7%
Bioavailability	Not reported

***Note[1,2,3]:** The median time to peak plasma concentration (Tmax) of sarecycline is 1.5 to 2.0 hours. When the medication is taken with a meal consisting of high fat (about 50% of total caloric content of the meal), high caloric (about 800 to 1,000 Kcal), and milk content the Tmax can be delayed by approximately 0.53 hours and the Cmax and AUC can be decreased by 31% and 27%, respectively.

Metabolism[1,2,3]: <15% metabolized by the liver; Inhibitor of P-gp.

Elimination[1,2,3]: Feces (42.6%; 14.9% as unchanged drug); Urine (44.1%; 24.7% as unchanged drug)

Efficacy:

Citation #1: Leyden JJ, Sniukiene V, Berk DR, Kaoukhov A. Efficacy and Safety of

Sarecycline, a Novel, Once-Daily, Narrow Spectrum Antibiotic for the Treatment of Moderate to Severe Facial Acne Vulgaris: Results of a Phase 2, Dose-Ranging Study. J Drugs Dermatol. 2018 Mar 1;17(3):333-338.

Study Design: Multicenter, double-blind, placebo-controlled study

Description of Study:

Methods: Patients aged 12 to 45 years with moderate to severe facial acne vulgaris characterized by 20 to 50 inflammatory lesions, 30 to 100 noninflammatory lesions, and no more than two facial nodules were randomized to receive either sarecycline 0.75mg/kg, 1.5mg/kg, 3.0mg/kg, or placebo once daily for 12 weeks. Inflammatory lesion counts and noninflammatory lesion counts were similar at baseline between treatment groups. Patients were excluded from the study if they had dermatologic conditions of the face or facial hair that could interfere with clinical evaluations of acne, facial sunburn, prolonged QTc interval (>450msec) on EKG, allergy to tetracycline-class antibiotics or any ingredient in the study drug, or had hepatitis, liver damage, or renal impairment. Overall, 285 patients were randomized to receive at least 1 dose of study drug or placebo. Primary outcome measure included change from baseline in inflammatory and noninflammatory lesion counts at week 12, with between-group comparisons using analysis of covariance.

Outcome Results: At week 12, sarecycline 1.5mg/kg and 3.0mg/kg groups demonstrated significantly reduced inflammatory lesions from baseline at 52.7% and 51.8% respectively vs. placebo 38.3%; p=0.02 and p=0.03, respectively. No results were reported for the sarecycline 0.75mg/kg group vs. placebo. Sarecycline was well tolerated with the most reported side effect being gastrointestinal discomfort with reported rates similar between the sarecycline and placebo groups.

Limitations: This study uses sareycline as monotherapy in the treatment of moderate to severe acne. However, monotherapy is typically not done in clinical practice as patient's are usually prescribed both oral medications in addition to topical medications. The study reported that sarecycline dosed at 1.5mg/kg or 3.0mg/kg was significant, however, they failed to report any results regarding the 0.75mg/kg dose. This is a potential bias as the results were focused on highly positive outcomes only. A majority of study participants had moderate acne while the minority of patients' acne was categorized as severe. The study was funded by Allergan, a drug manufacturer, and several authors of the trial are employed by the company and own stock options within the company leading to potential biases.

Conclusion: Once-daily sarecycline 1.5mg/kg significantly reduced inflammatory lesions vs. placebo and was safe and well tolerated. Sarecycline 3.0mg/kg did not result in additional efficacy vs. sarecycline 1.5mg/kg. Sarecycline dosed at 1.5mg/kg is a novel, once daily treatment for patients that can be used to treat moderate to severe acne. Future randomized trials should be conducted using an active control such as an oral antibacterial that is known to treat moderate to severe acne to compare available treatment options.

Citation #2: Moore A, Green LJ, Bruce S, Sadick N, Tschen E, Werschler P, et al. Once-Daily Oral Sarecycline 1.5 mg/kg/day Is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials. J Drugs Dermatol. 2018 Sep 1;17(9):987-996.

