APPLICATION NUMBER:

211527Orig1s000

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: 211527
PDUFA Goal Date: October 4, 2019
OSE RCM #: 2018-2154

Reviewer Name(s): Lindsey W. Crist, Pharm.D., BCPS
Team Leader: Donella Fitzgerald, Pharm.D.
Deputy Division Director: Jamie Wilkins, Pharm.D.
Review Completion Date: August 26, 2019
Subject: Evaluation of Need for a REMS

Established Name: Trifarotene
Trade Name: Aklief
Name of Applicant: Galderma Research and Development, LLC
Therapeutic Class: Retinoid acid receptor agonist, topical
Formulation(s): Topical cream with pump
Dosing Regimen: Apply a thin layer to affected areas once daily in the evening
Table of Contents

EXECUTIVE SUMMARY ......................................................................................................................................................... 3

1 Introduction ..................................................................................................................................................................... 3

2 Background ...................................................................................................................................................................... 3
   2.1 Product Information ........................................................................................................................................... 3
   2.2 Regulatory History............................................................................................................................................... 4

3 Therapeutic Context and Treatment Options .................................................................................................... 4
   3.1 Description of the Medical Condition .......................................................................................................... 4
   3.2 Description of Current Treatment Options ............................................................................................... 4

4 Benefit Assessment ....................................................................................................................................................... 5

5 Risk Assessment & Safe-Use Conditions .............................................................................................................. 7
   5.1 Serious Adverse Events ..................................................................................................................................... 7
   5.2 Adverse Events of Special Interest................................................................................................................ 8
      5.2.1 Embryofetal Toxicity ................................................................................................................................. 8

6 Expected Postmarket Use ........................................................................................................................................... 8

7 Risk Management Activities Proposed by the Applicant ................................................................................................. 9

8 Discussion of Need for a REMS............................................................................................................................................. 9

9 Conclusion & Recommendations ........................................................................................................................................... 9

10 Appendices ................................................................................................................................................................ 10
   10.1 References ..................................................................................................................................................... 10
   10.2 Currently Available Treatments for Acne Vulgaris .............................................................................. 10
EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Aklief (trifarotene) is necessary to ensure the benefits outweigh its risks. Galderma Research and Development, LLC submitted a New Drug Application (NDA) 211527 for trifarotene with the proposed indication for the topical treatment of acne vulgaris \(\text{a}^{(b)}\) in patients 9 years of age and older. The risks associated with trifarotene are consistent with the class effects of topical retinoids, most commonly local cutaneous reactions such as irritation, pruritis, and sunburn. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRISK) has determined that a REMS is not needed to ensure the benefits of trifarotene outweigh its risks. The safety concerns associated with trifarotene are well documented and consistent with known class effects of topical retinoids, therefore the prescribers of trifarotene are likely to be aware of the risks, and the risks can be communicated through labeling.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Aklief (trifarotene) is necessary to ensure the benefits outweigh its risks. Galderma Research and Development, LLC (Galderma) submitted a New Drug Application (NDA) 211527 for trifarotene with the proposed indication for the topical treatment of acne vulgaris \(\text{a}^{(b)}\) in patients 9 years of age and older. This application is under review in the Division of Dermatology and Dental Products (DDDP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Aklief (trifarotene), a new molecular entity\(^a\), is a retinoid acid receptor (RAR) agonist proposed for the topical treatment of acne vulgaris \(\text{a}^{(b)}\) in patients 9 years of age and older. Topical retinoids treat acne by normalizing follicular hyperkeratosis, preventing the formation of microcomedones, and through anti-inflammatory effects.\(^1\)

Trifarotene is proposed as a 0.005% cream available in 30, 45, and 75-gram pumps. Each gram of the cream contains 50 micrograms of trifarotene. The proposed dosing regimen is to apply a thin layer to the affected areas on the face and/or trunk every evening. Treatment continues until acne lesions improve or resolve but may also continue as maintenance therapy.\(^b\) The topical retinoid agents currently available for acne treatment do not require a REMS program for safe use. Trifarotene is not currently approved in any jurisdiction.

