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Adapalene/benzoyl peroxide gel 0.3%/2.5% for acne vulgaris

Acne vulgaris is typically treated with a combination of a topical retinoid plus an antimicrobial agent, as recommended by national and international evidence-based guidelines around the globe. Adapalene, a synthetic topical retinoid, is available in two concentrations (0.1% and 0.3%) and in once-daily fixed-dose combinations with benzoyl peroxide (BPO) 2.5%. Adapalene 0.3%/BPO 2.5% is approved for use for moderate-to-severe acne with proven efficacy, good safety and tolerability across a spectrum of patient variables (different ages, genders, and skin types) and disease severity. While some patients experience issues with transient tolerability during retinoid and BPO therapy, it is our clinical experience that good patient education to set expectations and provide strategies to minimize irritation can overcome the majority of issues. This article reviews the data supporting the use of adapalene 0.3%/2.5% in practice, including the complementary mechanism of action of adapalene and BPO, clinical data from a range of settings, and key aspects of patient education.

Key words: acne vulgaris, atrophic acne scars, scarring, adapalene, benzoyl peroxide, fixed-dose combination, severe acne

Acne vulgaris is one of the most common skin diseases encountered in practice, and it has been estimated that as many as 85% of people suffer from acne during their lives [1, 2]. While acne often begins at puberty and affects adolescents, it is increasingly reported to persist into later decades of life [3, 4]. The pathophysiology of acne is not completely understood, but it is accepted to be a multifactorial inflammatory disease centred around the pilosebaceous unit. There are four primary factors: (1) increase in quantity and change in quality of sebum due to effects of circulating androgens and bacterial actions on sebaceous glands; (2) abnormal keratinocyte desquamation, which plugs the follicle to create a microcomedo and retentional lesions; (3) colonization of the pilosebaceous unit with the bacteria *Cutibacterium acnes*; and (4) release of various inflammatory molecules and chemotactic factors as part of a local inflammatory response [5, 6]. Targeting as many of these factors as possible with acne treatments has been recommended in evidence-based guidelines, frequently starting with a combination of a topical retinoid plus an antimicrobial agent [7-9]. Due to concerns about the potential for antibiotic resistance and the typical need for prolonged treatment for acne, benzoyl peroxide (BPO) is preferred as the antimicrobial agent since it is bactericidal and has shown a very low potential for inducing resistance among skin microflora, however, BPO does not target the microcomedone (acne precursor lesion) [7, 9].

Adapalene 0.3%/BPO 2.5% (Epiduo® Forte Gel, Galderma Laboratories, LP, Fort Worth, Texas, USA) was approved by the United States FDA in July, 2015 and by the EMA for multiple European countries in 2016. It offers a potent, once-daily fixed-dose topical combination therapy for moderate-to-severe acne [10, 11]. The higher concentration of adapalene (0.3% vs the original 0.1%) provides increased benefits to patients compared with the lower concentration, perhaps due to increased anti-inflammatory effects [12, 13]. This paper reviews data supporting the use of adapalene 0.3%/BPO 2.5% fixed-dose combination for acne with suggested patient educational strategies to help minimize tolerability issues during initiation of therapy.

Complementary mechanisms of action for a potent effect

As mentioned above, experts recommend targeting multiple aspects of acne pathophysiology [8]. Adapalene 0.3%/BPO 2.5% targets several of the primary pathophysiological factors and, as a fixed-dose formulation, is convenient for patients [13]. Adapalene, a topical retinoid, normalizes desquamation, blocks important inflammatory pathways that are activated in acne, is comedolytic and anti-comedogenic, and targets the precursor lesion of acne (the microcomedo) [14]. Because of the actions of topical retinoids and the strongly supportive clinical data, retinoids are considered the cornerstone of acne therapy [15]. BPO is a non-antibiotic, broad-spectrum antimicrobial agent [16-19]. It is highly lipophilic, and can penetrate bacterial cell membranes where it has a bactericidal activity via the generation of oxygen free radicals [18]. These free radicals oxidize

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elements of the bacterial cell wall, destroying it [18]. BPO also has mild sebostatic and comedolytic effects [20]. It is suggested that the effects of adapalene, which alters the follicular microclimate, potentially enhances penetration of BPO. Conversely, since BPO is also keratolytic, it may enhance penetration of adapalene [21, 22].

