CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214510Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 6, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 214510
Product Name and Strength:	Epsolay (benzoyl peroxide) cream, 5%
Applicant/Sponsor Name:	Sol-Gel Technologies Ltd.
OSE RCM #:	2020-1355-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 30, 2021 for Epsolay. Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Epsolay (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel, M. Label and Labeling Review for Epsolay (NDA 214510). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 10. RCM No.: 2020-1355.

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/s/

MADHURI R PATEL
04/06/2021 11:05:37 AM

SEVAN H KOLEJIAN
04/07/2021 10:59:28 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 16, 2021
To:	Barbara Gould, MBA HCM Chief, Project Management Staff **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	EPSOLAY (benzoyl peroxide)
Dosage Form and Route:	cream, for topical use
Application Type/Number:	NDA 214510
Applicant:	Sol-Gel Technologies, Ltd.

1 INTRODUCTION

On June 26, 2020, Sol-Gel Technologies, Ltd. submitted for the Agency's review an original New Drug Application (NDA) 214510 for EPSOLAY (benozyl peroxide) cream, for topical use. The proposed indication for EPSOLAY (benzoyl peroxide) cream is for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on February 8, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EPSOLAY (benzoyl peroxide) cream.

2 MATERIAL REVIEWED

- Draft EPSOLAY (benozyl peroxide) cream PPI received on June 26, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 8, 2021.
- Draft EPSOLAY (benzoyl peroxide) cream Prescribing Information (PI) received on June 26, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 8, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
02/16/2021 09:45:14 AM

LAURIE J BUONACCORSI
02/16/2021 09:52:57 AM

BARBARA A FULLER
02/16/2021 10:28:13 AM

LASHAWN M GRIFFITHS
02/16/2021 10:31:35 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 11, 2021

To: Melinda McCord, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Gordana Diglisic, MD, Clinical Team Leader, DDD
Barbara Gould, Regulatory Project Manager, DDD
H.F. Van Horn, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for EPSOLAY® (benzoyl peroxide) cream, for topical use

NDA: 214510

In response to DDD's consult request dated February 8, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for EPSOLAY® (benzoyl peroxide) cream, for topical use (Epsolay).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on February 8, 2021 and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 26, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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Container/Carton Comments

1. We recommend that the established name be revised to have prominence commensurate with the proprietary name. The established name should be at least half as large as the letters comprising the proprietary name and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, according to 21 CFR 201.10 (g)(2). The (b) (4) font in the established name does not have a prominence commensurate with the bolded colorful stylized font in the proprietary name. We recommend revision. Please apply this comment to all carton and container labels.

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/s/

LAURIE J BUONACCORSI
02/11/2021 08:53:17 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	February 05, 2021
Reviewer:	Jonn Bailey, PharmD, BCACP, Safety Evaluator Division of Pharmacovigilance I LCDR Melissa Reyes, MD, MPH Division of Pharmacovigilance I
Team Leader:	CDR Vicky Chan, PharmD, BCPS, Team Leader Division of Pharmacovigilance I
Division Director:	Cindy Kortepeter, PharmD, Division Director Division of Pharmacovigilance I
Product Name:	Epsolay (benzoyl peroxide) cream, 5%
Subject:	Severe Hypersensitivity Reactions (Anaphylaxis, Angioedema, Urticaria)
Application Type/Number:	NDA 214510
Applicant:	Sol-Gel Technologies Ltd.
OSE RCM #:	2020-2383

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the literature for an association between benzoyl peroxide (BPO) only products, excluding Proactiv products, and severe hypersensitivity to include anaphylaxis, angioedema, and urticaria. The Division of Dermatology and Dentistry (DDD) requested the Division of Pharmacovigilance (DPV) review FAERS and literature to determine if labeling recommendations related to hypersensitivity in Section 4 CONTRAINDICATIONS and Section 5 WARNINGS AND PRECAUTIONS are warranted for BPO cream, 5%, new drug application (NDA) 214510.

The FAERS case series includes strong temporal associations between BPO product application and the development of anaphylaxis with positive dechallenge and rechallenge as well as angioedema with positive dechallenge. Although no FAERS case reports describing only urticaria were included, due to a lack of available detailed description of hives or documented medical diagnosis of such, multiple cases in the FAERS case series provide examples of hive-like reactions associated with the onset of anaphylaxis and angioedema. These findings align with findings from previously related reviews and provide further supportive evidence across multiple years for the association of BPO product use and the development of anaphylaxis, angioedema, or urticaria.

DPV's review of the medical literature, which is also referenced by the Applicant in their IR response, provides further supporting evidence for an association between BPO products and anaphylaxis, angioedema, and urticaria.

Based on the breadth of information analyzed and presented, DPV does not agree with the Applicant's assessment as provided in their IR response. When considering the severe and potentially life-threatening nature of the adverse events being discussed, the historical evidence available supporting an association between BPO products and severe hypersensitivity reactions, current product labeling for prescription products containing BPO, and the robust amount of information evaluated and included in this review, DPV supports inclusion of appropriate language into labeling to adequately inform the public of the potential for the development of severe hypersensitivity reactions including anaphylaxis, angioedema, and urticaria with BPO product use. Furthermore, BPO as a product active ingredient is associated with hypersensitivity as confirmed by a literature case reporting positive patch-testing; therefore, DPV believes that appropriate labeling to better inform providers of the association between BPO product use and severe hypersensitivity reactions would assist providers in their decision-making process, despite the Applicant's rationale that encapsulation improves patient tolerability of BPO. Reduction of local skin reactions (e.g., erythema, scaling) is not related to reduction in risk for hypersensitivity reactions.

In conclusion, we find an association between BPO products and anaphylaxis, angioedema, and urticaria. Based on this review, DPV recommends modification to the proposed Section 4 CONTRAINDICATIONS, addition to the proposed Section 17 PATIENT COUNSELING INFORMATION, and addition to the proposed PATIENT INFORMATION to reflect the potential risk of anaphylaxis, angioedema, and urticaria with BPO product use.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the literature for an association between benzoyl peroxide (BPO) only products, excluding Proactiv products, and severe hypersensitivity to include anaphylaxis, angioedema, and urticaria. The Division of Dermatology and Dentistry (DDD) requested the Division of Pharmacovigilance (DPV) review FAERS and literature to determine if labeling recommendations related to hypersensitivity in Section 4 CONTRAINDICATIONS and Section 5 WARNINGS AND PRECAUTIONS are warranted for BPO cream, 5%, new drug application (NDA) 214510.

1.1 BACKGROUND

Benzoyl Peroxide

BPO alone and in combination with other agents is indicated for the treatment of mild to moderate acne vulgaris. It exhibits mechanistic activity through the release of free-radical oxygen, which in turn oxidizes bacterial proteins in the sebaceous follicles thereby decreasing irritating-type free fatty acids and the number of anaerobic bacteria.[1]

Drug Hypersensitivity Reactions (DHRs)

DHRs are diverse adverse drug reactions secondary to an enhanced immunologic or inflammatory response to drug exposure. Drug hypersensitivity can be subdivided based on time of appearance of symptoms (immediate vs. delayed), mode of action of the drug on immune/inflammatory cells, or on immunologic mechanism (Type I to IV according to the Gell and Coombs system). Of the four types of immunologic mechanisms, medications cause Types I (immediate IgE and mast cells mediated) and IV (delayed T cell mediated) reactions far more commonly than Types II (delayed antibody mediated cell destruction) and III (IgG: drug immune complex deposition and complement activation). DHRs elicited by small molecule drugs and therapeutic biologics (e.g., monoclonal antibodies) can differ substantially in their modes of action and resulting adverse reactions. Product-specific factors (e.g., molecular structure, molecular weight, species origin, formulation components) can contribute to immunogenicity of therapeutic protein products. Anaphylaxis and angioedema are examples of Type I hypersensitivity reactions that may occur with drug exposure.[2]

DPV Reviews for DHRs with BPO Product Use

In 2013, the Division of Nonprescription Regulation Development (DNRD) requested that DPV provide an analysis of all serious reports associated with Proactiv and all other topical acne products regulated under the over-the-counter (OTC) monograph, including BPO products. The review concluded that in addition to the skin irritant effects associated with BPO, there is also evidence of an allergenic effect of allergic contact dermatitis (ACD). ACD is a Type IV delayed hypersensitivity reaction that involves a cell-mediated allergic response, with some BPO-associated ACD in patch testing demonstrating marked urticarial reactions. Furthermore, DPV's review found that BPO-associated ACD may manifest with edema and angioedema rather than the more commonly associated vesicular reactions. DPV identified cases of anaphylaxis with OTC topical acne monograph products containing BPO or salicylic acid, including Proactiv.

