Oral Antibiotics for Acne

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San Diego, California
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F005- Acne Boot Camp
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Neal Bhatia MD

F005-Acne Boot Camp: Oral Antibiotics for Acne

DISCLOSURES

Affiliations with Aclaris, Almirall, Biofrontera, BiopharmX, Dermira, EPI Health, Ferndale, Foamix, Intraderm, ISDIN, LaRoche-Posay, Leo, Mayne, Menlo, Ortho, Pierre-Fabre, Promius, SkinFix, SunPharma

Acknowledgments

Hilary Baldwin, Jim Del Rosso, Ted Rosen, Neil Shah, Josh Zeichner

Copies of pdf or questions: bhatiaharbor@gmail.com
Oral Antibiotics for Acne: Where are we headed?

- Good and Bad Behavior
- Match Antibiotics MOA to Pathogenesis
- Why Tetracyclines and why worry?
- Lower Doses to the rescue
- Sarecycline joins the team
Do you really need to take all those antibiotics?

How to be antibiotic-smart

So, what should we do about antibiotic courses?

Medicine in the 21st century is a team sport. You and your physician need to be partners in decision-making. If you are sick and your doctor mentions antibiotics to you, the first thing you should say is, "Hey, doc, do I really need the antibiotic?"

Doctors may otherwise prescribe an antibiotic even when you don't need one, out of fear that you will be unhappy without the prescription. Flip the script on them. Help them to know that you’d prefer not to take the antibiotic unless it is really necessary.

If your doctor says, "Yes, I believe you have a bacterial infection and you need the antibiotic," the next question is, "Okay, can we treat for a short course?"
So what do we do?
Consensus vs. Divergent Opinions

- Majority of published “guidelines” and consensus statements support use for inflammatory acne
  - Avoid monotherapy; use should be combined with topical therapy
  - Tetracycline recommended as “first-line” agents
- Limit use and duration due primarily to antibiotic resistance concerns
- Lack of head to head studies and comparative superiority
- Dosing? Amount? Frequency?
- Duration of therapy?
- Follow-up periods?
- Aside from lesion count, Costs and Demographics will always influence variability in prescribing plans

Evidence of Bad Behavior?

- **Dermatologists: more oral abx per prescriber than any other specialist**
  - Main use of antibiotics in dermatology is acne vulgaris
  - Tetracyclines= 75% of oral antibiotics prescribed in derm
  - Clindamycin by far most commonly prescribed topical
- **2011 Survey: 8,153,961 rx written by dermatologists for oral Abx**
  - 6,174,025 for Tetracyclines

*Total of 8,153,961 prescriptions written in 2011 by dermatologists.
*Total of 6,174,025 prescriptions in 2011 by dermatologists.
TMP/SMX = trimethoprim-sulfamethoxazole

Research Data

Pros:
- Controlled setting and dedicated efficacy and safety data
- Dose ranging study data helpful for real world tapering

Cons
- Not real world since monotherapy
- Impact on Comedogenesis?

Guidelines

Pros
- Helpful for eliminating or preventing bad habits
- Exploration of regimens based on MOA applied to phenotypes

Cons
- Derms don’t like to be told what to do
- Costs often overshadow logic
Inflammation: chicken or egg?

- Does inflammation precede or follow the formation of the microcomedone?
- Biopsies taken of
  - Uninvolved skin from acne patients (n=20)
  - Early inflamed lesions from acne patients (n=12)
  - Normal skin from control patients without acne (n=10)
- Inflammatory markers examined and compared
  - Examples include T cell types, neutrophils, macrophages
  - $\alpha_6$-integrin, interleukin-1 (IL-1)

Evolving Inflammatory Mechanisms

- Observed in uninvolved skin from acne patients prior to onset of comedogenesis

Large numbers of CD4+ T cells >> normal skin

Early follicular expression of IL-1

Does the inflammation precede, follow, or coincide with follicular hyperkeratinization?

