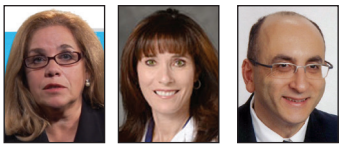
Insert to practical dermatology® July 2017

Sponsored by Galderma Laboratories, L.P.

Advances in Acne Vulgaris Treatment

Strategies predicated on targeting multiple pathogenic features of acne—especially inflammation—are in the best interest of patients.



BASED ON A PRESENTATION BY HILARY BALDWIN, MD; LINDA STEIN GOLD, MD; AND LEON KIRCIK, MD

Drs. Baldwin, Stein Gold, and Kircik are paid consultants for Galderma Laboratories, L. P.

Acne is the most common skin problem in the United States.[1] According to recent surveys, acne cases comprise over 60 percent of the cases seen by dermatologists. For context: the second highest category of patients, those seeking cosmetic services, constitute only about 20 percent of the average patient population in a dermatology clinic.[2]

Acne scarring is a common manifestation and occurs equally in male and female patients.[3] A study by Dreno et al showed that while acne scarring was most prevalent in patients with severe acne, it also occurs in 33 percent to 36 percent of cases with "almost clear" to "mild" acne,[4] and these findings have been noted in other studies, as well.[5] More importantly, the presence of acne scars can negatively impact patients' quality of life, including impaired self-image and psychological well-being, and is associated with feelings of anxiety, depression, lower self-esteem, anger, embarrassment, and humiliation.[5-15] One study noted that individuals with acne scars have increased unemployment rates.[10]

Despite these consequences, or perhaps because of them, patients often delay seeking treatment. Although this trend is reasonable given the psychological impact of acne—and acne scars in particular—delaying treatment is often detrimental.

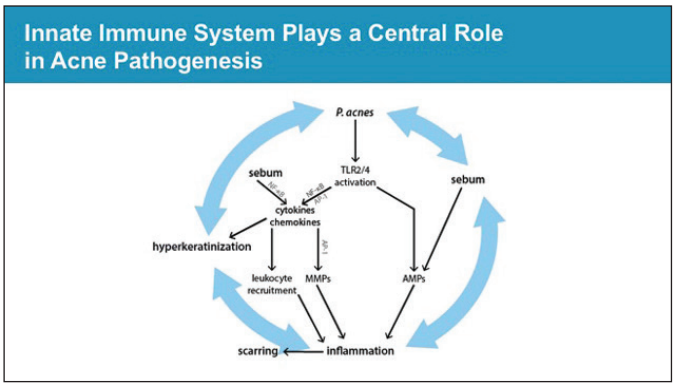


Figure 1

The degree of facial scarring present in acne is positively correlated with the duration of time before adequate acne treatment is initiated.[12]

Evidence is emerging that inflammation plays a significant role in the development of acne scars. More specifically, upregulation of toll-like receptor 2 (TLR-2) yields an inflammatory response that triggers downstream activation of matrix metalloproteinase proteins (MMPs), breakdown of collagen, and increased production of procollagen that contribute to scarring.[16] Furthermore, individuals who develop scars have increased T helper cells in peri-lesional infiltrate relative to non-scarrers, suggestive of a more specific, but less effective, immune response in patients who scar.[16]

EVOLVING UNDERSTANDING OF ACNE

The classic model of acne pathogenesis involves the interaction of four specific factors: an increase in sebum production under the influence of androgens during teenage years; an alteration in the keratinization process; *Propionibacterium acnes* (*P acnes*) proliferation; and a release of inflammatory mediators into the skin.[17] This has often been described as a linear process, with the increase in sebum production directly instigating the alteration in the keratinization process. As the follicle became sticky and clogged, the sebum built up behind the clog and served as nutrition for *P acnes*. In turn, as *P acnes* proliferated, free fatty acids were produced and lipases destroyed the lining of the follicle, leading to eventual rupture with the release of the inflammatory mediators into the skin.