Study Design: Two identical (SC1401 and SC1402) randomized, multicenter double-blinded, placebo-controlled trials

Description of Study:

Methods: Trial SC1401 randomized 968 participants with moderate to severe acne that were aged 9 to 45 years, had 20 to 50 inflammatory lesions, ≤100 noninflammatory lesions, and ≤2 nodules to receive either sarecycline tablets, 1.5mg/kg/day, taken orally once daily for 12 weeks or placebo-matching sarecycline tablets, taken orally once daily for 12 weeks. Patients randomized to the sarecycline group included 481 subjects while the placebo group had 483 subjects enrolled. Trial SC1402 enrolled 1,034 participants with moderate to severe acne that were aged 9 to 45 years, had 20 to 50 inflammatory lesions, ≤100 noninflammatory lesions, and ≤2 nodules to receive either sarecycline tablets, 1.5mg/kg/day, taken orally once daily for 12 weeks or placebo-matching sarecycline tablets, taken orally once daily for 12 weeks. Patients randomized to the sarecycline group included 513 subjects while the placebo group had 513 subjects enrolled. Patients were excluded from both studies if they had a dermatologic condition or facial hair, any chronic illness interfering with study evaluations, allergy or resistance to tetracyclines, drug-induced acne, hormonal contraceptive initiation, systemic retinoids, systemic corticosteroids, or androgens within 12 weeks prior to randomization. Primary outcome measures for both studies include absolute change in facial inflammatory lesion counts at week 12 compared to baseline and percentage of participants with Investigator Global Assesment (IGA) Success at week 12 compared to baseline. Treatment-emergent adverse events (TEAEs) were assessed at every visit and were patient reported.

Outcome Results for SC1401: Mean absolute change from baseline in noninflammatory lesion count was significantly greater in the sarecycline group compared to the placebo group beginning at week 6 of the study and continuing through week 12. Sarecycline-treated patients had an average change from baseline inflammatory lesion count at week 12 of -15.1 vs. -11.2 in the placebo group ($p<0.01$). Sarecycline had a significantly greater IGA success rate beginning at week 9; 21.9% of the sarecycline group vs. 10.5% of the placebo group achieved IGA success at week 12 ($p<0.0001$).

Outcome Results for SC1402: Mean absolute change from baseline in noninflammatory lesion count was significantly greater in the sarecycline group compared to the placebo group beginning at week 9 of the study and continuing through week 12. Sarecycline-treated patients had an average change from baseline inflammatory lesion count at week 12 of -16.2 vs. -13.4 in the placebo group ($p<0.01$) at week 12. Sarecycline had a significantly greater IGA success rate beginning at week 6; 22.6% of the sarecycline group vs. 15.3%% of the placebo group achieved IGA success at week 12 ($p=0.0038$). The most common TEAEs reported for both studies included headache, nausea, nasopharyngitis, and vomiting. The highest rate of any TEAE was headache that occurred in 4.9% of patients taking placebo in SC1402. There were reports of

photosensitivity associated with sarecycline use in both studies. Overall, sarecycline was well-tolerated.

Limitations: This study uses sareycline as monotherapy in the treatment of moderate to severe acne. However, monotherapy is typically not done in clinical practice as patients are usually prescribed both oral medications in addition to topical medications to treat acne. The study was also powered to determine efficacy for acne that is present on the face. The study was not however powered to determine the efficacy of acne treatment elsewhere on the body. The study sample consisted of a large white population and therefore, it is hard to extrapolate the findings of this study to a diverse population. Patients were only followed for 12 weeks. The outcome measure for the IGA is very subjective rather than objective. The study was funded by Allergan, a drug manufacturer, and several authors of the trial are employed by the company and own stock options within the company leading to potential biases. However, it is stated that Allergan did not provided honoraria or other forms of payment to authors.

Conclusion: Oral sarecycline dosed at 1.5mg/kg/day is effective for improving acne lesions and decreasing inflammatory lesions starting at week 6 of therapy. While the change in inflammatory lesions was significant in both studies, both trials found that sarecycline decreased the number of lesions by an average of 4. Although statistically significant, a decrease in 4 lesions may not be clinically significant. Sarecycline was well tolerated with low rates of side effects which included photosensitivity and gastrointestinal disturbances. Future randomized trials should be conducted using an active control such as an oral antibacterial that is known to treat moderate to severe acne to compare available treatment options.