As a result of the 2013 review, DPV recommended:

- Adding the risk of hypersensitivity and anaphylaxis to the labels of OTC topical acne monograph drug products containing BPO and salicylic acid as active ingredients.
- Disseminating a Drug Safety Communication to alert the public of this potential safety risk associated with these products.
- Contacting the manufacturer of Proactiv to discuss their safety reporting procedures.[3]

In response to the above review completed by DPV, DNRD consulted with DDD to provide subject matter expertise to characterize the hypersensitivity-related serious adverse events (SAEs) associated with OTC monograph topical acne products identified by DNRD and DPV while also providing input for communicating this risk to consumers and health care providers in a future Drug Safety Communication. DDD determined that the anaphylactic and non-anaphylactic hypersensitivity reactions described in FAERS for OTC monograph topical acne active ingredients appeared to be consistent with both irritant and ACD as well as Type I hypersensitivity reactions; however, although BPO and salicylic acid were implicated in the FAERS cases reviewed by DPV, DDD "did not agree that BPO or salicylic acid alone, or in combination, were the specific etiologic agent(s), as other excipients might be involved." In conclusion, DDD recommended the addition of a general statement to "contact the health care provider if any of the specific symptoms of irritant or allergic contact dermatitis occur."[4]

In response to the above findings, FDA released a Drug Safety Communication in June 2014 "warning that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. Consumers should stop using their topical acne product and seek emergency medical attention immediately if they experience hypersensitivity reactions such as throat tightness; difficulty breathing; feeling faint; or swelling of the eyes, face, lips, or tongue. Consumers should also stop using the product if they develop hives or itching." Furthermore, FDA stated that they "cannot determine if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both."[5]

In 2016, following the 2013 reformulation of the Proactiv+ system, the Division of Nonprescription Drug Products (DNDP; formerly DNRD) requested DPV to provide an update to the 2013 review discussed above, to identify trends in hypersensitivity/anaphylaxis cases reported with all Proactiv products. DPV identified additional FAERS cases of anaphylaxis and non-anaphylaxis hypersensitivity reactions associated with multiple Proactiv products and concluded that a Proactiv product was the likely causal agent in many of these cases. Furthermore, BPO was identified as the most frequently reported active ingredient in the Proactiv products associated with the adverse events of interest. As a result, DPV recommended that DNDP and OSE discuss potential next steps for future risk mitigation.[6]

In October 2020, DDD requested DPV to "review FAERS and the literature for hypersensitivity and allergic reactions associated with the use of benzyl peroxide (any dosage form) and provide recommendations for the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections of labeling" for benzoyl peroxide cream, 5% (NDA 214510).

Given the extensive 2013 review of all topical acne products regulated under the OTC monograph including Proactiv products, the 2016 review update of Proactiv products, and based on DPV's conversation with DDD in November 2020 regarding this review, DPV focused our review of FAERS reports received since the 2013 review on BPO only products, excluding Proactiv products, and serious hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.

1.2 REGULATORY HISTORY

On June 26, 2020, Sol-Gel Technologies Ltd. submitted NDA 214510 for benzoyl peroxide cream, 5% for the proposed indication of the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. The draft labeling does not include language to inform the prescriber of the potential for hypersensitivity reactions, as these adverse reactions were not reported in the development program. There are currently no approved prescription drug products containing BPO as the only product active ingredient. All of the current BPO only products are available under an OTC monograph and are indicated for the treatment of acne.

1.3 RELEVANT PRODUCT LABELING

1.3.1 Labeling for Prescription Benzoyl Peroxide Products

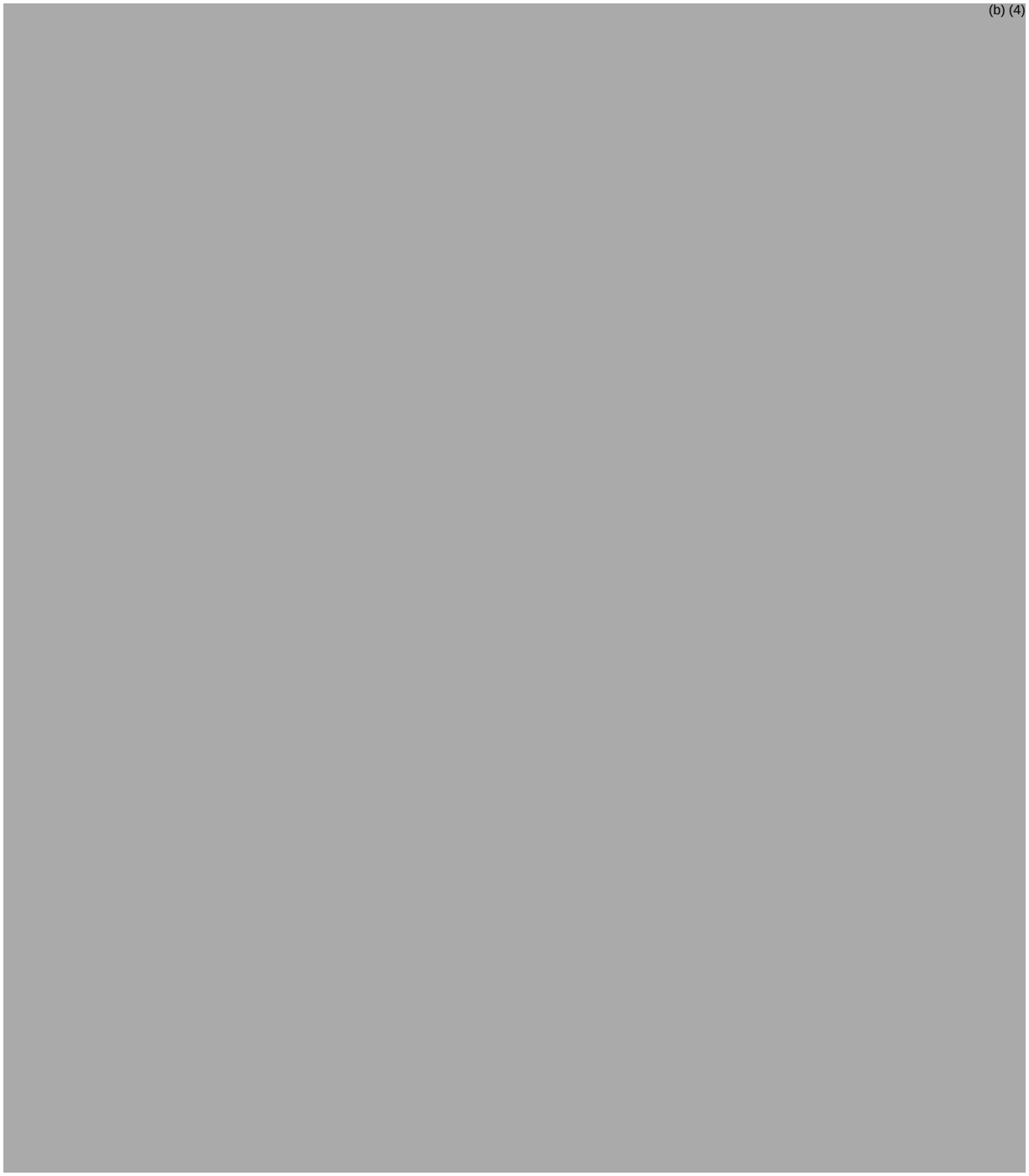
Labeling for prescription BPO products and severe Type 1 hypersensitivity reactions are provided in Table 1 below.