For decades, it was also postulated that lesion progression was similarly linear, that the microcomedo was the precursor for all lesions that followed, and the microcomedo would become either an open or a closed comedone. In this model, the comedones eventually differentiated into inflammatory lesions, which later healed and produced scars.

A more nuanced view of lesion progression has emerged. Recent evidence suggests that although the microcomedone may be the primary lesion (and probably still the most common precursor lesion), pimples can arise from normal skin, as well. Both open and closed comedones, inflammatory lesions, and even scars can emerge from what is considered normal skin.[17] The classical, linear model of acne development should be updated to include the influence of inflammation in the pathogenesis of acne vulgaris. There are now numerous studies demonstrating that subclinical inflammation precedes the formation of the microcomedone, and that inflammatory lesions may arise from clinically normal skin.[19-22]

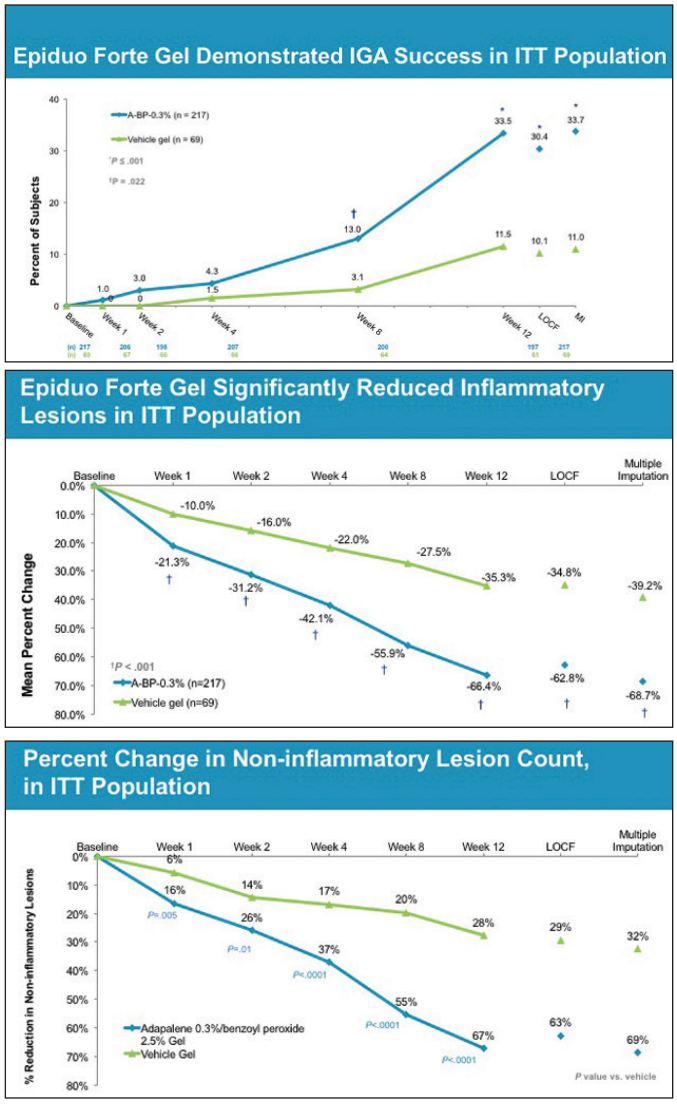
Evidence is also emerging about the role of the innate immune system in acne pathogenesis. Rather than being a linear process, acne development is, in fact, circuitous, with all four of the aforementioned factors interacting and influencing one another to drive formation of skin manifestations (Figure 1). Prominently, *P acnes* appears to activate TLR 2 and TLR 4, which results in an increase in MMPs. At the same time, an increase in NF-kappa-B, AP1 cytokines, and chemokines causes hyperkeratinization, which allows the recruitment of leukocytes into the area and spurs a positive feedback loop of MMP recruitment, as well as activation of gelantinases and elastases that break down the dermal structure.