Citation #3: Berk D. A Multi-Center Open-Label Evaluation of the Safety of Sarecycline Tablets in the Treatment of Acne Vulgaris. National Library of Medicine. 2019, February 1.

Study Design: Description of Study: Multi-center, open-label evaluation

Methods: Patients who successfully completed either trial SC1401 or SC1402 had the option to enroll in this open-label evaluation of the safety of sarecycline. This study had 490 participants and each participant received sarecycline 1.5mg/kg once daily administered orally as 60mg, 100mg, or 150mg based on patient's body weight until adequate improvement in facial acne is obtained (up to 40 weeks). The primary outcome measure was the number of patients with at least 1 treatment-emergent adverse event within a 40-week time frame.

Outcome Results: All-cause mortality throughout the entirety of the study was 0%. Serious treatment-emergent adverse events included anemia (affected: 4/483; at risk: 0.83%), peptic ulcer (affected: 1/483; at risk: 0.21%), dehydration (affected: 1/483; at risk: 0.21%), and severe headache (affected 1/483; at risk: 0.21%). Other non-serious adverse events with nasopharyngitis being reported as the most common non-serious side effects. Non-serious side effects total at risk percentage was 3.7%.

Limitations: This study only focused on the safety of sarecycline use while it would have been beneficial to also determine efficacy of sarecycline in the open-label trial. The trial only included patients who were enrolled in either the SC1401 or SC1402 trials. This could greatly limit the

study sample and not provide an accurate sample of the population. The study's inclusion/exclusion criteria does not specify if the participants were allowed to use topical acne medications at the same time. In open-label studies, both the investigators and patients know what they are receiving. Therefore, the investigators may be more likely to skew the results in favor of the experimental medication when in reality the results may be due to something else. The study was funded by Allergan, a drug manufacturer, and several authors of the trial are employed by the company and own stock options within the company. With the study being open-label there could be large biases present as the results are very positive and in favor of sarecycline.

Conclusion: Sarecycline is safe to use in patients to treat moderate to severe acne at a dose of 1.5mg/kg administered as 60mg, 100mg, or 150mg based off of the patient's weight. Serious side effects occurred at a very limited rate while patients were taking sarecycline.

Contraindications [1,2,3]: Known hypersensitivity to any of the tetracyclines

Precautions [1,2,3]:

Dermatologic: Photosensitivity has been seen in clinical trials and reported with other tetracycline-class antibacterial drugs; minimize or avoid exposure to sunlight and artificial sunlight.

Concomitant use: Concomitant use with isotretinoin should be avoided; increase risk of intracranial hypertension

Gastrointestinal: Clostridium difficile associated diarrhea has been reported with tetracyclines.

Immunologic: Bacterial resistance to tetracyclines may occur during therapy.

Immunologic: Over growth of unsusceptible organisms, including fungi, may occur.

Musculoskeletal: Decrease in fibula growth has been observed in premature infants given tetracycline; typically, reversible upon discontinuation of therapy.

Neurological: Central nervous system adverse effects including light-headedness, dizziness, or vertigo have been reported with tetracycline use.

Neurological: Intracranial hypertension has been reported with tetracycline use.

Teratogenic Effects: Sarecycline, like other tetracyclines, can cause fetal harm when administered to a pregnant woman.

Tooth Discoloration: Permanent discoloration of teeth may occur if used during tooth development (second and third trimesters of pregnancy, infancy, and childhood to the age of 8).

Risk of bacterial infections [3]:

Bacterial resistance to tetracyclines may occur during therapy.

Over growth of unsusceptible organisms, including fungi, may occur.

Adverse Effects[1,2,3] :

1 – 10%: Gastrointestinal: Nausea (3%)

<1%: post marketing, and/or case reports**:** Vulvovaginal candidiasis, vulvovaginal infection

***Note:** Other adverse effects reported under the precaution section may be serious but have unknown incidence rates.

Drug Interactions and Management of Drug Interactions[1,3]:

Aminolevulinic Acid (Systemic): Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid. Management: Avoid combination.

Aminolevulinic Acid (Topical): Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid. Management: Monitor therapy closely.

Antacids: May decrease the absorption of Tetracyclines. Management: Separate administration of antacids and oral tetracycline derivatives by several hours when possible to minimize the extent of this potential interaction.