Large macrophage presence equivalent in clinically apparent early inflammatory lesions (<6 hours)

Aberrant integrin expression in epidermis around uninvolved follicles and inflamed lesions

Cathelicidins are potential targets for Tetracyclines

- Cathelicidins have innate proinflammatory and antimicrobial properties directly involved in acne pathogenesis
  - Sebocytes express LL-37 that kill *P. acnes*
  - MMP-1 and MMP-9 are expressed in inflammatory acne
- *P. acnes* induces MMP-1, MMP-9
  - tissue inhibitor of metalloproteases (TIMP-1)

Kanada et al. Inhibition of Cathelicidin Processing Enzymes as Therapy for Rosacea. Poster #506 presented at SID meeting; May 2011; Jalian et al. *JID* 2008; 128: 2777-2782
Anti-inflammatory Activity of Tetracyclines

- Downregulation of proinflammatory cytokines (TNF-\(\alpha\), IL-1\(\beta\))\(^1,2\)
- Inhibition of neutrophil chemotaxis\(^1,3\)
- Reduction of arachidonic acid metabolites by inhibition of phospholipase A\(_2\)\(^1,2\)
- Inhibition of nitric oxide (NO) activity\(^2,3\)
- Suppression of neutrophil-derived production of reactive oxygen species (ROS)\(^1,4\)
- Inhibition of leukocyte-derived matrix metalloproteinases, including collagenases (MMP-8, -13), gelatinases (MMP-2, -9), elastases (MMP-12)\(^2,3\)
- Inhibition of activation of cathelicidin precursors and activity\(^2,3\)

Why not other antibiotics?

Azithromycin

- Used commonly for community acquired infection
- Short dosing due to long half life (68 hrs)
- Well tolerate—previous TCN fail or cannot tolerate other Abx
- Most acne studies – 3x / week4-5
  - As effective as minocycline?

TMP-SMZ

- Avoid in patients with sulfa allergy
- Data limited – can be highly effective in some refractory patients
- Severe potential toxicities
  - GI upset
  - Exanthem → SJS-TEN
  - Pancytopenia

Why not other antibiotics?

Amoxicillin

- Dosage?
- 2nd line agent—limited data
- Advantages: Pregnancy safety? well-tolerated but for how long?
- Consider in patients with previous drug intolerance, allergy, cost, pregnancy
- 2018 Retrospective review
  - 26 patients; 85% improvement

Cephalexin

- Dosage?
- Case series, 93 pts—78% had some improvement over 6 mo
  - 4% cleared, 45% “much improved,” 29% “somewhat improved,”
- 22% either no change or worse
- Risks of resistance, renal clearance of cephalosporins?


Reduction in *P. acnes* With Oral Antibiotic Therapy

Adapted from Leyden JJ. *Semin Cutan Med Surg.* 2001;20(3):139-143.
Infection vs. Inflammation

- Low dose 40mg vs. High dose 100mg Doxy impacts inflammation differently
  - In Vitro IL-8, TNF-α, and IL-6 gene expression in immortalized keratinocytes and HaCaT cells stimulated with LPS
  - High dose Doxy was better for reducing LPS-induced proinflammatory cytokines (IL-8, TNF-α, and IL-6) when LPS and doxycycline were present together in cell cultures
  - Low doses were more effective when added before (pretreatment) or after (posttreatment) LPS stimulation
  - Can low doxycycline doses could be safely used to control inflammation that is either recurrent or in progress?

Anti-Inflammatory Dose Doxycycline 40 mg vs Doxycycline 100 mg vs Placebo for Severe Acne

- Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study once daily for 16 weeks
- The study included patients aged 12 years or older with moderate to severe acne vulgaris and facial involvement (25–75 inflammatory lesions)

Eligible patients were randomized to receive:
- modified-release DC 40 mg tablets qD
- DC 100 mg capsules qD
- placebo qD

Moore, J "Efficacy and Safety of Subantimicrobial Dose, Modified-Release Doxycycline 40 mg vs Doxycycline 100 mg vs Placebo in the Treatment of Severe Acne J Drugs Dermatol. 2015 Jun;14(6):581-6."
Anti-Inflammatory Dose Doxycycline 40 mg vs Doxycycline 100 mg vs Placebo for Severe Acne

Doxy 40 mg was statistically superior to placebo in the reduction of inflammatory lesions (16.1 vs 12.6; \( p = .006 \))

Modified-release Doxy 40 mg performed better in the reduction of the number of inflammatory lesions and percent reduction of total lesions (41.7\% vs 35.9\%; \( P = .026 \)).

compared to Doxy 100 mg (16.1 vs 12.9; \( P = .024 \); Figure 1).

Table VI. Recommendations for systemic antibiotics

Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments.

Doxycycline and minocycline are more effective than tetracycline, but neither is superior to each other.

Although oral erythromycin and azithromycin can be effective in treating acne, its use should be limited to those who cannot use the tetracyclines (i.e., pregnant women or children <8 years of age). Erythromycin use should be restricted because of its increased risk of bacterial resistance.

