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COMMENTARY

Real-World Adverse Events Associated with Encapsulated Benzoyl Peroxide/Tretinoin, 3%/0.1%, and Encapsulated Benzoyl Peroxide, 5%

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ABSTRACT

Encapsulated benzoyl peroxide, 5%, for rosacea and a combined formulation of encapsulated benzoyl peroxide/tretinoin, 3%/0.1%, for acne vulgaris, utilize microencapsulation, a process by which active pharmaceutical agents are enclosed in inert, permeable silica shells that provide a buffer between the drug and the skin. The silica shells allow a gradual release of the drug while also allowing combinations of active ingredients that would not otherwise be possible. This technology allows benzoyl peroxide and tretinoin to be combined in the same vehicle without risking the benzoyl peroxide-mediated oxidative destruction of tretinoin. In the current study, we queried the Galderma pharmacovigilance database to quantify and categorize adverse events associated with using these products in the USA during a 12-month period from May 2022 through April 2023. The adverse events were generally mild and restricted to local irritation, pruritus, burning sensation, and erythema. The real-world incidence and type of adverse events reported by the community for encapsulated benzoyl peroxide/tretinoin, 3%/0.1%, and benzoyl peroxide, 5%, were consistent with the safety and tolerability findings from the phase III clinical studies of these treatments.

Keywords: Acne vulgaris; Benzoyl peroxide; E-BPO; E-BPO/T; Encapsulated benzoyl peroxide 5%; Encapsulated benzoyl peroxide 3%/tretinoin 0.1%; Microencapsulation; Rosacea; Topical; Tretinoin

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Key Summary Points

Microencapsulation is a new technology by which an active pharmaceutical ingredient is encased in silica microcapsules, enabling a gradual and sustained release of the drug, potentially improving both efficacy and tolerability

On the basis of robust results from phase III clinical studies, two products utilizing this technology have been recently approved. They are encapsulated benzoyl peroxide, 3%, plus tretinoin, 0.1% (E-BPO/T, 3%/0.1%) to treat acne vulgaris and encapsulated benzoyl peroxide, 5% (E-BPO, 5%) to treat rosacea

In this study, we searched Galderma's pharmacovigilance database to quantify and categorize adverse events associated with using E-BPO/T, 3%/0.1%, and E-BPO, 5%, during a 12-month period

The adverse events were generally mild and restricted to local irritation, pruritus, burning sensation, and erythema, with monthly reporting rates ranging from 0.01 to 0.04 for E-BPO/T, 3%/0.1%, and from 0 to 0.11 for E-BPO, 5%

The low reporting rates of adverse events for the two products in the community were consistent with the safety and tolerability findings from previous phase III clinical studies

INTRODUCTION

Topical treatment of common facial dermatological conditions involves balancing symptom reduction and local intolerability. Acne has been treated successfully for over 50 years with benzoyl peroxide (BPO) and for more than 30 years with tretinoin; however, both medications are concentration-dependent irritants. Furthermore, tretinoin is not stable in the presence of BPO in traditional formulations. The incompatibility and intolerability of these medications may impact efficacy, patient satisfaction, and treatment adherence [1–4]. BPO has antimicrobial activity without causing bacterial resistance, and it acts as a keratolytic, clearing the stratum corneum of debris to prevent clogged pores [1, 2, 5]. Although nonencapsulated formulations are available over the counter, with concentrations ranging from 2.5% to 10%, the efficacy of traditionally formulated BPO is compromised by irritation and burning at the application site, which reduces patient adherence [1, 2]. While it is widely recommended as an acne treatment, BPO has also been effective in treating rosacea lesions [6, 7]. However, patients with rosacea have very sensitive skin, and the irritant nature of traditionally formulated BPO reduces the likelihood that patients will adhere to treatment for the necessary length of time to achieve treatment success [8, 9].

The topical retinoid tretinoin has keratolytic, comedolytic, and anti-inflammatory properties. It is available for treating acne in concentrations from 0.025% to 0.1% [2, 8]. While beneficial as monotherapy in treating mild to moderate acne, tretinoin's efficacy is improved when combined with other topical agents. Like BPO, tretinoin is a concentration-dependent skin irritant and can cause dryness, desquamation, erythema, and increased photosensitivity. BPO and tretinoin are first-line choices to treat acne, yet combining them to form a single treatment has not been possible historically [8, 10]. Tretinoin is susceptible to oxidation, and BPO is a powerful oxidizer; therefore, the two drugs have been administered separately, ideally at different times of day, to be effective [8, 10].