Table 1. Labeling for Prescription Benzoyl Peroxide Products and Type 1 Hypersensitivity Reactions	
Product Active Ingredients (Trade Name)	**Labeling**
adapalene 0.1%/BPO 2.5% (Epiduo)[7]	Eyelid edema, swelling face, throat tightness (PME)
adapalene 0.3%/BPO 2.5% (Epiduo Forte)[8]	Eyelid edema, swelling face, throat tightness (PME)
clindamycin 1.2%/BPO 2.5% (Acanya)[9]	Contraindicated in those individuals who have shown hypersensitivity to any component of the formulation (C) Anaphylaxis, as well as allergic reactions leading to hospitalization (PME) Patients who develop allergic reactions such as severe swelling or shortness of breath (SOB) should discontinue use and contact their physician immediately (PtCouns) Stop using, call your doctor, and get help right away if you experience severe itching; swelling of your face, eyes, lips, tongue or throat; trouble breathing (PtInfo)
clindamycin 1.2%/BPO 3.75% (Onexton)[10]	Contraindicated in those individuals who have shown hypersensitivity to any component of the formulation (C) Anaphylaxis, as well as allergic reactions leading to hospitalization (PME) Patients who develop severe swelling or SOB should discontinue use and contact their physician immediately (PtCouns) Stop using, call your doctor, and get help right away if you experience severe itching; swelling of your face, eyes, lips, tongue or throat; trouble breathing (PtInfo)
clindamycin 1.2%/BPO 5% (Duac*)[11]	Contraindicated in patients who have demonstrated hypersensitivity to any components of the formulation (C) Anaphylaxis, as well as allergic reactions leading to hospitalization (PME) Urticaria has been reported (PME) Patients who develop severe swelling or SOB should discontinue use and contact their physician immediately (PtCouns) Stop using, call your doctor, and get help right away if you experience severe itching; swelling of your face, eyes, lips, tongue or throat; trouble breathing (PtInfo)
clindamycin 1%/BPO 5% (BenzaClin)[12]	Contraindicated in those individuals who have shown hypersensitivity to any of its components (C) Patients who develop allergic symptoms such as severe swelling or SOB should discontinue use and contact their physician immediately (Prec, PtInfo) Anaphylaxis, as well as allergic reactions leading to hospitalization have been reported (AR)

erythromycin 3%/BPO 5% (Benzamycin)[13]	Contraindicated in those individuals who have shown hypersensitivity to any of its components (C) Urticarial reaction (AR)
AR = Adverse Reactions, BPO = Benzoyl peroxide, C = Contraindications, PME = Postmarketing Experience, Prec = Precautions, PtCouns = Patient Counseling Information, PtInfo = Patient Information *Duac was included, but as of 11/27/2019, the brand formulation has been discontinued.	

1.3.2 Proposed Labeling for Benzoyl Peroxide Cream, 5% (NDA 214510)

(b) (4)



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2 METHODS AND MATERIALS

2.1 CASE DEFINITIONS

2.1.1 Anaphylaxis

Anaphylaxis[14] is diagnosed by a healthcare professional
OR
Acute onset within 24 hours to include involvement of the skin and/or mucosal tissue
AND at least one of the following:

- Respiratory compromise
- Reduced blood pressure (may present as fainting, dizziness, visual changes, collapse, or loss of consciousness)
- Associated symptoms of end-organ dysfunction

2.1.2 Angioedema

Angioedema[15,16,17] is diagnosed by a healthcare professional
OR
At least one of the following:

- Acute onset of edema of the tongue, pharynx, larynx, or face with lax tissue (e.g., lips)
- Acute onset of non-specified throat swelling associated with symptoms of difficulty swallowing or shortness of breath
- Acute onset of bowel wall edema supported by imaging

Exclusion Criteria:

- Presence of a dermatologic sequela after edema resolution, such as blisters or skin peeling
- Eye swelling without surrounding tissue swelling described

2.1.3 Urticaria

Urticaria[18] is diagnosed by a healthcare professional
OR

- "Wheal" OR skin lesion consistent with a vascular reaction (red to pink to pale skin color) that appear over minutes to hours

AND

- Does not last longer than 24 hours
- Does not leave residual skin changes (e.g., no pigmentation, petechiae) except those secondary to excoriation

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	November 9, 2020
Time period of search	January 29, 2013† - November 8, 2020
Search type	FDA Business Intelligence Solution (FBIS) Product-Manufacturer Reporting Summary
Product terms	Product Active Ingredient Benzoyl peroxide
MedDRA search terms (Version 23.1)	*Anaphylactic reaction (SMQ) Narrow search; Anaphylactic/anaphylactoid shock conditions (SMQ) Narrow search; Angioedema (SMQ) Narrow search;* PTs: *Application site urticaria, Urticaria, Urticaria contact, Urticarial dermatitis, Urticaria papular, Administration site urticaria*
* See Appendix A for a description of the FAERS database. † Initial FDA received date begins from the data lock date of the 2013 DPV review of topical OTC acne products. MedDRA=Medical dictionary for regulatory activities, PTs=Preferred terms, SMQ=Standardised MedDRA query	

2.3 LITERATURE SEARCH

DPV searched the medical literature with the strategy described in Table 3.

Table 3. Literature Search Strategy	
Dates of search	November 9, 2020; November 18, 2020; December 14, 2020
Database	Embase and PubMed@FDA
Search terms	Benzoyl Peroxide AND Anaphylaxis OR Angioedema OR Urticaria OR Hypersensitivity OR Hospitalization OR Epinephrine
Years included in search	All
Advanced search	Human

2.4 INFORMATION REQUEST

DDD submitted an information request (IR) to the Applicant dated November 25, 2020 requesting that the Applicant provide a review of available literature associated with the potential for serious hypersensitivity reactions including angioedema, urticaria, and anaphylaxis following treatment with benzoyl peroxide.[19]

3 RESULTS

3.1 FAERS Case Selection

The FAERS search retrieved 421 reports. After applying the case definitions in Section 2.1 and accounting for duplicate reports, 12 cases were included in the case series for anaphylaxis or angioedema reported with BPO use (see Figure 1).

Figure 1. FAERS Case Selection

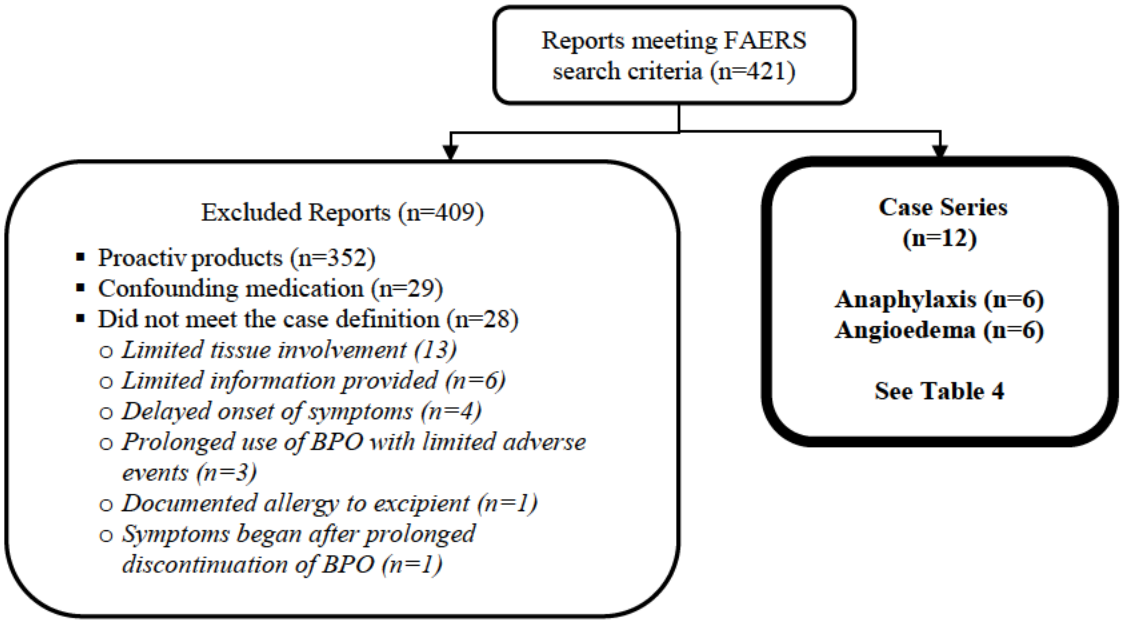


Table 4 summarizes the 12 FAERS cases of anaphylaxis or angioedema reported with BPO for this case series.