Despite all the complexity involved in acne pathogenesis, one thing remains clear: all pathways eventually lead to inflammation, and inflammation likely plays a significant role in scarring.

ACNE AND ACNE SCARS

There are myriad treatment options for acne scars, yet they remain a vexing clinical condition given the incomplete efficacy of management options. The clinical emphasis, therefore, should be on early initiation of treatment of acne, rather than its sequelae. More specifically, opportunities for earlier recognition that leads to earlier initiation of treatment should be identified, and serious effort should be made to break social stigmas that prevent patients from seeking the expertise of trained dermatologists for their acne.

According to evidence-based acne vulgaris treatment guidelines from the American Academy of Dermatology released in 2016, retinoids and benzoyl peroxide are at the core of topical acne therapy for all types of acne, including mild, moderate, and severe. Depending on the severity of acne, antibiotics, either topical or oral, may be added.[23] Fundamentally, combination topical retinoid with benzoyl peroxide therapy targets multiple factors in the pathogenesis of acne, leading to more complete treatment. We believe that a byproduct of such an approach, predicated on shut-



Figures 2a, 2b, 2c. Abbreviations: ITT, intent to treat; LOCF, last observation carried forward; MI, multiple imputation; A-BP 0.3%, adapalene 0.3%/benzoyl peroxide 2.5% Data on file. Fort Worth, TX; Galderma Laboratories, L.P.

ting down multiple components of the acne vulgaris pathologic pathway, is that it would serve to mediate the role of inflammation, thereby clearing acne and helping to prevent formation of scarring over time.

Though not always recognized as such, topical retinoids are potent anti-inflammatory molecules. Specifically, adapalene has been shown to inhibit release of proinflammatory mediators, modulate the epidermal immune system, stimulate collagen production, promote keratinization, and regulate cell turnover.[24,26] There is evidence that the anti-inflammatory properties of this agent function in a dose response manner: In one study, adapalene 0.3% resulted in higher acne clearance rates in a faster amount of time compared with adapalene 0.1%.[27]

Benzoyl peroxide is another critical component of the acne treatment armamentarium. It is a potent anti-bactericidal that yields up to 90 percent reduction in *P acnes* in seven days; as well, it has indirect anti-inflammatory activity, via inhibition of reactive oxygen species and reduction of free fatty acids, and comedolytic properties.[23,28]

EPIDUO FORTE GEL: PHASE 3 STUDY RESULTS

Epiduo® Forte (adapalene and benzoyl peroxide) Gel, 0.3%/2.5% is indicated for the topical treatment of acne vulgaris. It offers the efficacy of its individual ingredients in a convenient and easy to apply application. In the stringent phase 3 clinical trial, this agent was proven safe and well tolerated, resulting in greater efficacy over vehicle, even in severe acne manifestations.[29,30]

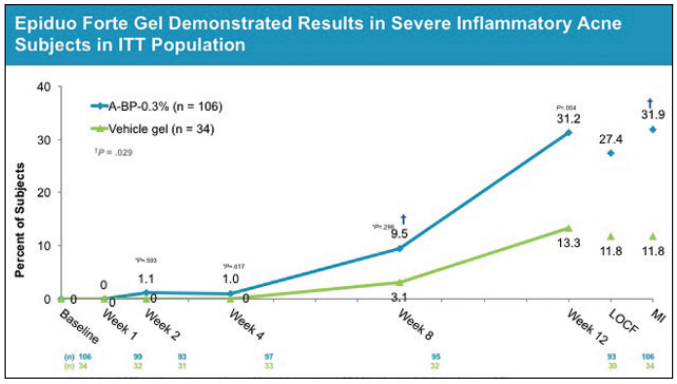
The population of patients recruited to this study is noteworthy. A total of 286 patients were randomized to two once-a-day treatment groups: Epiduo Forte Gel (group 1; n=217) or vehicle gel (group 2; n=69). The primary endpoints were (1) success rate (defined as percentage of subjects who were "clear" or "almost clear" on the Investigator's Global Assessment Scale [IGA]); (2) change in inflammatory lesion count; and (3) change in non-inflammatory lesion count. It is important to note that at baseline, 50 percent of the population was grade 3 on the IGA scale and 50 percent were IGA grade 4.