Microencapsulation is a technology that (1) allows the sustained delivery of a pharmaceutical agent to a target area while minimizing local irritation and (2) can overcome drug–drug interactions. Once the microencapsulated product is combined with a vehicle and applied to the skin, it is thought that lipids in the stratum corneum initiate the release of the drug. BPO and tretinoin are highly lipophilic and migrate from the porous microspheres to the skin's surface. This slow and sustained delivery may help protect the skin from concentration-

dependent irritation, burning, and erythema. The gradual release also allows prolonged exposure of the drug to the skin, which may increase the chance of treatment success [11]. This technology can be particularly beneficial for patients with rosacea, for whom BPO is efficacious but poorly tolerated because of the heightened skin sensitivity characteristic of the disease [1, 8].

Two products utilizing microencapsulation technology are approved for treating patients with acne vulgaris and rosacea. Encapsulated BPO, 3%, and encapsulated tretinoin, 0.1%, have been combined into a single-dose E-BPO/T cream, 3%/0.1%, that can be applied once daily to treat moderate to severe acne vulgaris. The second product is encapsulated E-BPO cream, 5% (E-BPO, 5%) for the treatment of inflammatory lesions in rosacea [12, 13]. E-BPO/T, 3%/0.1%, was approved in 2021 to treat acne vulgaris and has been available since April 2022. E-BPO cream, 5%, was approved in April 2022 to treat rosacea. The goal of this report is to quantify and categorize adverse events associated with using E-BPO/T, 3%/0.1%, and E-BPO, 5%, during a 12-month period from May 2022 through April 2023 by using the information in Galderma's pharmacovigilance database.

COMMENTARY

Phase III Clinical Studies of E-BPO/T, 3%/0.1%, for the Treatment of Acne Vulgaris

Two identical phase III, multicenter, randomized, double-blind, vehicle-controlled studies were conducted to evaluate the efficacy, safety, and tolerability of fixed-dose, combined E-BPO/T cream, 3%/0.1%, to treat acne vulgaris. A total of 858 participants, 9 years of age and older, with moderate to severe facial acne, were enrolled at 63 sites in the USA and were randomized 2:1 to receive either E-BPO/T, 3%/0.1%, or vehicle creams applied daily at bedtime for 12 weeks [12]. E-BPO/T, 3%/0.1%, showed significant improvement compared with vehicle in all coprimary endpoints (Investigator Global Assessment [IGA] success rate and the change in the absolute number of inflammatory and noninflammatory facial lesions from baseline to week 12).

In a combined analysis of both studies, E-BPO/T, 3%/0.1%, was well tolerated, with no reports of serious adverse events (AEs) or deaths related to treatment. Mild to moderate treatment-emergent adverse events (TEAEs) were reported by 24.7% of participants who received E-BPO/T, 3%/0.1%, and 11.9% of those who received the vehicle (pooled for both studies). The TEAEs were primarily cutaneous and restricted to the application site. The most common cutaneous TEAEs were pain (10.6% for E-BPO/T, 3%/0.1%, vs 0.4% for vehicle), dryness (4.9% vs 0.4%), exfoliation (4.1% vs 0%), erythema (4% vs 0%), dermatitis (1.3% vs 0.4%), pruritus (1.3% vs 0), and irritation (1.1% vs 0.4%) [12].

Phase III Clinical Studies of E-BPO Cream, 5%, for the Treatment of Rosacea Inflammatory Lesions

Two phase III, multicenter, randomized, double-blind, parallel-group, vehicle-controlled studies were conducted to evaluate the efficacy, safety, and tolerability of E-BPO cream, 5%, to treat moderate to severe rosacea. A total of 733 participants, 18 years of age and older, with moderate to severe rosacea, were enrolled at 54 sites in the USA and were randomized 2:1 to receive either E-BPO cream, 5%, or vehicle applied once daily for 12 weeks [13]. Coprimary efficacy endpoints were treatment success, defined by a rating of 0 (clear) or 1 (almost clear) on the IGA 5-point scale and change in the absolute number of inflammatory facial lesions. Both studies showed E-BPO cream, 5%, to be significantly more effective than vehicle alone for both endpoints.