Use of systemic antibiotics, other than the tetracyclines and macrolides, is discouraged because there are limited data for their use in acne. Trimethoprim-sulfamethoxazole and trimethoprim use should be restricted to patients who are unable to tolerate tetracyclines or in treatment-resistant patients.

Systemic antibiotic use should be limited to the shortest possible duration. Re-evaluate at 3-4 months to minimize the development of bacterial resistance. Monotherapy with systemic antibiotics is not recommended.

Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy.
<table>
<thead>
<tr>
<th>1st Line Treatment</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Line Treatment</strong></td>
<td>Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy**</td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>Moderate</strong></td>
<td>Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Antibiotic</td>
<td></td>
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<tr>
<td></td>
<td><strong>Severe</strong></td>
<td>Oral Antibiotic + Topical Combination Therapy**</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative Treatment</strong></td>
<td>Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin</td>
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</tbody>
</table>

**Fig 1.** Treatment algorithm for the management of acne vulgaris in adolescents and young adults. The double asterisks (**) indicate that the drug may be prescribed as a fixed combination product or as separate component. BP, Benzoyl peroxide.
Antibiotics and OCPs

**Clinical Review**

Oral contraceptive efficacy and antibiotic interaction: A myth debunked

Johanna S. M. Archer, MD, and David F. Archer, MD

Charleston, South Carolina, and Norfolk, Virginia

**Conclusion**

There are no pharmacokinetic data at this time to support the contention that oral antibiotic use decreases the efficacy of OCs, except for antituberculosis drugs such as rifampin. There are also no prospective, randomized clinical trials of OC efficacy and antibiotic use. Lastly, case reports used to support an effect of antibiotics on OC efficacy are anecdotal and subject to recall bias and lack adequate controls and medication documentation. Thus, there


J Am Acad Dermatol 2002;46:917-23
Hot off the Press
February 2018 JAAD, Volume 78, Issue 2, Supplement 1, S1-S23

Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne

Diane M. Thiboutot, MD, Chair, Brigitte Dréno, MD, PhD, Co-Chair, Abdullah Aaban, MD, Andrew F. Alexis, MD, MPH, Elena Araznavskaia, MD, PhD, Maria Isabel Barona Cabal, MD, Vincenzo Bettoli, MD, Hordelitz Casinatahan, MD, Steven Chow, MD, Adilson da Costa, MD, MSc, PhD, Tam El Ouazzani, MD, Chee-Leok Goh, MD, Harald P. M. Gollnick, MD, Minerva Gomez, MD, Nobukazu Hayashi, MD, PhD, Maria Isabel Herane, MD, Juan Honeyman, MD, Scowon Kang, MD, Lajos Kemény, MD, PhD, Raj Kulkka, MD, Julien Lambert, MD, PhD, Alison M. Layton, MB ChB, James J. Leyden, MD, Jose Luis Lopez-Escobarz, MD, PhD, Nipadon Noppakun, MD, Falk Ochsendorf, MD, Cristina Opirca, MD, PhD, Beatriz Orozco, MD, Montserrat Perez, MD, Jaime Piquero-Martin, MD, MSc, Jo-Aun See, MD, Dae Hun Sub, MD, PhD, Jerry Tan, MD, Vicente Torres Lozada, MD, Patricia Troielli, MD, and Leihong Flora Xiang, MD, PhD

1) Limit systemic antibiotics to 3-4 months
2) Severity of acne, Resistance potential, and Treatment responses will impact duration
3) Acne Recurrence and Patient Preference will limit use

Hershey, Pennsylvania; Nantes, France; Riyadh, Saudi Arabia; New York, New York; St. Petersburg, Russia; Cali and Medellin, Colombia; Ferrara, Italy; Manila, Philippines; Kuala Lumpur, Malaysia; Sao Paulo, Brazil; Casablanca, Morocco; Singapore; Magdeburg, Germany; Monterey, Mexico; Tokyo, Japan; Santiago, Chile; Baltimore, Maryland; Szeged, Hungary; New Delhi, India; Iedegem, Belgium; Harrogate, United Kingdom; Philadelphia, Pennsylvania; Madrid and Barcelona, Spain; Bangkok, Thailand; Frankfurt, Germany; Stockholm, Sweden; Caracas, Venezuela; Sydney, Australia; Seoul, South Korea; Windsor, Canada; Mexico City, Mexico; Buenos Aires, Argentina; and Shanghai, China
1) Limit systemic antibiotics to 3-4 months
2) Severity of acne, Resistance potential, and Treatment responses will impact duration
3) Acne Recurrence and Patient Preference will limit use
• Assessing risk-benefit analysis for systemic antibiotics should balance individual need versus public interest in preserving antibiotic effectiveness
  o Antibiotics should be avoided when effective alternatives are available