Overall, 33.7 percent and 11 percent of subjects in groups 1 and 2, respectively, achieved a 2-grade improvement in IGA score and "clear" or "almost clear." In terms of inflammatory lesions, the mean absolute reduction in number of lesions was 27.8 (68.7 percent) and 13.2 (39.2 percent); for non-inflammatory lesions, these values were 40.5 (68.3 percent) and 19.7 (37.4 percent) in groups 1 and 2, respectively.

APPLICATIONS FOR CLINICAL PRACTICE

The percent of patients achieving a 2-grade improvement in IGA score and "clear" or "almost clear" did not differ in the overall population until after week 4, but was statistically significantly better in the Epiduo Forte Gel arm than in the vehicle gel group at every point thereafter through week 12 (Figure 2a). However, in terms of reduction in both inflammatory and non-inflammatory lesions, differences were apparent at the 1 week follow-up and continued to get better over time, compared to the vehicle gel (Figures 2b and c).

Translating this finding to clinical practice, the implication is that patients will see dramatic reduction in lesion counts within a week of initiating treatment, even if they do not meet the strict definition of success at that time. Most dermatologists



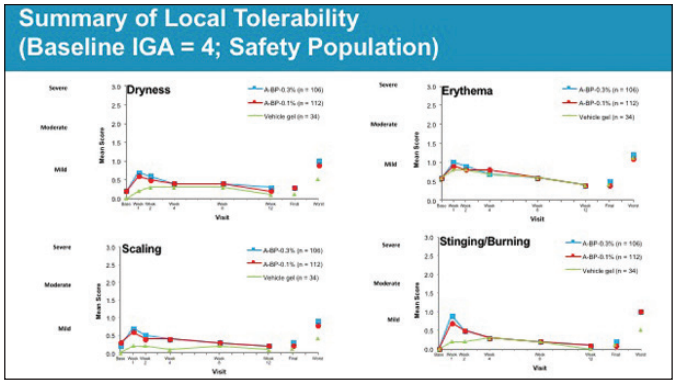


Figure 3 (left) and Figure 4 (right). Abbreviations: ITT, intent to treat; LOCF, last observation carried forward; MI, multiple imputation; A-BP 0.3%, adapalene 0.3%/benzoyl peroxide 2.5% Data on file. Fort Worth, TX; Galderma Laboratories, L.P.

will likely agree that a rapid onset of benefit can give patients confidence that their treatment is working, potentially leading to continued compliance.

Other clinically relevant findings from this study can be appreciated in an analysis of the subpopulation of patients with severe acne (IGA grade 4). Within this group, 31.9 percent of those in group 1 (Epiduo Forte; n=106) and 11.8 percent in group 2 (vehicle gel; n=34) achieved at least 3-grade improvement on the IGA scale and "clear" or "almost clear." The mean absolute reduction of inflammatory lesions was -37.25 and -14.28, while the mean absolute reduction of non-inflammatory lesions was -46.33 and -17.82 in groups 1 and 2, respectively (Figure 3).

Additionally, within the subgroup of patients with severe acne at baseline, Epiduo Forte Gel demonstrated a significantly greater success rate compared to vehicle with a treatment difference of 20.1 percent (31.9 percent vs. 11.8 percent; 95 percent CI; p = 0.029). This translated to an 11 percent difference between active treatments in favor of Epiduo Forte Gel.