Pooled safety data from both studies show that E-BPO cream, 5%, was safe and well tolerated. The percentages of patients reporting any AE were 20.3% for E-BPO, 5%, and 16.7% for vehicle. Only three patients reported severe treatment-related AEs, all of which were cutaneous and at the application site (severe erythema, severe pruritus, and severe site pain). There were no serious AEs in the vehicle cohort.

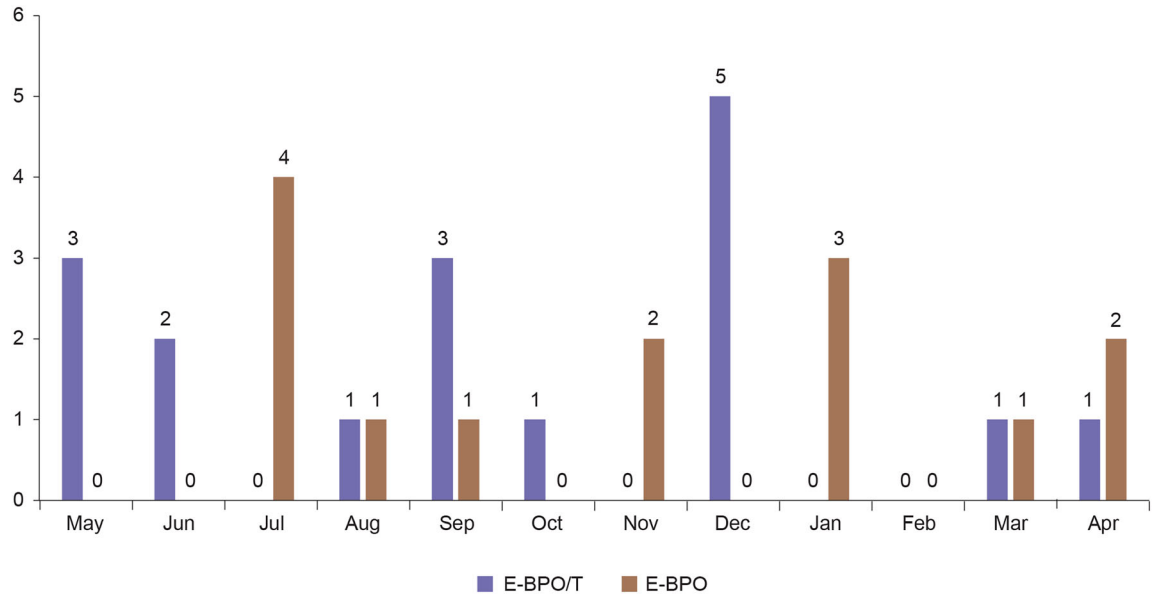

Fig. 1 Number of reports of adverse events per month in 2022–2023

Nine individuals (1.8%) from the E-BPO cream, 5%, group, and one participant (0.4%) from the vehicle group discontinued treatment as a result of AEs. Most treatment-related AEs were mild to moderate, cutaneous, and limited to the application site. The most common AEs were application site erythema (2.3% for E-BPO, 5%, vs 0.9% for vehicle), application site pain (1.6% vs 0.9%), and application site pruritus (1.2% vs 0.4%) [13]. An open-label extension study conducted over 40 weeks, which included the participants of both 12-week phase III studies, demonstrated continued IGA success with no new safety concerns [14].