Appendix B contains a line listing of the 12 cases in this case series.

Table 4. Descriptive Characteristics of Anaphylaxis or Angioedema With Benzoyl Peroxide in FAERS, Received by FDA from (January 29, 2013 to November 8, 2020) **N=12**	
Age, years	
Mean	26
Median	22
Range	(11-54)
Sex	
Female	10
Male	2
Report type	
Direct	6
Expedited	6
Initial FDA received year	
2013-2016	8
2017-2020	4
Reported Reason for Use	
Acne	7
Unspecified	5
Serious outcome(s)*	
Life threatening	2
Hospitalization	1
Other serious	10
Intervention†	
Emergency Room	5
Urgent Care	1
Self-treatment	3
Unspecified	4
Confirmatory Test	
Performed	1
Unspecified	11
Anaphylaxis	
Positive Dechallenge	2
Positive Dechallenge and Positive Rechallenge	2
Angioedema Positive Dechallenge	1

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.

† One case reported two separate occurrences of hypersensitivity reactions and two different interventions.

Below, we summarized three cases that reported a positive dechallenge of which two cases also reported a positive rechallenge. A positive dechallenge is defined as, "partial or complete disappearance of an adverse event (AE) after withdrawal of the suspect product", and a positive rechallenge is defined as, "reoccurrence of similar signs and symptoms upon reintroduction of the suspect product."[20]

Anaphylaxis

FAERS Case #9165308, Version 1, Expedited (15-Day), USA, Initial FDA Received date March 14, 2013, Hospitalization, UMC Report ID #A1013063A

A 54-year-old female reported that she used a single application of Panoxyl Soap with BPO and immediately experienced facial edema and difficulty breathing. She immediately discontinued use of the soap and was treated at the emergency room with an unspecified shot for an allergic reaction to BPO after which symptoms resolved. The patient stated that the physician performed a "test" and notified her that she was allergic to BPO. Many years later, while cleaning up some of her husband's unspecified BPO wash from a counter with a wipe, she experienced anaphylactic shock for which treatment was not reported. The patient's symptoms have since resolved.

Reviewer's Comment: This case represents a strong temporal relationship between use and accidental exposure to BPO and anaphylaxis requiring medical intervention. The case reports a positive dechallenge with treatment then a positive rechallenge years later with accidental exposure to an unspecified amount of BPO.

FAERS Case #10174269, Version 5, Expedited (15-Day), USA, Initial FDA Received date May 15, 2014, Other Serious, UMC Report ID #US-RB-065691-14

A 19-year-old female with no known allergies and no reported concomitant medications applied Clearasil Daily Clear Vanishing Cream with BPO and an unknown soap to her face for the first time and woke up the next day requiring an emergency room visit for difficulty breathing and periorbital edema resulting in her eyes being "swollen shut." The patient was treated with oral and injectable steroids and was discharged. She immediately discontinued use of the BPO product but resumed use of the soap with no further issues. Approximately 5 months later, the patient applied the same BPO cream to her face for the second time and woke up the next day with periorbital edema and facial hives. The patient immediately discontinued use of the benzoyl peroxide product. Due to a lack of insurance, the patient treated herself with diphenhydramine every 4 hours until the adverse events resolved.

Reviewer's Comment: Given the temporal association between BPO use and the development of symptoms consistent with anaphylaxis, the patient's continued use of the unspecified soap with no associated adverse events after resolution of the initial hypersensitivity reaction, and the development of a second severe hypersensitivity reaction including hives and periorbital edema as a result of reapplication of the BPO product months later, this case provides compelling evidence for an association between BPO product use and anaphylaxis.

FAERS Case #10422679, Version 1, Expedited (15-Day), USA, Initial FDA Received date September 02, 2014, Other Serious, UMC Report ID #US-JNJCP-30000237713

A 16-year-old female with no known medical history and no concomitant medications applied Neutrogena Clear Pore Cleanser/Mask with BPO to her face for the first time. A few hours later the patient experienced facial and periorbital edema, "hot" skin erythema with a blistery rash, and difficulty breathing. She immediately discontinued use of the cleanser/mask. The patient received medical care with steroids and other unspecified medications at the emergency room where she later recovered.

Reviewer's Comment: This case represents an example of a severe anaphylactic reaction to BPO that required emergency medical treatment in the absence of other confounding medications. Given the severity of the reaction including edema, hives, and respiratory compromise; strong temporal association; and lack of confounding medications, this case provides compelling evidence for an association between BPO product use and anaphylaxis.

Angioedema

FAERS Case #10040010, Version 2, Expedited (15-Day), USA, Initial FDA Received date March 26, 2014, Other Serious, UMC Report ID #US-JNJCP-30000211498

A 22-year-old female with unknown medical history applied Neutrogena On-the-Spot Acne Treatment with BPO to her skin on five to seven small spots. Fifteen minutes after the first application of the BPO product, she experienced a severe hypersensitivity reaction including pharyngeal and tongue edema requiring treatment with unspecified allergy medications. She discontinued use of the product with no further information provided.

Reviewer's Comment: Given the temporal association between initial application of the BPO product and rapid symptom development characteristic of angioedema that required treatment, the case provides compelling evidence for an association between BPO product use and angioedema.

FAERS Case #11154662, Version 1, Expedited (15-Day), USA, Initial FDA Received date May 29, 2015, Other Serious, UMC Report ID #2015-021352

An 11-year-old female with no reported medical history applied Step 1 of Up&Up 3-Step Acne Care System and woke up with periorbital, lip, and nose edema including facial welts. She required medical treatment including a steroid shot at the emergency department. The patient's symptoms were still resolving at the time of reporting, and it was not reported if the product was discontinued.

Reviewer's Comment: Given the severity of the adverse reaction, temporal association, required medical intervention, and reported use of only the BPO Step 1 component of the 3-step product, it is likely that the symptoms consistent with angioedema can be attributed to the patient's use of the BPO product. Additionally, the Up&Up 3-Step Acne Care System, which includes package labeling stating "Compare to Proactiv 3-Piece System," includes the same active ingredients, BPO 2.5% and (b) (4) *as Proactiv.*[6]

3.2 LITERATURE SEARCH

Two case reports of BPO use and angioedema and one case report of BPO use and urticaria were identified with the literature search described above. The three case reports are provided in detail below.