Confirming translational research, pooled data from three large-scale randomized controlled studies ($n = 3,855$) showed that the combination of adapalene 0.1% with BPO results in a synergistic effect, defined as a benefit of the combination that exceeds the sum of benefits from adapalene and BPO monotherapy [21]. At as early as one week, adapalene/BPO was significantly more effective than the respective monotherapies ($p < 0.05$) and the synergistic effect continued throughout the duration of the studies [21].

Clinical efficacy for the complete acne spectrum

Step therapy, strategies to optimize tolerability, and patient education

Adapalene 0.1% in several formulations (gel, lotion, cream), adapalene 0.3% gel, and fixed-dose combination adapalene 0.1%/BPO 2.5% and 0.3%/BPO 2.5% gels are available for treatment of acne. This variety of formulations and concentrations allows clinicians to implement step therapy as appropriate to accommodate patients' clinical presentations and preferences [23]. For very young patients and those with mild acne, clinicians may elect to prescribe adapalene 0.1% monotherapy. Higher concentration monotherapy and fixed-dose combinations can be effectively utilized for moderate-to-severe disease. Fixed-dose combinations can be a good choice for patients such as teenagers who may have a lower likelihood of adhering to therapy. In our clinical judgment, it is reasonable to try a fixed-dose combination of adapalene 0.3%/BPO 2.5% for patients with moderate-to-severe acne who are reluctant to use oral antibiotic therapy. Systemic therapy can be added for severe disease or if results are not acceptable. Further, clinicians may utilize a higher concentration of product to clear acne and then step-down to a lower concentration or monotherapy to maintain results.

To optimize tolerability, clinicians can utilize alternative dosing strategies such as reducing frequency to every other day and using a cleanser twice daily and a moisturizer at least once daily to prevent dryness and scaling [11, 13, 24]. Adapalene has been described as the best tolerated topical retinoid and 2.5% is the lowest and best tolerated concentration of BPO that is marketed [25]. However, strategies to improve tolerability at initiation of therapy may be used for patients with known sensitive skin or who experience irritation.

Educational efforts need not be onerous to the clinician. Creation of a basic fact sheet can help patients to know what to expect of their acne therapy in terms of time to effect and the potential for irritation. They should understand that irritation–which can consist of burning, redness, or stinging–is most likely to occur during the initiation of therapy, and that it is mild and diminishes with continuing therapy for most people. Patients should be educated to apply a thin film of adapalene 0.3%/BPO 2.5% once daily on the entire affected area (not including eyelids, lips, or mucous membranes) and to avoid spot treatment. To improve general skin care, clinicians are advised to suggest two to three acceptable non-aggressive cleansers and moisturizers for patients. Use of sun protection measures, such as an oil-free sunscreen and protective hat/clothing, are also recommended.

Severe acne

The assessment of moderate-to-severe acne is based on a multidimensional continuum and there is no universally accepted definition of where to start and stop. In the context of clinical trials, the validated investigator global assessment (IGA) defines moderate as involvement of more than half the face, with many acne lesions and up to one small nodule, while severe acne involves the entire face and may include a few nodules [26]. There are few efficacious topical therapies for severe acne, and for many years, clinicians would include an oral antibiotic for treatment of moderate-to-severe acne [11]. For both patient convenience and to reduce potential selective pressure on the microbial flora, there was interest in discovering a topical therapy strong enough to improve severe inflammatory acne [11].

Adapalene 0.3%/BPO 2.5% fixed-dose combination therapy

Weiss *et al*. first evaluated fixed-dose combination adapalene 0.3%/BPO 2.5% in patients with severe inflammatory acne and a very high number of lesions at baseline (mean: 109-114 total lesions), and reported that adapalene 0.3%/BPO 2.5% was superior to vehicle based on lesion count reduction and IGA success rates (score of 0/1 with at least Grade 2 improvement) [13]. While the study was not formally powered to compare the two active arms, adapalene 0.3%/BPO 2.5% had greater efficacy than adapalene 0.1%/BPO 2.5%. The IGA success rate with adapalene 0.3%/BPO 2.5% was 20.1% higher than vehicle (31.9% vs 11.8%, $p = 0.029$) but adapalene 0.1%/BPO 2.5% showed a treatment difference vs vehicle of 8.8% ($p = 0.443$). The authors noted that the enhanced efficacy of adapalene 0.3%/BPO 2.5% was "not surprising given its strong anti-inflammatory activity". In addition, adapalene 0.3%/BPO 2.5% was well tolerated, demonstrating a safety profile comparable to adapalene 0.1%/BPO 2.5% with one patient discontinuing due to adverse events in each of the adapalene/BPO groups and none in the vehicle groups [13]. Dose-related adverse events occurred in 19.8% of those in the adapalene 0.3%/BPO 2.5% group, 15.2% of the adapalene 0.1%/BPO 2.5%, and 20.5% of those in the vehicle groups. Adverse events considered treatment related were reported in 1.9% (two patients) in the adapalene 0.3%/BPO 2.5% group, 0.3% in the adapalene 0.1%/BPO 2.5% group, and 0% in the vehicle group. The authors reported that the local tolerability of the two adapalene formulations was comparable, with mean scores peaking at Week 1 and remaining below a score of 1 (mild) during the duration of the study. An every-other-day regimen was implemented for 5.7% of patients in the adapalene 0.3%/BPO 2.5% group and 2.7% in the adapalene 0.1%/BPO 2.5% group [13].