Pharmacovigilance Data for E-BPO Cream, 5%, and E-BPO/T, 3%/0.1%

We performed a search of the Galderma pharmacovigilance database for the year following the approval of both formulations to track the rate of AEs associated with E-BPO cream, 5%, and E-BPO/T, 3%/0.1%, in the USA. The Galderma pharmacovigilance system captures spontaneous reports of AEs from patients, clinicians, and publications. The search was conducted for the 12 months between May 2022 and April 2023. During this time, there were 17 reports of AEs for E-BPO/T, 3%/0.1%, and 14 reports for E-BPO cream, 5% (Fig. 1). The most common TEAEs for E-BPO/T, 3%/0.1%, were skin irritation, burning sensation, pruritus, acne, rash, pain, and dry skin (Table 1). The most common TEAEs for E-BPO cream, 5%, were dry skin, erythema, skin irritation, pruritus, skin-burning sensation, intentional underdose, and hypersensitivity (Table 2). No serious or severe AEs were reported. These data reinforce the safety findings from the phase III and extension clinical studies. AEs were reported throughout the year, with some months receiving no reports (Fig. 1). The monthly reporting rates are shown in Table 2 and range from 0 to 0.04% for E-BPO/T and from 0 to 0.11% for E-BPO (Fig. 2). Reporting rates were calculated by dividing the number of cases reported by the number of units sold. They also complement results from a Galderma Global Safety Database search for AE reports associated with over-the-counter topical acne medications containing BPO from 1992 to 2021. This search produced an AE reporting rate of approximately 0.014% [15].

Table 1 Adverse event reports for E-BPO/T, 3%/0.1%, 2022–2023

Adverse event	Number of reports
Skin irritation	6
Skin burning sensation	6
Pruritus	4
Acne	4
Rash	3
Pain of skin	3
Dry skin	3
Skin swelling	2
Erythema	2
Skin exfoliation	2
Sensitive skin	1
Dermatitis	1
Eye swelling	1
Intentional underdose	1
Intentional overdose	1
Off-label use	1
Skin infection	1
Urticaria	1
Hypersensitivity	1

Table 2 Adverse Event Reports for E-BPO, 5%, 2022–2023

Adverse event	Number of reports
Dry skin	5
Erythema	5
Skin irritation	4
Pruritus	3
Skin burning sensation	3
Intentional underdose	3
Hypersensitivity	3
Off-label use	2
Drug ineffective	2
Skin swelling	2
Blepharitis	1
Pain	1
Eyelid edema	1
Skin warm	1
Skin exfoliation	1
Sleep disorder	1

DISCUSSION

The safety and tolerability of E-BPO/T, 3%/0.1%, and E-BPO cream, 5%, were supported by clinical trial data and community follow-up. The search of Galderma's pharmacovigilance system uncovered a mere 17 and 14 reports of adverse events in the 12 months following the approval of E-BPO/T, 3%/0.1%, and E-BPO cream, 5%, respectively, producing an overall reporting rate of less than 0.1% for each product. The low reporting rate and the types of reported AEs mirror the results from the phase III clinical studies. These results support using E-BPO/T, 3%/0.1%, to treat acne and E-BPO cream, 5%, to treat rosacea.

One limitation of this study is that we did not directly compare the AE rates of E-BPO to those of unencapsulated formulations during the same period. Instead, we drew our comparison using 29 years' worth of over-the-counter BPO-associated AE reports and a single year of E-BPO-associated AE reports [15]. There are no prescription topical treatments available that have BPO as the sole ingredient. Another limitation inherent to any pharmacovigilance system is the probability that some AEs are not reported. Although we found the reporting rates for the AEs associated with BPO and E-BPO to be similar, the AEs related to BPO were more likely to be underreported because BPO is available without a prescription to individuals not under a physician's care. Meanwhile, E-BPO requires a prescription for treating inflammatory lesions in rosacea and monitoring by a physician. No combined BPO/tretinoin treatment is available