Angioedema

The first case report involves a 26-year-old female who initiated treatment with topical BPO 10% gel for acne and subsequently required medical care for symptoms consistent with severe angioedema to include facial edema and hives. The BPO product was withdrawn, and the patient recovered. The patient was patch tested with BPO 1% in white petrolatum and the BPO 10% gel product used by the patient resulting in strong positivity to both. The medical providers

concluded that multiple factors including the severe angioedematous reaction, strong patch-test results, temporal relationship, complete resolution of symptoms after drug withdrawal, and absence of other likely causes suggested an association between the application of the BPO containing product and the development of angioedema.[21]

Reviewer's comment: *The patient was patch tested to two BPO-containing products at different BPO concentrations. Though no excipients were included in the patch testing, the positive reactivity to two products may suggest that BPO is the culprit allergen.*

The second case report details a 52-year-old male with no known allergies; no concomitant medications except for a multivitamin, which he has taken for years; and history of sinusitis, herpetic cold sores, warts, and acne vulgaris who applied OTC BPO 2.5% cream for the first time in the evening. Of note, his skin was not irritated at baseline. The next morning, he noticed tenderness at the application site, but no rash. Within hours of a second application of BPO to a single spot on his cheek, the patient developed periorbital edema resulting in his eyes being swollen shut and erythema extending down his neck with absence of eczematous changes or pruritis. He discontinued use of the BPO product, self-administered diphenhydramine, and presented for medical care 24 hours later resulting in resolution of symptoms. The physician reported that the acute and severe nature of the observed adverse reactions suggested a Type 1 reaction such as angioedema; however, the physician also noted that the absence of shortness of breath and oral swelling could provide plausible counter evidence for this conclusion.[22]

Urticaria

A 13-year-old female was initiated with treatment for severe papulopustular cystic acne with a regimen that included a topical skin cleanser in the morning, application of 5% BPO gel in the evening, and oral tetracycline 250 mg once daily. The patient experienced hive-like lesions 20-30 minutes after initial application of the BPO that progressively became worse while using the product for 4 months. The BPO and tetracycline were discontinued, and the lesions resolved. Tetracycline was resumed and retinoic acid cream initiated with no further symptoms of urticaria. The patient was patch tested with a 6% Brij-30 in Specially Denatured Alcohol (SDA) 40 alcohol nonionic surfactant, 5% BPO in water, and blank gel as supplied by the BPO gel manufacturer. The patient developed a moderate wheal and flare reaction with pruritus to BPO and developed no reaction to the other agents that were tested. The physician concluded that because the reaction to BPO was immediate and not eczematous, the adverse event was likely urticarial.[23]

Reviewer's comment: *By conducting comprehensive patch testing, this case identified BPO and excluded the excipients in the OTC BPO product as the allergen triggering an urticarial reaction. Urticaria is typically seen in type I hypersensitivity reactions.[24] Though patch testing typically identifies allergens triggering type IV hypersensitivity[25], under certain circumstances, T cells (type IV hypersensitivity) can activate mast cells to release histamine resulting in urticaria.[26]*

3.3 INFORMATION REQUEST

The Applicant conducted a PubMed search for "benzoyl peroxide, rosacea" and "benzoyl peroxide" plus "hypersensitivity", "angioedema", or "urticaria" or " anaphylaxis". In addition,

the Applicant conducted a Cochrane database review of "interventions for rosacea". Four publications describing 3 clinical studies using topical BPO alone or in combination for the treatment of rosacea were reported. No drug related adverse events were reported in the 3 clinical studies, and the Applicant concluded that "no AEs reported in the studies, however, suggested an otherwise undetected risk for use of encapsulated benzoyl peroxide (E-BPO) cream in the treatment of rosacea." The Applicant noted that "between 1989 and 2017, there were only 4 case reports of AEs for benzoyl peroxide in the treatment of rosacea," with multiple reports related to adverse events for BPO in the treatment of acne. Several case reports including those for BPO in the treatment of rosacea and acne described the development of allergic contact dermatitis. Of note, the applicant likewise referenced the two case reports provided in Section 3.2 above describing the development of angioedema with the use of BPO for the treatment of acne. In the Applicant's review and assessment of the totality of published literature gathered from the Applicant's search, the Applicant stated that "none of the published information indicates any relationship between use of benzoyl peroxide and systemic AEs." Furthermore, the Applicant stated, "the AEs reported in the literature are consistent with those observed in the clinical studies conducted with E-BPO Cream and provide further evidence that the product is generally safe and well tolerated when used in the treatment of rosacea."[27]

4 DISCUSSION

The information provided above, along with the DPV review conducted in 2012 and 2016, support an association between topical BPO products and anaphylaxis, angioedema, and urticaria.

The FAERS case series includes strong temporal associations between BPO product application and the development of anaphylaxis with positive dechallenge and rechallenge, as well as angioedema with positive dechallenge. Four of the cases that reported positive dechallenge or both positive dechallenge and rechallenge describe resolution of the adverse events after administration of urgent or emergency therapeutic interventions with steroids, diphenhydramine, and/or unspecified medications. Despite the fact that the outcomes are confounded by the treatment received, per the Best Practices in Case Definition Development and Causal Association Assessment for OSE/DPV Staff, the cases are still considered examples of a positive dechallenge and/or rechallenge resulting from BPO product administration.[20] Although no FAERS case reports describing only urticaria were included due to a lack of available detailed description of hives or documented medical diagnosis of such, multiple cases in the FAERS case series provide examples of hive-like reactions associated with the onset of anaphylaxis and angioedema. These findings align with findings from previously related reviews as presented in Section 1.1 above and provide further supportive evidence across multiple years for the association of BPO product use and the development of anaphylaxis, angioedema, or urticaria.

DPV's review of the medical literature, which is also referenced by the Applicant in their IR response, provides further supporting evidence for an association between BPO products and anaphylaxis, angioedema, and urticaria. Of note, this includes a detailed and compelling case report that identified BPO as the allergen causing an urticarial reaction and excluded non-BPO excipients.

We acknowledge the limitations in the review of spontaneous reports and medical literature cases in determining if BPO alone versus the BPO product, which includes excipients, is the trigger for anaphylaxis, angioedema, or urticaria. Skin prick testing is typically used to identify allergens that trigger Type I hypersensitivity reactions (e.g., anaphylaxis), while patch testing is typically used to identify allergens that trigger Type IV hypersensitivity reactions;[25] our FAERS case series did not include this type of diagnostic work-up, while two of the three literature cases included patch testing information. In addition, BPO in OTC products is covered under the Final Monograph *Topical Anti-Microbial Drug Products for Over-the-Counter Human Use*[28] as an active ingredient in products used to treat acne. Approximately half of the FAERS cases report acne as the reason for use, while the remainder report use of an acne care product without specifying a reason for use. The conditions of acne and rosacea are similar in that both may have papulopustular lesions and skin barrier dysfunction though the pathophysiology of the conditions differs.[29,30] Patients with rosacea report symptoms of burning and stinging, as well as irritation and aggravated symptoms with skin care products;[30] the literature supports that patients with rosacea have severely impaired skin barrier function.[31] Though none of the FAERS or medical literature cases report use for rosacea, it would be reasonable to extrapolate the findings of BPO products in acne to patients using BPO products for rosacea. Based on the Applicant's proposed labeling language, it appears that the safety profile between EPSOLAY and the vehicle are similar.

Based on the breadth of information analyzed and presented above, DPV does not agree with the Applicant's assessment as provided in their IR response. When considering the severe and potentially life-threatening nature of the adverse events being discussed, the historical evidence available supporting an association between BPO products and severe hypersensitivity reactions, current product labeling for prescription products containing BPO, and the robust amount of information evaluated and included in this review, DPV supports inclusion of appropriate language into labeling to adequately inform the public of the potential for the development of severe hypersensitivity reactions including anaphylaxis, angioedema, and urticaria with BPO product use. Furthermore, BPO as a product active ingredient is associated with hypersensitivity as confirmed by a literature case reporting positive patch test results; therefore, DPV believes that appropriate labeling to better inform providers of the association between BPO product use and severe hypersensitivity reactions would assist providers in their decision-making process, despite the Applicant's rationale that encapsulation improves patient tolerability of BPO. Reduction of local skin reactions (e.g., erythema, scaling) is not related to reduction in risk for hypersensitivity reactions.