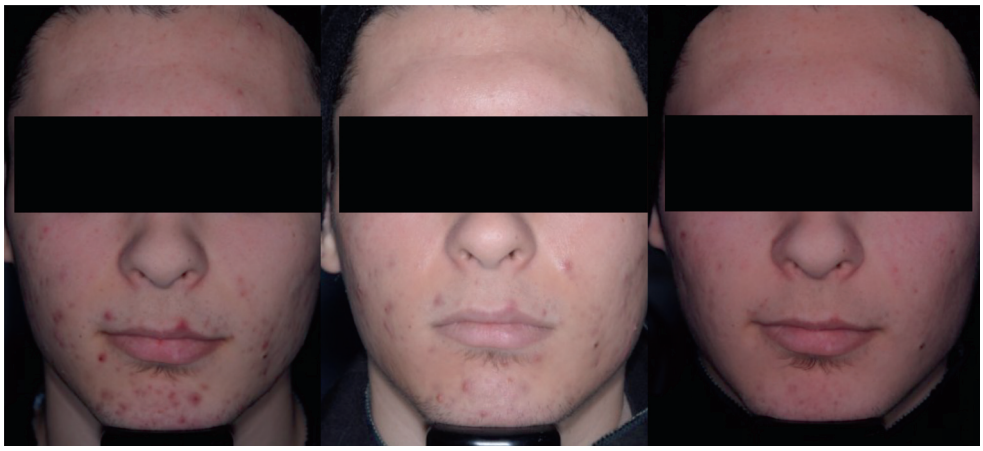

Figure 1. Patient treated with adapalene 0.3%/BPO 2.5% monotherapy (taken from Stein-Gold *et al*., with permission [11]).

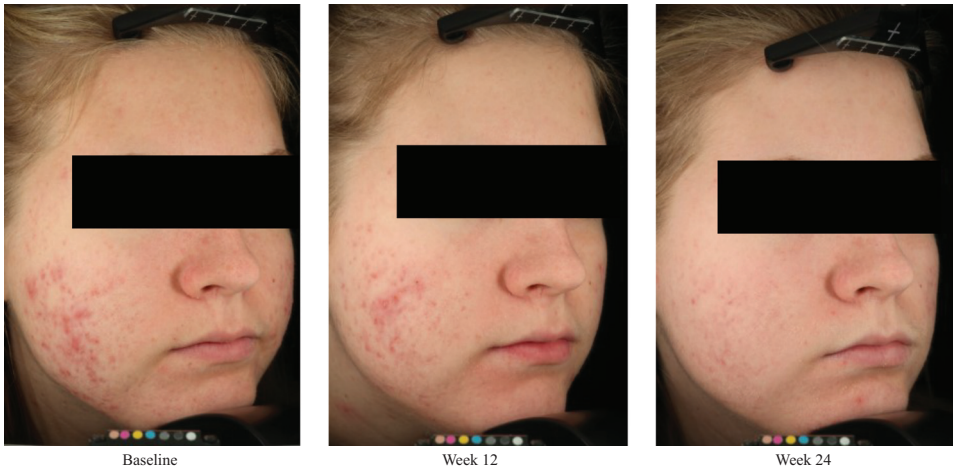

Figure 2. Clinical improvement with adapalene 0.3%/BPO 2.5% monotherapy.