• Oral antibiotics are indicated when inflammatory acne is not responding well to topical treatments and acne involving trunk or multiple bodily areas
  o Response to therapy should be evaluated at 6-8 weeks
  o Target duration of therapy less than 3-4 months
  o A topical retinoid and BPO or azelaic acid can be used at discontinuation of antibiotic
Doxycycline and Minocycline for the Management of Acne: A Review of Efficacy and Safety With Emphasis on Clinical Implications

Leon H. Kirzick MD
Clinical Associate Professor of Dermatology, Mount Sinai Medical Center, New York, NY

ABSTRACT

A significant number of patients with moderate-to-severe inflammatory acne are candidates for oral antibiotic therapy. Use of tetracycline for acne has yielded to second-generation molecules doxycycline and minocycline, which are associated with numerous benefits over their predecessor, especially less frequent dosing and improved safety. Nonetheless, these agents are associated with certain potential side effects, including gastrointestinal (GI) concerns, staining of developing teeth in children, candidiasis, vestibular concerns and, somewhat more controversially, photosensitivity. Additionally, minocycline may be associated with the development of autoantibodies, including anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA) and anti-phospholipid antibodies with or without associated clinical symptoms. Given their similar efficacy for the management of moderate-to-severe acne vulgaris, the choice of doxycycline or minocycline may depend on specific clinical considerations, including patient satisfaction with therapy, compliance and convenience. Data and clinical experience suggest that enteric-coated doxycycline, with its low rate of GI symptoms, may represent a more tolerable treatment option for many acne patients and therefore be associated with better likelihood of compliance.
Relative *in vivo* Antimicrobial Effects of Tetracyclines


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Net Reductions in <em>P. acnes</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 3</td>
<td></td>
</tr>
<tr>
<td>minocycline 200 mg</td>
<td></td>
</tr>
<tr>
<td>doxycycline 200 mg</td>
<td></td>
</tr>
<tr>
<td>tetracycline 1000 mg</td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td></td>
</tr>
<tr>
<td>minocycline 200 mg</td>
<td></td>
</tr>
<tr>
<td>doxycycline 200 mg</td>
<td></td>
</tr>
<tr>
<td>tetracycline 1000 mg</td>
<td></td>
</tr>
<tr>
<td>Follow-up Week 9</td>
<td></td>
</tr>
</tbody>
</table>

† Differences versus baseline
Doxycycline 101

- Two different salt forms:
  - Monohydrate (poorly water soluble)
    Fewer GI side effects
  - Hyclate (highly water soluble)—active ingredient 85%
  - Both converted to active doxycycline after absorption and equally effective
- Newer formulations--enhance tolerability
  - Enteric coating, delayed release, smaller pills

- Available doses
  - Sub-antimicrobial dose: 20mg, 40 (30/10) mg,
  - Immediate release: 50mg, 75mg, 100mg, 150mg
  - Delayed release: 50mg, 120 mg, 200 mg (branded),
  - 75mg, 100 mg, 150 mg (generic)
What does Doxycycline do that Minocycline does not?

- Doxy causes more GI issues, depending on formulations: hyclate>monohydrate
  - Absorption impacted by food, dairy, and use of enteric coatings
  - Pill “esophagitis” can occur when not ingested with water
- Photosensitivity potential higher with doxy
- Higher risks of vaginal candidiasis given dosage and duration of therapy

Strategies to Reduce Risk of Adverse Effects with Doxycycline

- GI distress and esophagitis\(^1,2\)
  - Large glass of water and food\(^1-3\)
  - Remain upright for at least a few hours after ingestion
  - Do not take before bedtime\(^3\)
  - Enteric-coated formulation

- Dose-related phototoxicity
  - Photoprotection education
  - Proper use of sunblocks\(^3\)

- With Food or Empty Stomach?
  - Decrease in absorption if co-ingested with metal ions present in foods
    - antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, iron
  - Dairy, fortified cereals, vitamin/mineral supplements, antacids with calcium, magnesium, and/or aluminum\(^17,18\)

- Probiotics?
  - Add protective flora back to GI tract
  - May reduce diarrhea and nausea
  - No impact on antibiotic efficacy