---

\(^{a}\) Section 505-1 (a) of the FD&C Act: \textit{FDAAA factor (F): Whether the drug is a new molecular entity.}

\(^{b}\) Section 505-1 (a) of the FD&C Act: \textit{FDAAA factor (D): The expected or actual duration of treatment with the drug.}
2.2 **REGULATORY HISTORY**

The following is a summary of the regulatory history for NDA 211527 relevant to this review:

- 10/4/2018: NDA 211527 submission for the topical treatment of acne vulgaris in patients 9 years of age and older received.²
- 03/18/2019: 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 trifarotene.

3 **Therapeutic Context and Treatment Options**

3.1 **DESCRIPTION OF THE MEDICAL CONDITION**

Acne vulgaris (AV) is a common dermatologic disorder in the United States, affecting around 50 million people.³ AV is considered a disorder of adolescence with about 85% of people 12 to 25 years reporting acne.⁴,⁵ However, acne may persist into adulthood with about 26% of women and 12% of men reporting acne into their forties.⁵

AV is a chronic, inflammatory disease of pilosebaceous follicles that is multifactorial in etiology. Important factors in the formation of acne lesions include increased sebum production, follicular hyperkeratinization, altered immune and inflammatory responses, and colonization of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*). There are two major types of acne lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe cases, nodules/nodulocystic lesions). Microcomedones are the precursor for both lesion types. AV varies in severity according to lesion types, numbers, and extent of involvement.

The clinical course is characterized by remissions and recurrences. AV can result in decreased quality of life and significant psychosocial morbidity including higher rates of depression, anxiety, and low self-worth. Long-term consequences may include permanent scarring and post-inflammatory hyperpigmentation.⁴,⁵

3.2 **DESCRIPTION OF CURRENT TREATMENT OPTIONS**

Several topical and systemic drugs are available for the treatment of AV. Guidelines from the American Academy of Dermatology provide an algorithm for selecting treatment options based on severity.³ Topical therapies such as benzoyl peroxide or retinoids are recommended as first-line options as monotherapy or in combination with other topical or systemic agents depending on acne severity and patient response. Choice of a specific agent depends on patient preference, skin type, and acne distribution. Systemic agents are reserved for severe, recalcitrant, nodulocystic AV. Combination

---

² Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

³ Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

Reference ID: 4482385
therapy utilizing agents with complementary mechanisms is often required for treatment success.\textsuperscript{3,4} See Table 1 in the Appendix, for more details about available acne treatments.

## 4 Benefit Assessment

The efficacy and safety of trifarotene 0.005% cream for the treatment of acne vulgaris was demonstrated in two pivotal phase 3 studies (Study 18251, NCT02566369 and Study 18252, NCT02556788). A Phase 3 open-label study (Study 18250, NCT02189629) provided additional long-term safety and efficacy evidence.\textsuperscript{7}

The two pivotal studies were identical in design: multicenter, randomized, double-blind, parallel-group, and placebo (vehicle)-controlled. The eligibility criteria for both pivotal trials were consistent: moderate\textsuperscript{e} facial acne for patients 9 and older and moderate facial and truncal acne for patients 12 and older. The presence of truncal acne was optional for patients 9 to 11 years old. Patients were randomized (1:1) to trifarotene 0.005% cream or a vehicle cream applied daily to the face (and trunk if applicable) for 12 weeks. Both studies had the following co-primary endpoints: success on the Investigator’s Global Assessment (IGA)\textsuperscript{f}, absolute change in facial noninflammatory lesion count, and absolute change in facial inflammatory lesion count at Week 12. The co-secondary endpoints evaluated truncal acne and included success on the Physician’s Global Assessment (PGA) Scale, absolute change in truncal noninflammatory lesion count, and absolute change in truncal inflammatory lesion count at Week 12.