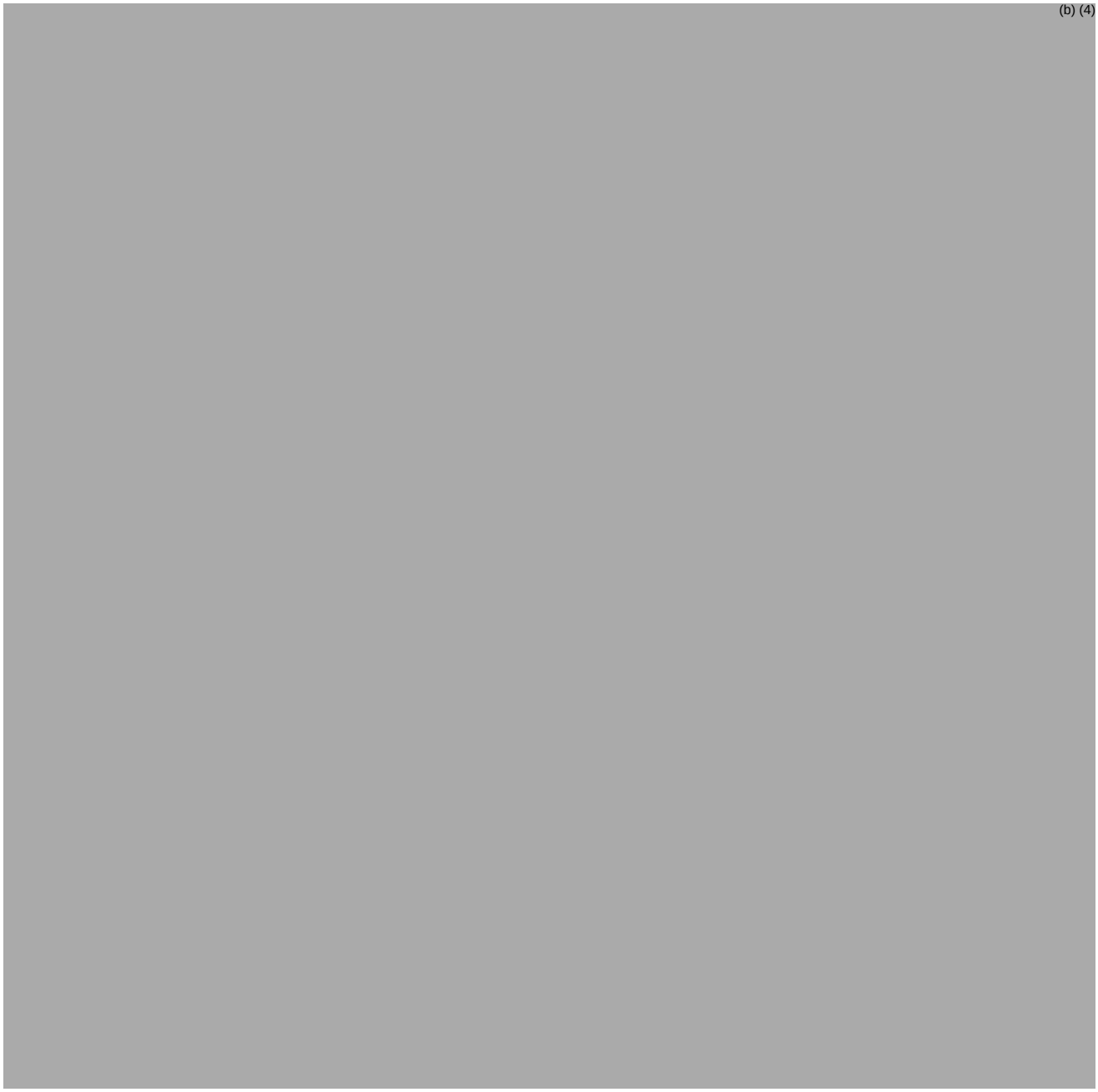
Despite the limitations described above, given the large patient population associated with BPO product use, drug utilization potential for this product, several patients seeking emergency medical care, and attempts by multiple patients in the case series to self-treat symptoms that were reported as being severe and potentially life-threatening, we recommend incorporation of appropriate language to mitigate serious outcomes associated with BPO product use and the development of anaphylaxis, angioedema, and urticaria.

5 CONCLUSION

In conclusion, we find an association between BPO products and anaphylaxis, angioedema, and urticaria.

6 RECOMMENDATIONS

Based on this review, DPV recommends modification to the proposed Section 4 CONTRAINDICATIONS, addition to the proposed section 17 PATIENT COUNSELING INFORMATION, and addition to the proposed PATIENT INFORMATION to reflect the potential risk of anaphylaxis, angioedema, and urticaria with BPO product use. Proposed additions are underlined, and deletions are indicated by a ~~strikethrough~~.



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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF BENZOYL PEROXIDE AND ANAPHYLAXIS, ANGIOEDEMA CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	03/14/2013	9165308	1	A1013063A	Expedited (15-Day)	54	FEMALE	USA	HO
2	09/16/2013	9539299	1	97573	Expedited (15-Day)	13	MALE	USA	OT
3	03/26/2014	10040010	2	US-JNJCP-30000211498	Expedited (15-Day)	22	FEMALE	USA	OT
4	05/15/2014	10174269	5	US-RB-065691-14	Expedited (15-Day)	19	FEMALE	USA	OT
5	09/02/2014	10422679	1	US-JNJCP-30000237713	Expedited (15-Day)	16	FEMALE	USA	OT
6	02/06/2015	10777360	1		Direct	34	FEMALE	USA	OT
7	05/29/2015	11154662	1	2015-021352	Expedited (15-Day)	11	FEMALE	USA	OT
8	02/23/2016	12109363	1		Direct	36	FEMALE	USA	OT
9	12/23/2017	14324941	1		Direct	20	FEMALE	USA	OT
10	11/15/2019	17066969	1		Direct	22	MALE	CHL	LT
11	11/30/2019	17099165	1		Direct	31	FEMALE	USA	OT
12	05/06/2020	17755639	1	A1013063A	Direct	39	FEMALE	USA	LT,OT

*As per 21 CFR 314.80, the regulatory definition of serious is 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, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: CHL=Chile, HO=hospitalization, LT= life-threatening, OT=other medically significant, USA=United States of America

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: 1/25/21 **Date Consulted:** 7/22/20

From: Jane Liedtka M.D., Medical Officer (MO), Maternal Health
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Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Melinda McCord, M.D., MO
Division of Dermatology and Dental (DDD)

Drug: Epsolay [benzoyl peroxide (BP)] cream, 5%

NDA: 214510

Indication: for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

Applicant: Sol-Gel Technologies Ltd.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) language (505(b)(2) NDA)

Materials Reviewed:

- Applicant's background package for BLA 214510 submitted on 6/26/20.

Consult Question: Please review the submission and provide recommendations for Section 8 of labeling and evaluate the pregnancy data included in the submission.