BCG (Intravesical): Antibiotics may diminish the therapeutic effect of BCG (Intravesical). Management: Avoid combination.

BCG Vaccine (Immunization): Antibiotics may diminish the therapeutic effect of BCG Vaccine (Immunization). Management: consider risks vs. benefits of receiving the vaccine. If administered, monitor closely.

Bile Acid Sequestrants: May decrease the absorption of Tetracyclines. Management: Monitor closely. Consider therapy modification.

Bismuth Subcitrate: May decrease the serum concentration of Tetracyclines. Management: Avoid administration of oral tetracyclines within 30 minutes of bismuth subcitrate administration.

Bismuth Subsalicylate: May decrease the serum concentration of Tetracyclines. Management: Consider dosing tetracyclines 2 hours before or 6 hours after bismuth.

Calcium Salts: May decrease the serum concentration of Tetracyclines. Management: If coadministration of oral calcium with oral tetracyclines can not be avoided, consider separating administration of each agent by several hours.

Cholera Vaccine: Antibiotics may diminish the therapeutic effect of Cholera Vaccine. Management: Avoid cholera vaccine in patients receiving systemic antibiotics, and within 14 days following the use of oral or parenteral antibiotics.

Digoxin: Sarecycline may increase the serum concentration of Digoxin. Management: monitor closely.

Iron Salts: Tetracyclines may decrease the absorption of Iron Salts. Iron Salts may decrease the serum concentration of Tetracyclines. **Exceptions:** Ferric Carboxymaltose; Ferric Gluconate; Ferric Hydroxide Polymaltose Complex; Ferric Pyrophosphate Citrate; Ferumoxytol; Iron Dextran Complex; Iron Isomaltoside; Iron Sucrose. Management: monitor closely and consider alternative therapy.

Lactobacillus and Estriol: Antibiotics may diminish the therapeutic effect of Lactobacillus and Estriol. Management: monitor therapy.

Lanthanum: May decrease the serum concentration of Tetracyclines. Management: Administer oral tetracycline antibiotics at least two hours before or after lanthanum.

Magnesium Dimecrotate: May interact via an unknown mechanism with Tetracyclines. Management: monitor therapy.

Magnesium Salts: May decrease the absorption of Tetracyclines. Only applicable to oral preparations of each agent. Management: consider use of alternative agent.

Mecamylamine: Tetracyclines may enhance the neuromuscular-blocking effect of Mecamylamine. Management: do not use combination.

Methoxyflurane: Tetracyclines may enhance the nephrotoxic effect of Methoxyflurane. Management: do not use combination.

Mipomersen: Tetracyclines may enhance the hepatotoxic effect of Mipomersen. Management: monitor closely.

Multivitamins/Minerals May decrease the serum concentration of Tetracyclines. Management: If coadministration of a polyvalent cation-containing multivitamin with oral tetracyclines cannot be avoided, separate administration of each agent by several hours.

Neuromuscular-Blocking Agents: Tetracyclines may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Management: monitor closely

Penicillins: Tetracyclines may diminish the therapeutic effect of Penicillins. Management: consider alternative antibacterial agent.

Porfimer: Photosensitizing Agents may enhance the photosensitizing effect of Porfimer. Management: minimize exposure to sunlight and artificial sunlight

Quinapril: May decrease the serum concentration of Tetracyclines. Management: Separate doses of quinapril and oral tetracycline derivatives by at least 2 hours in order to reduce the risk of interaction. Monitor for reduced efficacy of the tetracycline if these products are used concomitantly.

Retinoic Acid Derivatives: Tetracyclines may enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. **Exceptions:** Adapalene; Bexarotene (Topical); Tretinoin (Topical). Management: avoid combination.

Sodium Picosulfate: Antibiotics may diminish the therapeutic effect of Sodium Picosulfate. Management: Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic.

Strontium Ranelate: May decrease the serum concentration of Tetracyclines. Management: In order to minimize any potential impact of strontium ranelate on tetracycline antibiotic concentrations, it is recommended that strontium ranelate treatment be interrupted during tetracycline therapy.

Sucralfate: May decrease the absorption of Tetracyclines. Management: Administer the tetracycline derivative at least 2 hours prior to sucralfate in order to minimize the impact of this interaction.