The long-term safety and efficacy of trifarotene was evaluated in Study 18250. This was a multicenter, open-label, non-comparative study for up to 52 weeks. Eligibility criteria and efficacy endpoints were similar to the pivotal trials.

### Results

The pivotal Phase 3 studies, 18251 and 18252, enrolled a total of 2420 subjects 9 years of age and older. A total of 2206 subjects (91.2%) completed the studies. Trifarotene treatment resulted in statistically significant improvements in the co-primary and co-secondary endpoints compared to the vehicle groups in both studies. Treatment results for the pivotal study co-primary (face) and co-secondary (trunk) endpoints are summarized below in the Table 1 and Table 2.

\textsuperscript{e} Defined as Investigator’s Global Assessment (IGA) grade 3 and a minimum of 20 inflammatory lesions and 25 non-inflammatory lesions on the face at screening and baseline.

\textsuperscript{f} IGA Success Rate defined as the percentage of subjects who achieved an IGA score of 1 (almost clear) or 0 (clear) and at least a 2-grade improvement from baseline to week 12
Table 1. Results for the Co-Primary (Face) Endpoints

<table>
<thead>
<tr>
<th>Study 18251</th>
<th>Study 18252</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trifarotene N=612</td>
<td>Trifarotene N=602</td>
</tr>
<tr>
<td>Vehicle N=596</td>
<td>Vehicle N=610</td>
</tr>
<tr>
<td><strong>IGA Success (Face)</strong></td>
<td><strong>IGA Success (Face)</strong></td>
</tr>
<tr>
<td>29.4%</td>
<td>42.3%</td>
</tr>
<tr>
<td>19.5%</td>
<td>25.7%</td>
</tr>
<tr>
<td>9.8% (&lt;0.001)</td>
<td>16.6% (&lt;0.001)</td>
</tr>
</tbody>
</table>

**Inflammatory Lesions**
- Baseline Mean: 34.7 34.8
- Week 12 Mean: 15.7 19.3
- Change, LS Mean: -19.0 -15.4 -3.6 (<0.001)

**Non-Inflammatory Lesions**
- Baseline Mean: 54.0 52.8
- Week 12 Mean: 28.0 34.5
- Change, LS Mean: -25.0 -17.9 -7.1 (<0.001)

Source: Division of Dermatology and Dental Products. Draft Multidisciplinary Review for trifarotene, NDA 211527

Table 2. Results for the Co-Secondary (Trunk) Endpoints

<table>
<thead>
<tr>
<th>Study 18251</th>
<th>Study 18252</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trifarotene N=600</td>
<td>Trifarotene N=598</td>
</tr>
<tr>
<td>Vehicle N=585</td>
<td>Vehicle N=609</td>
</tr>
<tr>
<td><strong>PGA Success (Trunk)</strong></td>
<td><strong>PGA Success (Trunk)</strong></td>
</tr>
<tr>
<td>35.7%</td>
<td>42.6%</td>
</tr>
<tr>
<td>25.0%</td>
<td>29.9%</td>
</tr>
<tr>
<td>10.7% (&lt;0.001)</td>
<td>12.7% (&lt;0.001)</td>
</tr>
</tbody>
</table>

**Inflammatory Lesions**
- Baseline Mean: 37.5 36.2
- Week 12 Mean: 15.9 17.9
- Change, LS Mean: -21.4 -18.8 -2.5 (<0.001)

**Non-Inflammatory Lesions**
- Baseline Mean: 47.0 48.3
- Week 12 Mean: 24.5 29.4
- Change, LS Mean: -21.9 -17.8 -4.1 (0.001)

Source: Division of Dermatology and Dental Products. Draft Multidisciplinary Review for trifarotene, NDA 211527

Long-term efficacy was evaluated in Study 18250 as a secondary endpoint. A total of 455 subjects were enrolled and 348 (76.5%) completed the study. The effectiveness of trifarotene improved over time with IGA success in 65.1% and PGA success in 66.9% of patients, respectively, by Week 52.