While generalizing findings from clinical trials to general practice is difficult, we believe these data demonstrate that Epiduo Forte Gel is efficacious across the spectrum of acne severity. The data among severe acne sufferers is at least comparable to that in the overall population. This should supply confidence to providers as to the robustness and validity of findings from the clinical trial.

ADDITIONAL CONTEXT: THE IMPORTANCE OF TRIAL DESIGN

While the results of the phase 3 trial are impressive on their own, they should be understood in the context of the study's design. Mean reduction of acne lesion provides a semi-objective measure of efficacy (although one that is subject to investigator bias) and has been used as an endpoint in clinical trials since 1966.[31] However, in the view of the FDA, "Use of lesion count assessments alone as an endpoint may be less than reliable because of the lack of appreciation for the variable expression of acne vulgaris with a strictly quantitative definition."[32] As such, in addition to lesion counts, investigators in the trial were also tasked with assessing the quality of the acne lesions using the IGA scale.

These regulatory requirements are in turn a consideration when selecting a study population. If, for example, only patients with mild acne (i.e., IGA 2) are enrolled, only a one-step improvement is necessary to achieve clear or almost clear (IGA 1). Whereas, enrolling moderate patients (IGA 3), or even severe acne (IGA 4), establishes a much higher bar for success.

What is unique about the Epiduo Forte Gel phase 3 study, then, is that 50 percent of the study population was comprised of individuals with severe acne (IGA 4). In fact, this was the first topical acne clinical trial to include such a significant proportion of severe acne subjects.

Because the study used stringent efficacy requirements, it may be the case that certain cases that did not qualify for success had clinically important benefits represented in secondary outcomes. For example, a patient with 194 total lesions (82 inflammatory) at baseline who had 85 percent clearance by study end is deemed a failure, despite reduction to 30 total lesions (13 inflammatory). Our collective clinical assessment of such a patient is that significant clearance of acne vulgaris is likely to make a patient very happy.

SAFETY AND TOLERABILITY

Epiduo Forte Gel was well tolerated in the clinical trial, including among the subpopulation of patients with severe acne—a subset one would expect to have a more profound response to the dual active ingredients. Tolerability, including skin dryness, erythema, scaling, and stinging and/or burning were infrequent and comparable in all treatment groups (Figure 4).

CONCLUSION

A growing body of evidence is reforming the classic model of acne vulgaris pathogenesis. Whereas we previously believed acne formation to be a linear process, a more dynamic model is emerging, wherein skin manifestations typically associated with mild, moderate, or severe disease are understood to emerge at any stage of severity. Fundamentally, a growing appreciation of the role of inflammation in acne vulgaris etiology challenges our notions of acne severity and how it relates to formation of pimples. It seems evident that strategies aimed at impacting the inflammatory cascade would yield benefit across the range of acne severity.

As in many areas of medicine, there is growing appreciation for the benefits of early recognition and initiation of treatment of acne vulgaris. We believe that achieving such a treatment paradigm would be greatly facilitated by by efforts to increase awareness around the risk of scarring associated with acne. We look forward to ongoing research that elucidates the potential psychological consequences of acne and how they may be overcome.

In the meantime, dermatologists can be confident that very good treatment options are available that significantly reduce acne vulgaris lesion counts and improve subjective grading across the gamut of severity. Combination Epiduo Forte Gel offers the efficacy of adapalene and benzoyl peroxide in a convenient and easy to apply application. The most common adverse events reported in clinical trials were erythema, scaling, dryness, stinging/burning, irritant and allergic contact dermatitis.

The results of a phase 3 clinical trial show this agent to be safe and well tolerated, as well as highly effective in treating acne, including among individuals with more severe clinical manifestations.