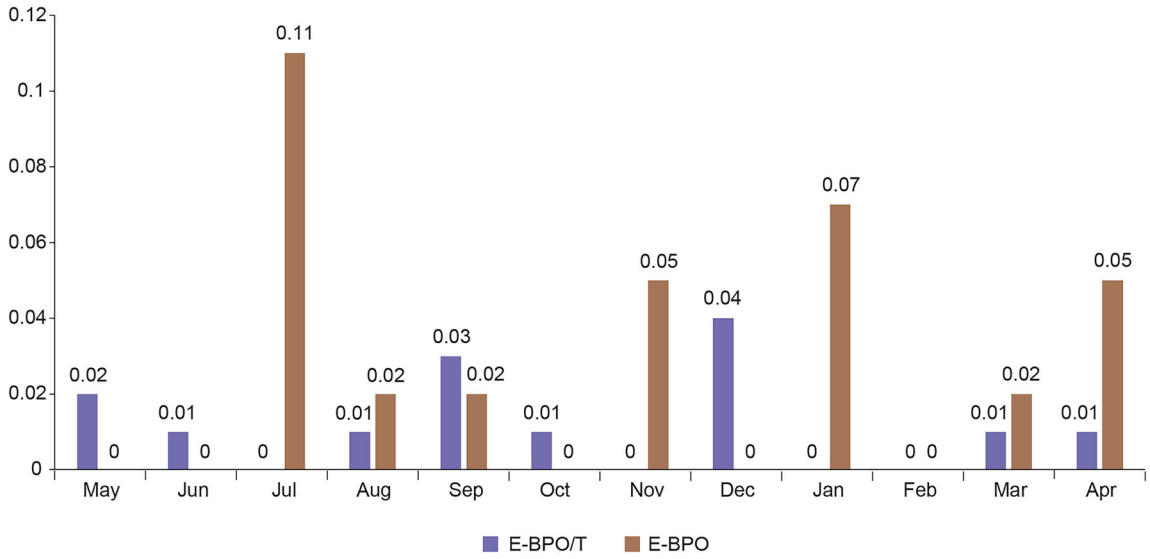

Fig. 2 Adverse event reporting rates per month in 2022–2023

to compare with E-BPO/T. There are combination products available that contain BPO and either adapalene or an antibiotic, all of which are indicated for acne vulgaris treatment. While the most common AEs were local reactions, products containing antibiotics have an increased risk of colitis [16–18].

Although the focus of this commentary is on the safety and tolerability of E-BPO/T, 3%/0.1%, and E-BPO cream, 5%, it is worth noting that microencapsulation of BPO and tretinoin carries the added benefit of potentially improving adherence, and by extension, efficacy. Previous studies have shown that combining two topical acne treatments into a single once-daily formulation improved adherence [19]. Another study found that in people with acne vulgaris, patients who experienced skin irritation with clindamycin–5% BPO reduced their use of this medication [20]. Vehicle characteristics are important to patient comfort, and optimizing the method of drug delivery may improve adherence, particularly when treating the face [21–23]. Future work is needed to understand how often patients reduce use of E-BPO/T, 3%/0.1%, and E-BPO cream, 5%, in response to an AE. Skin discomfort influences patients' preferences, choices, and quality of life [24]. Appropriate, gentle skin care is important for optimal tolerability and patient adherence to treatment. If an otherwise effective topical medication is intolerable, especially on an area as cosmetically important as the face, patients may be more likely to discontinue treatment or use a dose that is inadequate for optimal results [8, 22, 24]. Microencapsulation of BPO for rosacea and microencapsulation of BPO plus tretinoin for acne were both found to have a low rate of AE reporting during a 12-month period and can potentially improve treatment adherence, thus increasing the efficacy of drugs already known to be beneficial.

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Data Availability. The datasets analyzed in this article are not publicly available due to confidentiality.

Declarations

Conflict of Interest. Amy Poteate and JP York work for Galderma. Ofra Levy-Hacham is an employee of Sol–Gel Technologies.

Ethical Approval. Ethics committee approval was not required because this article only details collected pharmacovigilance data from real-world use.

REFERENCES

1. Green LJ, Lain E, Prunty T, Rhoades R. Enhancing topical pharmacotherapy for acne and rosacea: vehicle choices and outcomes. J Clin Aesthet Dermatol. 2022;15(5):36–40.

2. Erlich M, Arie T, Koifman N, Talmon Y. Structure elucidation of silica-based core-shell microencapsulated drugs for topical applications by cryogenic scanning electron microscopy. J Colloid Interface Sci. 2020;579:778–85.

3. Zaenglein AL. Acne vulgaris. N Engl J Med. 2018;379(14):1343–52. https://doi.org/10.1056/NEJMcp1702493.

4. Oge LK, Broussard A, Marshall MD. Acne vulgaris: diagnosis and treatment. Am Fam Physician. 2019;100(8):475–84.

5. Dréno B, Pécastaings S, Corvec S, Veraldi S, Khammari A, Roques C. Cutibacterium acnes (*Propionibacterium acnes*) and acne vulgaris: a brief look at the latest updates. J Eur Acad Dermatol Venereol. 2018;32(suppl 2):5–14.