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Minocycline advantages

- Highly lipophilic: High penetration into sebum and high follicular concentrations
- Minimal-no effect of stomach contents; unaffected by dairy
- Multiple anti-inflammatory effects
  - Blocks the production/inhibits inflammatory mediators
  - Inhibits \textit{P acnes} lipase enzyme
  - Prevents neutrophil chemotaxis/Inhibits phagocytosis
  - Reduces the impact of reactive oxygen species
- Log reductions in \textit{P acnes} counts:
  - minocycline > doxycycline > tetra > erythromycin

Minocycline 101

- Multiple uses—Infections and inflammation—Sub antimicrobial dose?
- Capsules and Tablets: HCl base
  - Immediate release: 50mg, 75 mg, 100mg
  - Suspension: 50 mg/5 ml
- Weight based daily doses:
  - 45 to 49 kg: 45 mg
  - 50 to 59 kg: 55 mg
  - 60 to 71 kg: 65 mg
  - 72 to 84 kg: 80 mg
  - 85 to 96 kg: 90 mg
  - 97 to 110 kg: 105 mg
  - 111 to 125 kg: 115 mg
  - 126 to 136 kg: 135 mg

Minocycline History

- 39 RCTs (n=6013)—small trials, rare meta-analysis
- Minocycline historically effective treatment but no evidence that it is superior to any other commonly-used acne treatments.”
- “No trials have been conducted using minocycline in where acne is resistant to other therapies.”
  - No evidence to guide what dose should be used.
- The risk of autoimmune reactions increases with duration
- No evidence that extended-release minocycline is safer than standard dosage preparations.

Minocycline Hyperpigmentation

- Dermal and/or Epidermal pigment
  - Blue-black near scars
  - Blue-gray hyperpigmentation in normal skin of extremities
  - Diffuse brown pigment in photoexposed

- Pigmentation occurred in 4% of patients taking minocycline 200 mg/day
- All pigmentation cases occurred after a minimum treatment duration of 8 months and a minimum total cumulative dose of 70 g of minocycline

Sarecycline

- Approved for moderate to severe acne in Oct. 2018 (SEYSARA™)—ages 9 and up
- Weight-based dose tablets, once daily with or without food:
  - 33-54 kg → 60 mg
  - 55-84 kg → 100 mg
  - 85-136 kg → 150 mg
- Binds to 30S ribosome as TCNs but no AA-tRNA binding
  - Anti-inflammatory but also blocks protein synthesis
- Same warnings as other TCNs: Teeth Staining before age 8, Intracranial Pressure, and Pseudomembranous Colitis
Once-Daily Oral Sarecycline 1.5 mg/kg/day for Moderate to Severe Acne: Two Phase 3 Pivotal Studies

- Pts 9 to 45 years old, acne IGA score ≥3
  - 20-50 inflammatory lesions, ≤100 noninflammatory lesions
  - Placebo vs. Sarecycline 1.5 mg/kg/day x 12 weeks
  - 60-mg, 100-mg, or 150-mg tablets

- ≥2-grade improvement + IGA 0 (clear) or 1 (almost clear)

- Post hoc analysis:
  - Change from baseline in *noninflammatory lesion counts* at week 12 in patients with ≥10 noninflammatory lesions at baseline
Sarecycline Superior to Placebo for Inflammatory Lesions Starting at Week 3

Least Squares Mean Change From Baseline in Inflammatory Lesions, %

Week

Sarecycline (n=1002) Placebo (n=1000)

*P<0.0001 (Pooled ITT Population)
Sarecycline Reductions in Noninflammatory Lesions by Week 6

Results were consistent with post hoc analyses in patients with $\geq 5$, $\geq 20$, and $\geq 30$ baseline noninflammatory lesions.

(Post Hoc Analysis)
Sarecycline Improvement in Acne Severity vs Placebo at Week 12

(Pooled ITT Population)
## Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Sarecycline (n=994)</th>
<th>Placebo (n=996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal effects, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (3.2)</td>
<td>17 (1.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (1.3)</td>
<td>9 (0.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (1.1)</td>
<td>14 (1.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (0.9)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>7 (0.7)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (0.5)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Vestibular effects, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (0.5)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Phototoxic effects, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunburn</td>
<td>7 (0.7)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>1 (0.1)</td>
<td>0</td>
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<tr>
<td>Vaginal yeast infections in females, n (%)</td>
<td></td>
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<tr>
<td>Vulvovaginal candidiasis(^a)</td>
<td>4 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Vulvovaginal mycotic infection(^a)</td>
<td>5 (0.9)</td>
<td>0</td>
</tr>
</tbody>
</table>