The results of the phase 3 clinical trial are highly intriguing and relatable to regular clinical practice. The particular study design and population of patients included in the analysis should supply additional confidence that the data are highly significant for the kinds of patients dermatologists encounter on a regular basis. ■

1. American Academy of Dermatology. Acne. https://www.aad.org/dermatology-a-to-z/diseases-and-treatments/a---d/acne. Accessed January 17, 2016.

2. Harris Williams & Company. Dermatology Market Overview. August 2013. http://www.harriswilliams.com/sites/default/files/industry_reports/dermatology_industry_presentation_aug2013.pdf. Accessed January 17, 2016.

3. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. Clin Exp Dermatol. 1994 Jul;19(4):303–8.

4. Dreno et al., 2014 poster presented at EADV.

5. Tan JK, Tang J, Fung K, Gupta AK, Richard Thomas D, Sapra S, Lynde C, Poulin Y, Gulliver W, Sebaldt RJ. Development and validation of a Scale for Acne Scar Severity (SCAR-S) of the face and trunk. J Cutan Med Surg. 2010 Jul-Aug;14(4):156-60.

6. Goulden V, Clark SM, Cunliffe WJ. Post-adolescent acne: a review of clinical features. Br J Dermatol. 1997 Jan;136(1):66-70.

7. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. Br J Dermatol. 1998 Nov;139(5):846-50.

8. Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. Arch Dermatol. 1998 Apr;134(4):454-8.

9. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br J Dermatol. 1999 Apr;140(4):672-6.

10. Cunliffe WJ. Acne and unemployment. Br J Dermatol. 1986 Sep;115(3):386.

11. Dalgard F, Gieler U, Holm JØ, Bjertness E, Hauser S. Self-esteem and body satisfaction among late adolescents with acne: results from a population survey. J Am Acad Dermatol. 2008 Nov;59(5):746-51.

12. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. Clin Exp Dermatol. 1994 Jul;19(4):303-8.

13. Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. Br J Dermatol. 1997 Aug;137(2):246-50.

14. Plewig G, et al. Acne and Rosacea 2000.

15. Kang S, Cho S, Chung JH, Hammerberg C, Fisher GJ, Voorhees JJ. Inflammation and extracellular matrix degradation mediated by activated transcription factors nuclear factor-kappaB and activator protein-1 in inflammatory acne lesions in vivo. Am J Pathol. 2005 Jun;166(6):1691-9.

16. Holland DB, Jeremy AH, Roberts SG, Seukeran DC, Layton AM, Cunliffe WJ. Inflammation in acne scarring: a comparison of the responses in lesions from patients prone and not prone to scar. Br J Dermatol. 2004 Jan;150(1):72-81.

17. Thiboutot D, Gollnick H, Bettoli V, Dréno B, Kang S, Leyden JJ, Shalita AR, Lozada VT, Berson D, Finlay A, Goh CL, Herane MI, Kaminsky A, Kubba R, Layton A, Miyachi Y, Perez M, Martin JP, Ramos-E-Silva M, See JA, Shear N, Wolf J Jr; Global Alliance to Improve Outcomes in Acne. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. J Am Acad Dermatol. 2009 May;60(5 Suppl):S1-50.

18. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, Shalita AR, Thiboutot D; Global Alliance to Improve Outcomes in Acne. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol. 2003 Jul;49(1 Suppl):S1-37.

19. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol. 2003 Jul;121(1):20-7.

20. Do TT, Zarkhin S, Orringer JS, Nemeth S, Hamilton T, Sachs D, Voorhees JJ, Kang S. Computer-assisted alignment and tracking of acne lesions indicate that most inflammatory lesions arise from comedones and de novo. J Am Acad Dermatol. 2008 Apr;58(4):603-8.

21. Vowels BR, Yang S, Leyden JJ. Induction of proinflammatory cytokines by a soluble factor of Propionibacterium acnes: implications for chronic inflammatory acne. Infect Immun. 1995 Aug;63(8):3158-65.