Stein Gold *et al*. studied a population of patients with moderate-to-severe acne (50% moderate and 50% severe) and analysed efficacy of adapalene 0.3%/BPO 2.5% in patients with severe disease separately from those with moderate disease [11]. Adapalene 0.3%/BPO 2.5% was significantly superior to vehicle in achieving treatment success (IGA 0/1 and at least Grade 2 improvement; 33.7% vs 11.0%, $p < 0.001$) and also showed greater efficacy in reducing all acne lesion types ($p < 0.001$ for all). *Figure 1* shows two patients treated with adapalene 0.3%/BPO 2.5%; one considered a success and the other a treatment failure due to an IGA score of 3 (an improvement from Grade 4, but still moderate acne) at the study endpoint. A good safety profile was reported, and the authors noted that adapalene 0.3%/BPO 2.5% could "be an appropriate treatment, alone or in combination with other therapies, prior to the potential need for step-up treatment for oral isotretinoin" [11]. *Figure 1* shows a patient treated with adapalene 0.3%/BPO 2.5%.

Adapalene 0.3%/BPO 2.5% plus oral antibiotic

Stressing the relatively limited treatment options for patients with severe acne, Kircik *et al*. studied adapalene 0.3%/BPO 2.5% plus anti-inflammatory dose doxycycline (40 mg: 30 mg immediate release and 10 mg delayed-release formulation) in an open-label study of 20 patients with severe acne [27]. At Week 12, 95% of study patients had a ≥Grade 2 improvement in IGA score [27]. In the context of severe disease, lesion reductions were significant by Week 4 and continued through Week 12; nodules were also resolved, with 70% of subjects having no nodules vs 20% at baseline [27]. Overall, adapalene 0.3%/BPO 2.5% therapy was well tolerated and no serious adverse events occurred [27]. This is consistent with the study of Del Rosso *et al*., who found adapalene 0.3%/BPO 2.5% plus oral doxycycline (100 mg) to be an effective and safe treatment option for severe inflammatory acne in patients before starting treatment with oral isotretinoin or as an alternative when isotretinoin could not be used [28]. The latter study included 186 patients who were isotretinoin candidates at baseline (as judged by investigators) due to severe inflammatory acne. Over the course of 12 weeks, combination therapy with oral doxycycline and adapalene 0.3%BPO 2.5% achieved IGA success (clear or almost clear) in 37.1% of patients ($p < 0.0001$). In addition, 90.2% of patients reported moderate or better improvement in their acne and 83.2% were satisfied/very satisfied with the results of their