INTRODUCTION AND BACKGROUND

- On 6/26/2020, the applicant (Sol-Gel Technologies Ltd.) submitted a 505 (b)(2) new drug application for Epsolay (encapsulated benzoyl peroxide cream), NDA 214510, with a proposed indication for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. The applicant has chosen the 505 (b)(2) pathway due to a reliance on published literature for components of the package for benzoyl peroxide.
- Sol-Gel uses a patented process to encapsulate benzoyl peroxide in silicon dioxide (silica) microcapsules. According to the applicant, the microcapsules create a shell that is a matrix of layers which is designed to allow the benzoyl peroxide to slowly diffuse, resulting in a continuous flow of benzoyl peroxide. The microcapsules serve as a barrier between the benzoyl peroxide crystals and the skin, allowing slow migration of dissolved benzoyl peroxide from the microcapsules and delivery of effective doses to the skin while the barrier improves tolerability of benzoyl peroxide.
- Benzoyl peroxide has been marketed for over 40 years, and it is Generally Recognized as Safe (GRAS) as an active ingredient in over-the-counter (OTC) topical products for the treatment of acne at concentrations of 2.5 to 10%. There are currently more than 80 benzoyl peroxide products available in the US. Benzoyl peroxide is also the active ingredient in several fixed-dose combination drugs approved as NDAs for the treatment of acne at concentrations of 2.5 and 5% [e.g. Acanya (clindamycin phosphate and benzoyl peroxide) gel 1.2%/2.5% N50819, Epiduo (Adapalene and BP) gel 0.1%/2.5% N22320].
- Approximately 5% of topically applied benzoyl peroxide is absorbed through the human skin in vitro[1]. Other in vitro studies have demonstrated that permeation is both concentration and time-dependent[2], but benzoyl peroxide does not penetrate below the upper layers of the human skin. Benzoyl peroxide is known to metabolize in the skin to benzoic acid, (an endogenous substance, also found in foods and used as a pH adjuster and a preservative in cosmetics) that is rapidly eliminated in urine with very limited systemic exposure. For this reason, PK assessment for benzoyl peroxide was not conducted by the applicant nor requested by the Agency.
- Acceptable daily intakes for benzoic acid were established by the World Health Organization at 5mg/kg[3]. Benzoic acid is generally recognized as safe (GRAS) in foods according to the U.S. Food and Drug Administration. Benzoic acid was associated with an increased number of resorptions and malformations in hamsters, but there were no reproductive or developmental toxicity findings for benzoic acid in two rat studies. Genotoxicity tests for these ingredients were mostly negative, but there were some assays that were positive. Carcinogenicity studies, however, were negative.

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- On 7/22/20, DDD consulted DPMH to provide input regarding the appropriate format and content of Section 8 of Epsolay (BP) cream 5%, NDA 214510 labeling for compliance with the PLLR format.

Current State of the Labeling for Benzoyl Peroxide (BP)[4]

- The most recently revised labeling containing information on benzoyl peroxide is for Acanya (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/2.5% which was approved in Feb of 2020. It is in Physician Labeling Rule (PLR) and PLLR format.
- There is no boxed warning.
- Contraindications include
    - Hypersensitivity (e.g., anaphylaxis) to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin
    - Patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis (due to the clindamycin component)
- Warnings and Precautions include
    - Colitis (due to the clindamycin component)
    - Ultraviolet Light and Environmental Exposure (due to the BP component)
- Under subsection 8.1, Pregnancy, the labeling states

  Risk Summary

  There are no available data on ACANYA Gel use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes...

  There was no specific information about benzoyl peroxide included in either the Risk Summary or Data sections of 8.1.
- Under subsection 8.2, Lactation, the labeling states

  Risk Summary

  There are no data on the presence of clindamycin or benzoyl peroxide in human milk, the effects on the breastfed child, or the effects on milk production following topical administration. However, clindamycin has been reported to be present in breast milk in small amounts following oral and parenteral administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACANYA Gel and any potential adverse effects on the breastfed child from ACANYA Gel or from the underlying maternal condition.

  Clinical Considerations

  If used during lactation and ACANYA Gel is applied to the chest, care should be taken to avoid accidental ingestion by the infant.
- Under subsection 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, the labeling states

[4]Acanya (clindamycin phosphate and benzoyl peroxide) gel, 1.2%/2.5% label approved in Feb 2020.

- Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.
- Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times the MRHD for clindamycin and 3.6, 10.8, and 60 times the MRHD for benzoyl peroxide, respectively, based on BSA comparisons) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900, and 3000 mg/kg/day (1.2, 3.6, and 12 times the MRHD for clindamycin and 2.4, 7.2, and 24 times the MRHD for benzoyl peroxide, respectively, based on BSA comparisons) for up to 97 weeks did not cause any increase in tumors.
- Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in S. typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

REVIEW

Pregnancy

Nonclinical Experience

Animal reproductive studies have not been conducted with EPSOLAY Cream. See above under "Current State of the Labeling" for information from nonclinical studies that have been incorporated into labeling for other products containing BP that have recently been approved. The applicant is relying on published literature for the nonclinical component of the submission except for two studies

- Good Laboratory Practice (GLP) compliant 13-week repeat-dose dermal toxicity study in minipigs (E-BPO Cream, 5 and 10%) and
- Phototoxicity study (E-BPO Cream, 5%)

Applicant's Review of Literature

The applicant conducted a literature search in PubMed regarding the use of benzoyl peroxide during pregnancy. There were no publications describing clinical studies in which benzoyl peroxide was used by pregnant women. Several review papers, however, assessed the potential risk of topical benzoyl peroxide during pregnancy. See Table 1 below for details.

Table 1: Publications Regarding Use of BP during Pregnancy

Citation	Type of Publication	Recommendation/ Comment Regarding BP
Chien[5] AL et al. 2016	Review Article (RA) on treatment of acne in pregnancy	Topical azelaic acid or BP can be recommended as baseline therapy during pregnancy.
Meredith[6] and Ormerod 2013	RA on treatment of acne in pregnancy	As only about 5 % of the BP applied topically was found to be absorbed in one study, the potential risk during pregnancy is low.
Akhavan[7] And Bershad 2003	RA on treatment of acne in pregnancy (one section on pregnancy)	The safety of topically applied BP during lactation was unknown and benzoyl peroxide should be used during pregnancy only if clearly needed.
Ives[8] 1992	RA on benzoyl peroxide	Topically applied BP should be used during pregnancy only if the possible benefit justifies the potential risk.
Rothman[9] 1988	RA on treatment of acne in pregnancy	Approximately 5% of topically applied BP is absorbed through the skin[1,10]. The drug is completely metabolized to benzoic acid within the skin. It enters the blood vessels in the dermis as benzoate, where it is transported to the kidneys and excreted unchanged in the urine. Because this small amount of benzoate is easily handled by the kidneys, systemic effects on a pregnant patient or her fetus would not be expected. No studies on the chronic use of the drug in pregnant patients have been published. On the basis of available data, however, the drug is safe to use in pregnancy.
Kong[11] 2013	RA on treatment of acne in pregnancy	BP is safe for use during lactation and pregnancy.
Pugashetti[12] 2013	RA on treatment of acne in pregnancy	With skin absorption of approximately 5%, BP use on limited areas for acne treatment in pregnant patients is now generally recognized as safe. BP is metabolized to benzoic acid within the skin and subsequently excreted in urine unchanged.

Source: Reviewer's Table

Review of Pharmacovigilance Database (PVDB)

A review was performed of the sponsor's PVDB, two subjects had positive pregnancy tests during the development program for Epsolay. One delivered a healthy baby with no

[5] Chien AL et al. Clinical Review: Treatment of Acne in Pregnancy. J Am Board Fam Med 2016;29:254–262.
[6] Meredith FM and Ormerod AD. The Management of Acne Vulgaris in Pregnancy. Am J Clin Dermatol 2013; 14:351–358.
[7] Akhavan A and Bershad S. Topical Acne Drugs Review of Clinical Properties, Systemic Exposure, and Safety. Am J Clin Dermatol. 2003; 4 (7): 473-492.
[8] Ives TJ. Benzoyl peroxide. Am Pharm. 1992;NS32(8):33-8.
[9] Rothman KF and Pochi PE. Use of oral and topical agents for acne in pregnancy. J Am Acad Dermatol. 1988;19(3):431-42.
[10] Yeong D, Nacht S, Bucks D, Maibach HI. Benzoyl peroxide: percutaneous penetration and metabolic disposition. II. Effect of concentration. JAAD. 1983;9:920-4.
[11] Kong YL and Tey HL. Treatment of acne vulgaris during pregnancy and lactation. Drugs.2013;73(8):779-87.
[12] Pugashetti R and Shinkai K. Treatment of acne vulgaris in pregnant patients. Dermatologic Therapy. 2013; 26: 302–311.

complications during the pregnancy, the other pregnancy is still pending delivery with no issues to this point.