22. Lee WJ, Jung HJ, Lim HJ, Jang YH, Lee SJ, Kim DW. Serial sections of atrophic acne scars help in the interpretation of microscopic findings and the selection of good therapeutic modalities. J Eur Acad Dermatol Venereol. 2013 May;27(5):643-6.

23. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, Bowe WP, Graber EM, Harper JC, Kang S, Keri JE, Leyden JJ, Reynolds RV, Silverberg NB, Stein Gold LF, Tollefson MM, Weiss JS, Dolan NC, Sagan AA, Stern M, Boyer KM, Bhushan R. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945-73.e33.

24. Czernielewski J, Michel S, Bouclier M, Baker M, Hensby JC. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. J Eur Acad Dermatol Venereol. 2001;15 Suppl 3:5-12.

25. Patel J, et al. J Am Acad Dermatol. 2014;70(Suppl 1); AB1-AB294.

26. Leyden JJ. Topical treatment of acne vulgaris: retinoids and cutaneous irritation. J Am Acad Dermatol. 1998 Apr;38(4):S1-4

27. Thiboutot D, Pariser DM, Egan N, Flores J, Herndon JH Jr, Kanof NB, Kempers SE, Maddin S, Poulin YP, Wilson DC, Hwa J, Liu Y, Graeber M; Adapalene Study Group. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. J Am Acad Dermatol. 2006 Feb;54(2):242-50.

28. Hegemann L, Toso SM, Kitay K, Webster GF. Anti-inflammatory actions of benzoyl peroxide: effects on the generation of reactive oxygen species by leucocytes and the activity of protein kinase C and calmodulin. Br J Dermatol. 1994 May;130(5):569-75.

29. Stein Gold L, Weiss J, Rueda MJ, Liu H, Tanghetti E. Moderate and Severe Inflammatory Acne Vulgaris Effectively Treated with Single-Agent Therapy by a New Fixed-Dose Combination Adapalene 0.3 %/Benzoyl Peroxide 2.5 % Gel: A Randomized, Double-Blind, Parallel-Group, Controlled Study. Am J Clin Dermatol. 2016 Jun;17(3):293-303.

30. Weiss J, Stein Gold L, Leoni M, Rueda MJ, Liu H, Tanghetti E. Customized Single-agent Therapy Management of Severe Inflammatory Acne: A Randomized, Double-blind, Parallel-group, Controlled Study of a New Treatment--Adapalene 0.3%-Benzoyl Peroxide 2.5% Gel. J Drugs Dermatol. 2015 Dec;14(12):1427-35.

31. Witkowski JA, Simons HM. Objective evaluation of demethylchlortetracycline hydrochloride in the treatment of acne. JAMA. 1966 May 2;196(5):397-400.

32. Center for Drug Evaluation and Research (CDER) Guidance for Industry Acne Vulgaris: Developing Drugs for Treatment; 2005,8

IMPORTANT INFORMATION ABOUT

EPIDUO® FORTE

(adapalene and benzoyl peroxide) Gel, 0.3% / 2.5%

BRIEF SUMMARY

This summary contains important information about EPIDUO FORTE (Ep-E-Do-Oh For-Tay) Gel. It is not meant to take the place of your doctor's instructions. Read this information carefully before you start using EPIDUO FORTE Gel. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about EPIDUO FORTE Gel. For full Prescribing Information and Patient Information, please see the package insert.

WHAT IS EPIDUO FORTE GEL?
EPIDUO FORTE Gel is a prescription medicine used on the skin (topical) to treat acne vulgaris. Acne vulgaris is a condition in which the skin has blackheads, whiteheads, and pimples.

WHO IS EPIDUO FORTE GEL FOR?
EPIDUO FORTE Gel is for use in people 12 years of age and older. It is not known if EPIDUO FORTE Gel is safe and effective for children younger than 12 years old.

Do not use EPIDUO FORTE Gel for a condition for which it was not prescribed. Do not give EPIDUO FORTE Gel to other people, even if they have the same symptoms you have. It may harm them.