Sucroferric Oxyhydroxide: May decrease the serum concentration of Tetracyclines. Management: Administer oral/enteral doxycycline at least 1 hour before sucroferric oxyhydroxide. Specific dose separation guidelines for other tetracyclines are not presently available. No interaction is anticipated with parenteral administration of tetracyclines.

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. Management: Vaccination with live attenuated typhoid vaccine (Ty21a) should be avoided in patients being treated with systemic antibacterial agents. Use of this vaccine should be postponed until at least 3 days after cessation of antibacterial agents.

Verteporfin: Photosensitizing Agents may enhance the photosensitizing effect of Verteporfin. Management: avoid exposure to sunlight and artificial sunlight.

Vitamin K Antagonists (eg, warfarin): Tetracyclines may enhance the anticoagulant effect of Vitamin K Antagonists. Management: monitor therapy.

Zinc Salts: May decrease the absorption of Tetracyclines. Only a concern when both products are administered orally. Management: Consider doxycycline as a noninteracting tetracycline derivative. Separate dose administration of oral tetracycline derivative and oral zinc salts by at least 2 hours to minimize interaction. **Exceptions:** Zinc Chloride.

Dosing/Administration[1,2,3]: Approved for those 9 years of age and older

Administration: orally with or without food. Administer with adequate fluid to decrease the risk of esophageal irritation and ulceration.

Adult Dosing (based on body weight):

33 to 54 kg: 60mg orally once daily

55 to 84 kg: 100mg orally once daily

85 to 136 kg: 150mg orally once daily

Renal impairment: There are no dosage adjustments provided in the manufacturer's labeling.

Hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling.

Use in Special Populations:

Pediatrics Dosing (based on body weight): **Patient must be 9 years of age or older to use sarecycline.**

- See adult dosing section

Elderly Dosing (based on body weight):

- See adult dosing section

Pregnancy: May cause fetal harm, permanent discoloration of teeth, and reversible inhibition of bone growth when administered during pregnancy. The limited available human data are not sufficient to inform a drug-associated risk for birth defects or miscarriage. Tetracyclines are known to cross the placental barrier; therefore, sarecycline may be transmitted from the mother to the developing fetus. The potential risk to the fetus outweighs the potential benefit to the mother from sarecycline use during pregnancy; therefore, pregnant patients should discontinue sarecycline as soon as pregnancy is realized.

Lactation: Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions on bone and tooth development in nursing infants from tetracycline-class antibiotics, advise a woman that breastfeeding is not recommended with sarecycline therapy.

Over dosage[1,2,3]: In case of overdose, discontinue medication, treat symptomatically, and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdose.

Conclusion: Oral sarecycline, a novel tetracycline used for the treatment of moderate to severe acne in patients over the age of 9 is effective for improving acne lesions and decreasing inflammatory lesions starting at week 6 of therapy when dosed at 1.5mg/kg/day. Sarecycline was well tolerated with low rates of side effects which included photosensitivity and gastrointestinal disturbances which are commonly observed with other oral tetracyclines. Serious side effects noted included anemia, peptic ulcer disease, dehydration, and severe headache. While sarecycline was significantly better at improving acne lesions and decreasing inflammatory lesions, participants in all 3 of the studies used sarecycline as monotherapy for acne treatment. Monotherapy with oral antiacne medications is uncommon in clinical practice as patients typically use both oral antiacne medications in addition to topical antiacne medications. Therefore, the data from these studies should be extrapolated to the population with caution if sarecycline is not going to be used as monotherapy. For a 30-day supply, sarecycline costs $1,032 at a rate of $34.40 per 60mg, 100mg, or 150mg tablet.[8] This price is largely elevated compared to other available oral acne medications. Therefore, there is a need for additional randomized trials comparing sarecycline to active oral antibacterial controls that are known to treat moderate to severe acne effectively. These studies should not only be conducted to compare efficacy between medications, but also to compare the cost vs. benefit of sarecycline.

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7. Berk D. A Multi-Center Open-Label Evaluation of the Safety of Sarecycline Tablets in the Treatment of Acne Vulgaris. National Library of Medicine. 2019, February 1.
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