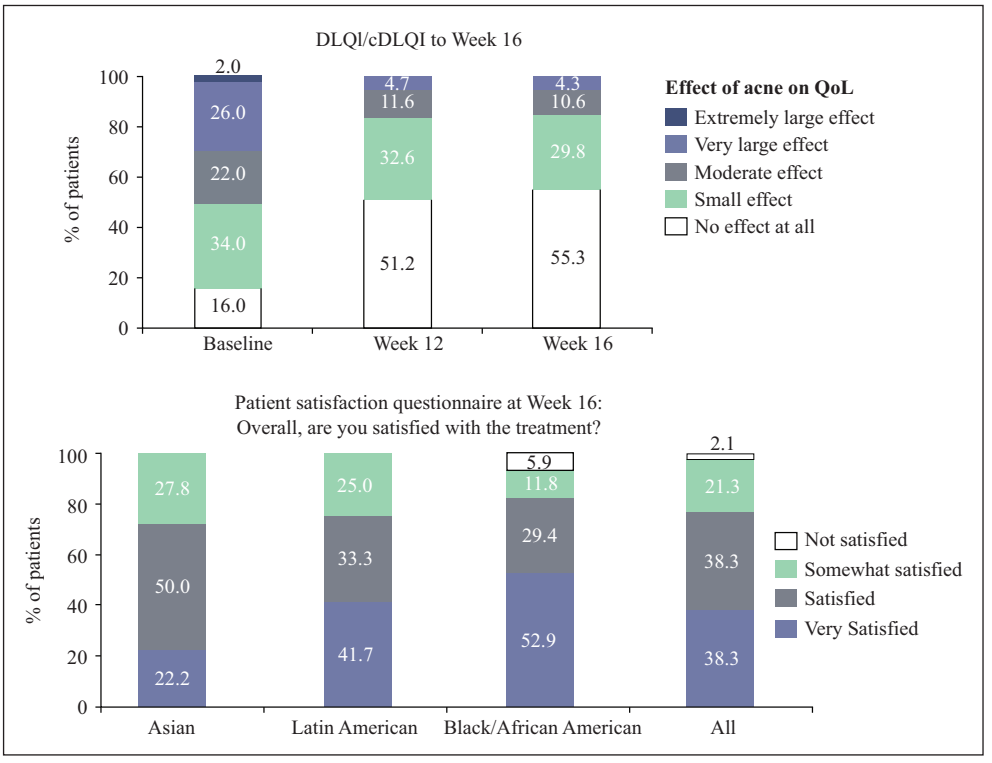

Figure 3. Patient-reported outcomes with adapalene 0.3%/BPO 2.5% monotherapy in patients with skin of colour (taken from DuBois *et al*., with permission [30]).

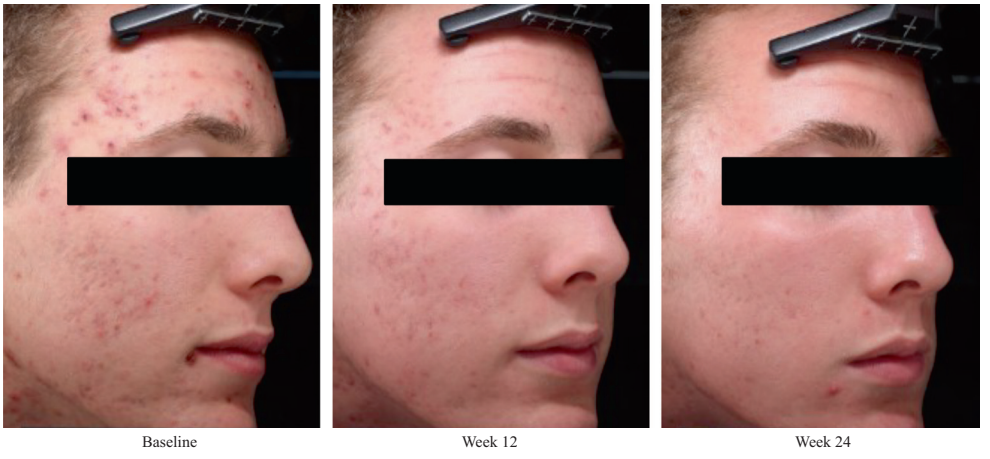

Figure 4. Effect of adapalene 0.3%/BPO 2.5% monotherapy on atrophic acne scars and acne lesions over a 24-week period.

treatment. At four weeks, 41.9% of patients were no longer deemed candidates for isotretinoin and by 12 weeks, only 19.9% were considered to have acne severe enough for isotretinoin. The combined treatment regimen was also judged safe and well-tolerated [28]. *Figure 2* shows an example of clinical improvement.

Efficacy across demographic groups

Adapalene 0.3%/BPO 2.5% has proven efficacy across a broad range of demographics, including ethnic background, age group, gender, and skin phototypes [10, 29, 30]. A high level of satisfaction with adapalene 0.3%/BPO 2.5% was reported in patients of Asian, Latin-American, or Black/African-American ethnicities with moderate-to-severe acne ($n = 50$) in an open-label, 16-week interventional Phase IV study [30]. Patients reported that their treatment was associated with good tolerability and improved quality of life (*figure 3*). The treatment was efficacious, resulting in 56% of patients with success on IGA (clear/almost clear) and improvement or clearance of post-inflammatory hyperpigmentation in 75% of patients. Stein-Gold *et al*. evaluated Phase 3 study data to determine whether the efficacy of adapalene 0.3%/BPO 2.5% was affected by age or gender, and reported equal effectiveness and safety in younger (12-17 years old) vs older

(≥18 years) patients and for both genders [29]. Similarly, Alexis *et al*. reviewed Phase 3 data and found adapalene 0.3%/BPO 2.5% to be safe and effective in patients with moderate-to-severe acne across all Fitzpatrick skin phototypes, assuring clinicians that this fixed-dose combination is a good choice for the large majority of patient types [10]. Adapalene 0.3%/BPO 2.5% may not be a good choice for patients sensitive to either adapalene or BPO.