WHAT SHOULD I TELL MY DOCTOR BEFORE USING EPIDUO FORTE GEL?
Before you use EPIDUO FORTE Gel, tell your doctor if you:

- have other skin problems, including cuts or sunburn.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if EPIDUO FORTE Gel can harm your unborn baby. Talk to your doctor if you are pregnant or planning to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if EPIDUO FORTE Gel passes into your breast milk and if it can harm your baby. Talk to your doctor about the best way to feed your baby if you use EPIDUO FORTE Gel.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using other topical acne products may increase the irritation of your skin when used with EPIDUO FORTE Gel.

WHAT SHOULD I AVOID WHILE USING EPIDUO FORTE GEL?

- You should avoid spending time in sunlight or artificial sunlight, such as tanning beds or sunlamps. EPIDUO FORTE Gel can make your skin sensitive to sun and the light from tanning beds and sunlamps. You should use sunscreen and wear a hat and clothes that cover the areas treated with EPIDUO FORTE Gel if you have to be in the sunlight.
- You should avoid weather extremes such as wind and cold as this may cause irritation to your skin.
- You should avoid applying EPIDUO FORTE Gel to cuts, abrasions and sunburned skin.
- You should avoid skin products that may dry or irritate your skin such as medicated or harsh soaps, astringents, cosmetics that have strong skin drying effects and products containing high levels of alcohol, spices or limes.
- You should avoid the use of "waxing" as a hair removal method on skin treated with EPIDUO FORTE Gel.
- EPIDUO FORTE Gel may bleach your clothes or hair. Allow EPIDUO FORTE Gel to dry completely before dressing to prevent bleaching of your clothes.

WHAT ARE THE MOST COMMON SIDE EFFECTS OF EPIDUO FORTE GEL?
EPIDUO FORTE Gel may cause serious side effects including:

- Local skin reactions. Local skin reactions are most likely to happen during the first 4 weeks of treatment and usually lessen with continued use of EPIDUO FORTE Gel. Signs and symptoms of local skin reaction include:
  - Redness
  - Dryness
  - Scaling
  - Stinging or burning

Tell your doctor right away if these side effects continue for longer than 4 weeks or get worse; you may have to stop using EPIDUO FORTE Gel.

These are not all of the possible side effects of EPIDUO FORTE Gel. For more information, ask your doctor or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA at *www.fda.gov/medwatch or call 1-800-FDA-1088*. You may also contact GALDERMA LABORATORIES, L.P. at 1-866-735-4137.

HOW SHOULD I USE EPIDUO FORTE GEL?

- Use EPIDUO FORTE Gel exactly as your doctor tells you to use it. EPIDUO FORTE Gel is for use on the skin only (topical). Do not use EPIDUO FORTE Gel in or on your mouth, eyes or vagina.
- Apply EPIDUO FORTE Gel 1 time a day.
- Do not use more EPIDUO FORTE Gel than you need to cover the treatment area. Using too much EPIDUO FORTE Gel or using it more than 1 time a day may increase your chance of skin irritation.

APPLYING EPIDUO FORTE GEL:

- Wash the area where the Gel will be applied with a mild or soapless cleanser and pat dry.
- EPIDUO FORTE Gel comes in a pump. Depress the pump to dispense a small amount (about the size of a pea) of EPIDUO FORTE Gel and spread a thin layer over the affected area.
- Wash your hands after applying the Gel.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT EPIDUO FORTE GEL?

- Talk to your doctor or pharmacist.
- Go to **www.EPIDUOFORTE.com** or call **1-866-735-4137.**

GALDERMA LABORATORIES, L.P., Fort Worth, Texas 76177 USA
Revised: July 2015
20089-0415-BS

GALDERMA

EPIDUO® FORTE
(adapalene and benzoyl peroxide) Gel 0.3% / 2.5%