The clinical review team concluded that the data from the 2 adequate and well-controlled trials provided substantial evidence of the effectiveness of trifarotene for the treatment of acne vulgaris in the population age 9 years and older. 

---

*Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Reference ID: 4482385
5 Risk Assessment & Safe-Use Conditions

The primary safety analysis for trifarotene in acne vulgaris is based on the pooled data from the two pivotal phase 3 trials (Study 18251 and Study 18252). The analysis included subjects who received 12 weeks of trifarotene 0.005% cream (N=1220) or vehicle cream (N=1200) to the face and trunk. Additional safety data was provided from Study 18250, the long-term safety trial, which consisted of 453 subjects treated with trifarotene therapy for 52 weeks.\(^h\)

The most common treatment emergent adverse events (TEAEs) related to trifarotene treatment in the primary safety analysis included application site irritation (7.5%, [91/1220]), application site pruritus (2.4%, [29/1220]), and sunburn (2.6%, [32/1220]). Cutaneous reactions were also the most common reported adverse reaction in the long-term trial. Most reactions were mild to moderate and improved over time. Local tolerability adverse events (erythema, dryness, scaling, stinging/burning) were actively assessed by investigators at baseline and at least one follow-up visit. A higher proportion of subjects treated with trifarotene had worsening symptoms of local tolerability from baseline compared to vehicle cream.

Rates of treatment discontinuation were similar between trifarotene (9.6% [117/1220]) compared to vehicle cream (8.1%, [97/1200]) in the pivotal studies. Discontinuation due to adverse events was low overall, however, higher in the trifarotene group (1.9%, [23/1220]) compared to vehicle group (0.2%, [2/1200]). The most common TEAE leading to discontinuation in the trifarotene group was application site irritation. In the long-term safety study, the primary reasons for discontinuation were withdrawal by subject (11.6%, [53/455]) and adverse event (3.5%, [16/455]). All of the TEAEs that led to discontinuation in the long-term study were cutaneous reactions with the exception of 1 event of polycystic ovaries.

5.1 Serious Adverse Events\(^h, j\)

There were no deaths in the studies. In the double-blind safety population, the frequency of treatment-emergent serious adverse events (SAE) was the same in the trifarotene group (6 patients (0.5%) reporting 7 serious TEAEs) and the vehicle cream group (6 patients (0.5%) reporting 7 serious TEAEs).

\(^h\) Study 18250 enrolled 455 subjects, however, only 453 subjects received treatment and were included in the analysis.

\(^j\) 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.

\(^i\) Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Reference ID: 4482385
The 7 SAEs in the trifarotene group included facial bone fracture, ligament sprain, procedural dizziness, cellulitis, infectious mononucleosis, suicide attempt, and major depression. The 7 SAEs in the vehicle group included appendicitis, atypical pneumonia, sinusitis, suicide attempt, hereditary angioedema, urinary tract infection, and asthma. None of the SAEs were considered related to the study drug by the Applicant or clinical reviewer.6,8

Twelve SAEs were reported by 10 patients (2.2%) in the long-term safety study. Severe SAEs included nasal septum deviation, acute pyelonephritis, post-procedural hemorrhage following adenotomy, abortion spontaneous, and complex partial seizures. None of the SAEs were considered related to the study drug.6,8

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Embryofetal Toxicity
Systemic exposure to retinoids is associated with embryofetal toxicity. The oral retinoid, isotretinoin, is subject to a REMS to mitigate the risk of embryofetal toxicity. Topical retinoids are not subject to a REMS, however, labeling for the approved topical retinoids communicates the data on teratogenicity in Section 8, Special populations with the exception of tazarotene which is contraindicated in pregnancy (See Table 1 in the Appendix for more detail). There are case reports of embryofetal toxicity in pregnant women exposed to topical retinoids, however, there is not a clear pattern or association. A consult by the Division of Pediatric and Maternal Health (DPMH) summarized that observational studies also do not find increased risk of major malformations or spontaneous abortions with topical retinoids.9