DPMH's Review of the Literature
DPMH conducted a search of published literature in PubMed using the search terms "benzoyl peroxide and pregnancy" "benzoyl peroxide and pregnant women," "benzoyl peroxide and pregnancy and birth defects," "benzoyl peroxide and pregnancy and congenital malformations," "benzoyl peroxide and pregnancy and stillbirth," "benzoyl peroxide and spontaneous abortion" and "benzoyl peroxide and pregnancy and miscarriage" covering up through 12/28/20. No relevant publications were identified beyond those in the applicant's review.

Benzoyl peroxide is not referenced in Briggs[13] *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk.* Micromedex[14] notes that it is "unknown if it crosses the placenta", and that "Infant risk cannot be ruled out". Reprotox[14]notes that "BP does not increase congenital malformations in rats. We did not locate human data."

TERIS[5] notes "Magnitude of Teratogenic Risk to Child Born After Exposure During Gestation is undetermined. The Quality and Quantity of Data on Which Risk Estimate is Based is none. A small risk cannot be excluded, but a high risk of congenital anomalies in the children of women treated with BP during pregnancy is unlikely.

Lactation

Nonclinical Experience
There are no animal studies of BP use during lactation.

Applicant's Review of Literature
The applicant conducted a literature search regarding the use of topical BP during lactation and cited the two publications (Kong[11] 2013, Pugashetti[12] 2013) included in Table 1 above.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed through 12/28/20 using the search terms " benzoyl peroxide and lactation" and "benzoyl peroxide and breastfeeding" and found no additional publications.

BP is not referenced in Briggs[3] *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. BP is referenced in Hale's *Medications and Mother's Milk[15]*, the author states

> …there are no data on its transfer into human milk. BP if ingested would be largely destroyed almost instantly by tissue and stomach esterases. It is

[13] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[14] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 2/19/20.
[15] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.

> unlikely that any would be absorbed systemically. Because only about 5% of topically applied BP is absorbed (and rapidly converted to benzoic acid in the skin), it is thought to be of low risk to a nursing infant.

In LactMed[16], the Summary of Use during Lactation" states

> Topical BP has not been studied during breastfeeding. Because only about 5% is absorbed following topical application, it is considered a low risk to the nursing infant[17,18]. Ensure that the infant's skin does not come into direct contact with the areas of skin that have been treated. Only water-miscible cream or gel products should be applied to the breast because ointments may expose the infant to high levels of mineral paraffins via licking[19].

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Applicant's Review of Literature
The Applicant did not identify any publications regarding the use of BP and its effects on fertility.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed through 12/28/20 regarding the use of BP and its effects on fertility and found no relevant publications.

DISCUSSION AND CONCLUSIONS

Pregnancy
Due to the low systemic exposure noted in the literature discussing the metabolism of benzoyl peroxide in the skin, maternal use of benzoyl peroxide is not expected to result in fetal exposure to the drug. See DPMH proposed labeling below for further details.

In addition, since benzoyl peroxide is minimally absorbed, a pregnancy registry study is not required.

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[16] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed August 30, 2019.
[17]Leachman SA and Reed BR. The use of dermatologic drugs in pregnancy and lactation. Dermatol Clin. 2006;24:167-97.
[18] Zip C. Common sense dermatological drug suggestions for women who are breast-feeding. Skin Therapy Lett. 2002;7:5-7.
[19]Noti A, Grob K, Biedermann M et al. Exposure of babies to C(15)-C(45) mineral paraffins from human milk and breast salves. Regul Toxicol Pharmacol. 2003;38:317-25

Lactation

Due to the low systemic exposure noted in the literature discussing the metabolism of benzoyl peroxide in the skin, breastfeeding is not expected to result in the exposure of the nursing child to clinically relevant amounts of benzoyl peroxide. There are no data on the presence of benzoyl peroxide in human milk, effects of benzoyl peroxide on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benzoyl peroxide and any potential adverse effects on the breastfed child from benzoyl peroxide, or from the underlying maternal condition.

In addition, since benzoyl peroxide is minimally absorbed, a clinical lactation study is not required.

Females and Males of Reproductive Potential

There are no concerns leading to a need for pregnancy testing or contraception. No evidence of fertility effects were found in the published literature. Therefore, DPMH recommends omitting subsection 8.3 from labeling for BP.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of BP labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DDD on 1/27/2021. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Epsolay (benzoyl peroxide) for Injection Pregnancy and Lactation Labeling

(b) (4)

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 10, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 214510
Product Name, Dosage Form, and Strength:	Epsolay (benzoyl peroxide)[a] cream, 5%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sol-Gel Technologies Ltd.
FDA Received Date:	June 26, 2020
OSE RCM #:	2020-1355
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

[a] We note the Applicant submitted the established name as (b) (4) benzoyl peroxide". However, per the Division of Dermatology and Dentistry email communication from November 18, 2020, (b) (4) is to be removed from the established name.

1 REASON FOR REVIEW

As part of the approval process for Epsolay (benzoyl peroxide) cream, 5%, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Patient Package Insert (PPI), container labels and carton labeling. We note the PI and MG can be improved to prevent wrong technique and wrong dose errors. The PI can also be improved to facilitate product identification. Additionally, the container labels and carton labeling can be improved for consistency, to facilitate product identification and to prevent drug selection and deteriorated drug errors.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labeling for Epsolay cream can be improved. We recommend the following be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Prescribing Information

1. Dosage and Administration Section

a. If the pump requires priming prior to first use, consider adding information on how to prime the pump bottle. As currently presented, there is only the statement [redacted] (b) (4)

2. How Supplied/Storage and Handling Section

a. We note the use of the placeholders 'XXXXX-XXX-XX' for the National Drug Code (NDC) and recommend replacing these NDC placeholders with the actual NDC when it is determined.

B. Patient Package Insert (PPI)

1. If the pump requires priming prior to first use, consider adding information on how to prime the pump bottle. As currently presented, there is only the statement [redacted] (b) (4)

4.2 RECOMMENDATIONS FOR SOL-GEL TECHNOLOGIES LTD.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXX-X). Replace these NDC placeholders with the actual NDC when it is determined and submit the revised labels and labeling to the Agency for review.
2. Remove [redacted] (b) (4) from the established name.
3. The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
4. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read "Recommended Dosage: See prescribing information."
5. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Container Labels

1. Relocate the route of administration to the principal display panel (PDP), as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epsolay received on June 26, 2020 from Sol-Gel Technologies Ltd..

Table 2. Relevant Product Information for Epsolay	
Initial Approval Date	N/A
Active Ingredient	benzoyl peroxide[b]
Indication	treatment of inflammatory lesions of rosacea
Route of Administration	topical
Dosage Form	cream
Strength	5%
Dose and Frequency	Prime pump bottle before initial use. Apply a pea-size amount of EPSOLAY Cream once daily to each area of the face (forehead, chin, nose, each cheek) on clean and dry skin. Spread as a thin layer, covering the entire face. Avoid the eyes, lips and mouth
How Supplied	50 gram airless pump, 30 gram airless pump (professional sample)
Storage	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F)
Container Closure	Airless pump

[b] We note the Applicant submitted the established name as "(b) (4) benzoyl peroxide". However, per the Division of Dermatology and Dentistry email communication from November 18, 2020, (b) (4) is to be removed from the established name.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Epsolay labels and labeling submitted by Sol-Gel Technologies Ltd..

- Container Label received on June 26, 2020
- Carton Labeling received on June 26, 2020
- Professional Sample Container Label received on June 26, 2020
- Prescribing Information and Patient Package Insert (Images not shown) received on June 26, 2020, available from \\CDSESUB1\evsprod\nda214510\0001\m1\us\114-labeling\draft\labeling\pdf.pdf

G.2 Label and Labeling Images

Container Labels

(b) (4)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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