6. Montes LF, Cordero AA, Kriner J, Loder J, Flanagan AD. Topical treatment of acne rosacea with benzoyl peroxide acetone gel. Cutis. 1983;32(2):185–90.

7. Leyden JJ, Thiboutot D, Shalita A. Photographic review of results from a clinical study comparing benzoyl peroxide 5%/clindamycin 1% topical gel with vehicle in the treatment of rosacea. Cutis. 2004;73(6)(Suppl):11–7.

8. Stein Gold L, Kwong P, Draelos Z, et al. Impact of topical vehicles and cutaneous delivery technologies on patient adherence and treatment outcomes in acne and rosacea. J Clin Aesthet Dermatol. 2023;16(5):26–34.

9. Kircik LH. Importance of vehicles in acne therapy. J Drugs Dermatol. 2011;10(6):s17–23.

10. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945–973.e33.

11. Ciriminna R, Sciortino M, Alonzo G, de Schrijver A, Pagliaro M. From molecules to systems: sol–gel microencapsulation in silica-based materials. Chem Rev. 2011;111(2):765–89.

12. Del Rosso J, Sugarman J, Green L, et al. Efficacy and safety of microencapsulated benzoyl peroxide and microencapsulated tretinoin for the treatment of acne vulgaris: results from two phase 3 double-blind, randomized, vehicle-controlled studies. J Am Acad Dermatol. 2023. https://doi.org/10.1016/j.jaad.2023.05.093. Accessed 14 Sep 2023.

13. Bhatia N, Werschler WP, Baldwin H, et al. Efficacy and safety of microencapsulated benzoyl peroxide cream, 5%, in rosacea: results from two phase III, randomized, vehicle-controlled trials. J Clin Aesthet Dermatol. 2023;16(8):34–40.

14. Werschler W, Sugarman J, Bhatia N, et al. Long-term efficacy and safety of microencapsulated benzoyl peroxide cream, 5%, in rosacea: results from an extension of two phase III, vehicle-controlled trials. J Clin Aesthet Dermatol. 2023;16(8):27–33.

15. Szymanski L, Arekapudi KL. Adverse-event reports in over-the-counter topical acne drug products containing benzoyl peroxide from a specific

pharmaceutical company in the USA. Dermatol Ther (Heidelb). 2022;12(11):2397–400.

16. Onexton (clindamycin phosphate and benzoyl peroxide gel) [package insert]. Bridgewater, NJ: Bausch Health US, LLC; 2020.

17. Benzamycin (erythromycin-benzoyl peroxide gel) [package insert]. Berwyn, PA: Dermik Laboratories;2003.

18. Epiduo forte (adapalene and benzoyl peroxide) [package insert]. Fort Worth, Tx: Galderma Laboratories LP;2015.

19. Yentzer BA, Ade RA, Fountain JM, et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: a randomized controlled trial. Cutis. 2010;86(2):103–8.

20. Draelos ZD, Callender V, Young C, Dhawan SS. The effect of vehicle formulation on acne medication tolerability. Cutis. 2008;82(4):281–4.

21. Feldman SR, Chen DM. How patients experience and manage dryness and irritation from acne treatment. J Drugs Dermatol. 2011;10(6):605–8.

22. Del Rosso JQ, Kircik LH, Zeichner J, Stein GL. The clinical relevance and therapeutic benefit of established active ingredients incorporated into advanced foam vehicles: vehicle characteristics can influence and improve patient outcomes. J Drugs Dermatol. 2019;18(2s):s100–7.

23. Barnes TM, Mijaljica D, Townley JP, Spada F, Harrison IP. Vehicles for drug delivery and cosmetic moisturizers: review and comparison. Pharmaceutics. 2021;13(12):2012.

24. Williamson T, Cheng WY, McCormick N, Vekeman F. Patient preferences and therapeutic satisfaction with topical agents for rosacea: a survey-based study. Am Health Drug Benefits. 2018;11(2):97–106.