Beneficial effects on acne sequela: scarring and PIH

Acne is associated with facial scarring, particularly when it is not effectively treated at an early timepoint after onset [31]. The ability of fixed-dose combination adapalene 0.3%/BPO 2.5% to prevent and reduce the occurrence of atrophic acne scarring in patients with mostly moderate acne and mild scars was shown by Dréno *et al*. [31, 32]. Over a 24-week duration (Part 1 of the study which employed a split-face methodology to compare adapalene 0.3%/BPO 2.5% vs vehicle), the scar count decreased by 21.7% in patients treated with adapalene 0.3%/BPO 2.5% but increased by 14.4% with vehicle, with an approximately 30% difference between the groups ($p < 0.0001$). Part 2 of the study was an open-label extension phase for an additional 24 weeks during which adapalene 0.3%/BPO 2.5% was applied to the entire face ($n = 45$) [32]. Treatment with adapalene 0.3%/BPO 2.5% was associated with greater rates of success based on scar global assessment (clear/almost clear) and excellent reductions in acne lesion counts were also seen (*figure 4*). Long-term treatment was safe and well-tolerated, with the most common treatment-related adverse events being dry skin (4.4%) and skin irritation (4.4%) [32]. The authors noted that an "additional improvement in atrophic scar count with 48 weeks of A0.3/BPO2.5 treatment, compared to delayed application at 24 weeks, highlights the importance of early initiation of effective acne treatment to prevent and reduce the formation of acne scars" [32]. The action of adapalene 0.3%/BPO 2.5% on atrophic acne scars is perhaps not surprising, since A/BPO 0.1%/2.5% was also shown to reduce the risk of scarring, and A/BPO 0.3%/2.5% is more potent [33]. Adapalene 0.3% alone was also shown to improve acne scarring in patients with a past history of scars and moderate-to-severe facial atrophic acne scars [34]. After 24 weeks of treatment with adapalene 0.3% once daily for four weeks and twice daily for 20 weeks, >80% of subjects reported improvements in skin texture/atrophic scars, and 50% of investigator assessments judged improvements in texture/scarring. Further, the adapalene-treated patients reported an improved quality of life [34]. The European EMA included scar data in the labelling for adapalene 0.3%/BPO 2.5%, and it may be used to manage patients with acne and scarring in this setting.

Recently, the Personalizing Acne: Consensus of Experts (PACE) panel published recommendations for management of acne sequelae based on a modified Delphi approach [35]. The group noted that acne sequelae cause a substantial burden to patients, stressing that acne-induced scarring may affect from 43% to 90.8% of patients, and can occur even with mild or moderate acne severity. Since patients can have a disproportionate perception of scarring severity, the panel recommended that clinicians should assess risk of acne-induced scarring in patients at diagnosis and discuss acne sequelae at that time and continue to review the topic with patients frequently. To help manage patients' expectations about scarring, PACE suggests providers discuss concerns about the disease and its treatment with patients, emphasize that improvement is likely to be visible only over the long-term, be realistic, highlight the need for good control of acne to reduce risk of scarring, and educate about modifiable risk factors such as excoriation and medication adherence. For treatment, the PACE group recommended "early aggressive therapy with combination regimes targeting acne pathophysiology" that include topical retinoids to prevent scarring [35]. They note that there is data indicating that retinoids may help repair acne-induced atrophic scars in the absence of primary lesions (as discussed above) and that "fixed-dose combinations such as adapalene/BPO have synergistic effects on acne lesions and mitigation of acne scars" [35].

Conclusions: the role of adapalene 0.3%/BPO 2.5% in therapy today

Adapalene 0.3%/BPO 2.5% is a good therapeutic option for moderate-to-severe acne vulgaris, offering clinicians a potent treatment that has proven utility for a variety of patient demographics and across a spectrum of disease severity. It is an antibiotic-sparing regimen, which is important for a disease that frequently requires relatively long treatment periods to maintain good control. For these reasons, adapalene 0.3%/BPO 2.5% is a therapy recommended for all degrees of severity of moderate-to-severe acne, in combination with short-term oral antibiotic therapy, as needed, and a maintenance therapy, as recommended by the recent National Institute for Health and Care Excellence (NICE) guidelines. Adapalene at both 0.3% and 0.1% concentrations has been consistently well tolerated; and the fixed-dose combination of adapalene/BPO also has excellent tolerability. While it has been reported that all topical retinoids approved for the treatment of acne are generally well tolerated, a recent systematic review of the literature by Kolli *et al.* found that adapalene 0.3% is better tolerated than tretinoin 0.05% or tazarotene [36, 37]. At a once-daily, fixed-dose combination, adapalene 0.3%/BPO 2.5% provides efficacy in a convenient form with dosing flexibility that contributes to good patient satisfaction.

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