In animal reproductive studies, oral trifarotene had teratogenic effects in animals at levels greater than 500 times the maximum recommended human dose.8 Although the use of a highly effective contraceptive method was required in the clinical studies for trifarotene, 12 pregnancies were reported during the clinical development program (8 on trifarotene and 4 on vehicle) Of the 8 subjects on trifarotene, there were 4 miscarriages, 1 normal delivery, 1 baby with temporary respiratory distress, and 2 lost to follow up. Of the subjects on vehicle, there was 1 miscarriage, 2 normal deliveries, and 1 elective abortion. None of the miscarriages were considered related to study drug. The DPMH reviewer concluded that the data is too limited to make definitive conclusions on the teratogenicity potential for trifarotene.9 Section 8, Special Populations will summarize the paucity of data for the use of trifarotene in pregnant women.

6 Expected Postmarket Use

Trifarotene 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. These prescribers are likely to be familiar with the management of adverse events associated with topical retinoids. Trifarotene is likely to be used by patients in the outpatient setting.
7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for trifarotene beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The review team recommends approval of trifarotene for the topical treatment of acne vulgaris in patients 9 years of age and older based on the available efficacy and safety information.6

Acne vulgaris is the most common dermatological disorder in the US. It is a chronic disease of sebaceous follicles that is multifactorial in etiology. The severity can vary according to lesion types, numbers, and extent of involvement. Acne vulgaris can result in decreased quality of life, psychosocial morbidity, permanent scarring, and post-inflammatory hyperpigmentation. Several topical and systemic products are approved for treatment of acne vulgaris.

The benefit of trifarotene was demonstrated in two phase 3 clinical studies. Trifarotene cream was statistically superior to a vehicle cream in the co-primary endpoints of success on the IGA, absolute change in facial noninflammatory lesion count, and absolute change in facial inflammatory lesion count at Week 12. Co-secondary endpoints evaluating truncal acne were also statistically superior in the trifarotene group compared to the vehicle group.

The safety profile for trifarotene appears similar to other topical retinoids used for treatment of acne vulgaris. The most common adverse reactions were local cutaneous reactions such as site irritation, pruritis, and sunburn. Similar to other topical retinoids, the proposed label includes the potential for local cutaneous reactions and effects of ultraviolet light and environmental exposure in the Warnings and Precaution section. The proposed label also summarizes the limited data on teratogenicity. Adverse event profiles of other topical retinoids are well characterized and do not require a REMS. The clinical reviewer concluded that trifarotene’s risks can be communicated with labeling and routine pharmacovigilance.6

Therefore, based on the data available, and the prescribing community’s familiarity with the risks associated with trifarotene, which do not pose unique REMS considerations compared with the risks associated with other topical retinoid therapies, DRISK is not recommending a REMS for the management of the risks of trifarotene therapy.

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 trifarotene use are well documented and similar to other topical retinoid agents. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.
Should DDDP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES


10.2 CURRENTLY AVAILABLE TREATMENTS FOR ACNE VULGARIS:

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Products</th>
<th>Safety and Tolerability Issues</th>
<th>Risk Management Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Multiple products</td>
<td>Skin irritation, dryness, allergic reactions, avoid eye contact</td>
<td>Labeling - over the counter (OTC) warnings</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>Multiple products</td>
<td>Avoid contact with eyes or mucous membrane, skin irritation, dryness, photosensitivity, allergic reactions</td>
<td>Labeling - OTC warnings</td>
</tr>
<tr>
<td>Sulfa products</td>
<td>Sulfacetamide, Sulfur</td>
<td>Hypersensitivity, possible cross-sensitivity with sulfonamides, severe skin reactions</td>
<td>Labeling - OTC warnings</td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>Multiple products</td>
<td>Skin irritation (burning, pruritis, stinging), hypopigmentation, exacerbation of asthma (gel), hypersensitivity reactions</td>
<td>Labeling – Warnings and Precautions</td>
</tr>
<tr>
<td>Retinoids</td>
<td>Tretinoin</td>
<td>Skin irritation (dryness, pain, erythema, irritation, and exfoliation),</td>
<td>Labeling – Warnings and Precautions</td>
</tr>
<tr>
<td>Product</td>
<td>Description</td>
<td>Labeling</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td><strong>Adapalene</strong></td>
<td>Ultraviolet light and environmental exposure, skin irritation (erythema, scaling, dryness, and stinging/burning)</td>
<td>Warnings and Precautions</td>
<td></td>
</tr>
<tr>
<td><strong>Tazarotene</strong></td>
<td>Embryofetal toxicity</td>
<td>Warnings and Precautions</td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>Clindamycin</td>
<td>Diarrhea, Clostridium difficile-associated diarrhea (CDAD)</td>
<td>Warnings and Precautions</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Pseudomembranous colitis, skin irritation</td>
<td>Warnings and Precautions</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>Carcinogenesis (animal data), peripheral neuropathy, blood dyscrasias, eye irritation - avoid contact with eyes, skin irritation</td>
<td>Warnings and Precautions</td>
</tr>
<tr>
<td></td>
<td>Dapsone</td>
<td>Methemoglobinemia, hemolysis associated with G6PD deficiency</td>
<td>Warnings and Precautions</td>
</tr>
<tr>
<td><strong>Combination products</strong></td>
<td>Various fixed-dose product combinations of benzoyl peroxide, antibiotics, and/or retinoids (safety dependent on individual drug components as described above)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic products</strong></td>
<td>Tetracycline</td>
<td>Teratogenic effects, CDAD, intracranial hypertension/pseudotumor cerebri, photosensitivity</td>
<td>Warnings and Precautions</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>Teratogenic effects, CDAD, intracranial hypertension/pseudotumor cerebri, esophagitis/ulcerations, hepatotoxicity photosensitivity, development of drug resistant bacteria</td>
<td>Warnings and Precautions</td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td>Teratogenic effects, photosensitivity, CNS effects, intracranial hypertension/pseudotumor cerebri, superinfection, development of drug resistant bacteria</td>
<td>Warnings and Precautions</td>
</tr>
<tr>
<td></td>
<td>Sarecycline</td>
<td>Teratogenic effects, intracranial hypertension, CNS effects (light-headedness, dizziness), CDAD, photosensitivity</td>
<td>Warnings and Precautions</td>
</tr>
<tr>
<td>Retinoids</td>
<td>Isotretinoin</td>
<td>Teratogenicity</td>
<td>REMS (iPLEDGE Program) – includes medication guide, elements to assure safe use</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Labeling - Boxed Warning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Psychiatric disorders, pseudotumor cerebri, serious skin reactions, pancreatitis, elevated triglycerides, hearing impairment, hepatotoxicity, inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Labeling - Warnings and Precautions</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Ethinyl estradiol and norgestimate</td>
<td>Cigarette smoking and serious cardiovascular events</td>
<td>Labeling – Boxed Warning</td>
</tr>
<tr>
<td></td>
<td>Ethinyl estradiol and norgestimate</td>
<td>Thromboembolism, liver disease, 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</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethinyl estradiol and drospirenone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-androgen</td>
<td>Spironolactone</td>
<td>Fluid or electrolyte imbalance (hyperkalemia, hypomagnesemia, hyponatremia, hypochloremic alkalosis), gynecomastia, somnolence and dizziness, hypotension and worsening renal function</td>
<td>Labeling – Warnings and Precautions</td>
</tr>
</tbody>
</table>

*a Not an FDA-approved indication

*b Systemic exposure is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals.

*c Additional warnings and precautions specific to each product exist
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LINDSEY W CRIST  
08/26/2019 10:57:17 AM

DONELLA A FITZGERALD  
08/26/2019 11:00:51 AM

JAMIE C WILKINS PARKER  
08/26/2019 11:25:13 AM