Acnatac®

clindamycin 1% and tretinoin 0.025%

A novel, effective, skin-friendly fixed-dose combination topical formulation for adolescents with acne

From a satellite symposium held on June 13th, 2014 at the 12th Congress of the European Society for Pediatric Dermatology (ESPD), Kiel, Germany

MEDA

SUMMARY

Prof Vincenzo Bettoli and Prof José Luis López Estebaranz explained the key benefits of fixed-dose combination topical therapy for acne and the properties of Acnatac®, a novel fixed-dose combination containing clindamycin 1% and tretinoin 0.025%, which make it particularly suitable for the treatment of adolescents with acne.

- Fixed-dose combination topical treatments for acne have many advantages over topical monotherapies such as targeting more of the underlying pathogenic causes of acne, being more effective at clearing acne lesions, and being more convenient for patients than applying two medications separately
- Acne affects over 80% of teenagers and can cause psychological effects such as depression and anxiety, as well as personal and social difficulties due to the impact of the disease on their body image
- Acnatac® is very well suited for the treatment of adolescent acne since it is highly effective against inflammatory and non-inflammatory acne lesions in this age group with a rapid onset of action and a very good tolerability profile. In addition, Acnatac® does not cause bleaching of hair and coloured fabrics, and teenagers will find the medication to be easy to apply and handle

Speakers

Prof Vincenzo Bettoli
University of Ferrara, Italy

Prof José Luis López Estebaranz
Rey Juan Carlos University, Spain

FIXED-DOSE COMBINATION TOPICAL TREATMENTS FOR ACNE: ADVANTAGES OVER MONOTHERAPIES

Prof Bettoli

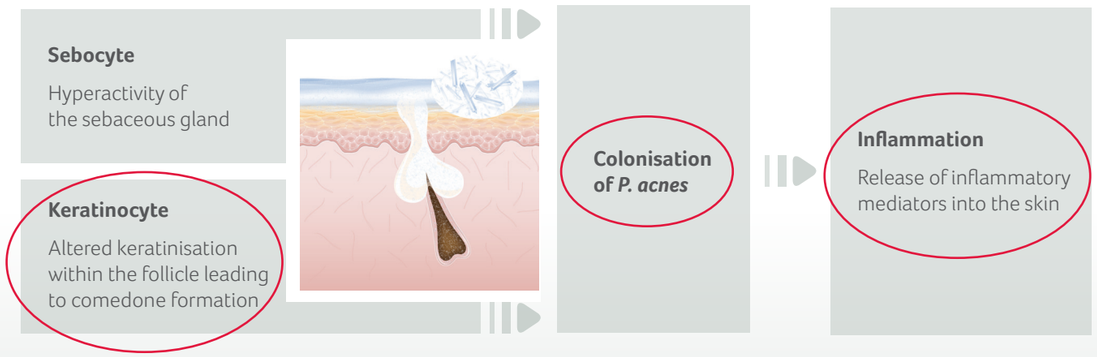
The pathogenesis of acne involves four main disease mechanisms (Figure 1):[1]

1. Hyperactivity of the sebaceous gland
2. Altered keratinisation within the follicle leading to the formation of comedones
3. Colonisation of the follicles by *Propionibacterium acnes (P. acnes)*
4. Release of inflammatory mediators into the skin

According to the lecture given by Prof Bettoli, **fixed-dose combination topical treatments** for acne which combine a retinoid with an antimicrobial agent **have several advantages** over topical monotherapies:

- The two active ingredients have **complementary mechanisms of action.** This means that the combination product is able to target more of the pathogenic factors of acne than either monotherapy alone. Retinoids normalise desquamation within the follicle and inhibit the formation of microcomedones, whereas antibiotics inhibit the growth and activity of *P. acnes.* In addition, both retinoids and antibiotics have direct and indirect anti-inflammatory effects. **Ultimately, by targeting three out of the four pathogenic factors of acne, the combination of these two active ingredients results in faster and more complete eradication of acne lesions (Figure 1).[1]**

Figure 1. Pathogenic factors of acne targeted by topical retinoid / antibiotic fixed-dose combination treatments for acne



- **They are more convenient for patients than applying two medications separately.** This improves adherence with the treatment regimen which subsequently translates into improved clinical outcomes.[2] Adherence with acne treatments is currently a major issue with approximately 50% of acne patients having poor adherence with their medication and **adolescents being a high-risk group for non-adherence[3,4]**
- **They are not associated with the development of antibiotic resistant *P. acnes* in contrast to antibiotic monotherapy**

As a result of these many advantages, the **Global Alliance to Improve Outcomes in Acne Group recommends retinoid-based combination therapy for almost all patients with acne.[1]** Similarly, the **S3 guidelines from the European Dermatology Forum endorse topical retinoid and antimicrobial combinations with a high strength of recommendation for patients with mild-to-moderate papulopustular acne.[5]** Fixed-dose combinations which contain two antimicrobial agents are regarded as suboptimal since they do not contain a retinoid to target microcomedones and comedones, and so are less effective for the treatment of non-inflammatory acne lesions. In contrast, combination treatment with a topical retinoid and an antimicrobial may be considered as the cornerstone of acne management except for patients with the most severe acne.

"All kinds of acne patients can benefit from the use of a topical retinoid or retinoid-based combination therapy except for patients with the most severe disease who are under treatment with oral isotretinoin…Fixed-dose combination products target three of the four pathogenic factors which may induce the production of acne and so the clearance of lesions is faster than with the individual products." Prof Bettoli

ACNATAC®: A NEW TOPICAL FIXED-DOSE FORMULATION WELL SUITED FOR THE TREATMENT OF ADOLESCENT ACNE

Prof López Estebaranz

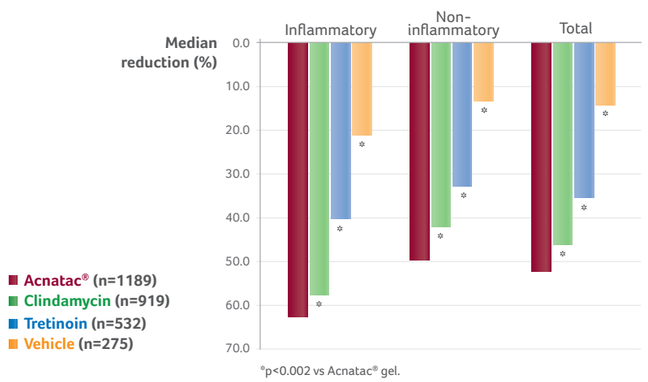
Acnatac® is a novel fixed-dose combination topical treatment for acne containing clindamycin 1% (as clindamycin phosphate 1.2%) and tretinoin 0.025% in an aqueous-based alcohol-free gel. Acnatac® was recently approved in Europe for the treatment of patients with acne when comedones, papules and pustules are present,[6] although it has been available in the US since 2006. This disease affects over 80% of teenagers and can have a profound impact on these patients' quality of life causing personal and social difficulties due to the impact of the disease on their body image and psychological effects such as depression and anxiety.[7-9] **Of particular concern for adolescents, acne can lead to facial scarring in up to 20% of affected patients.**[10]

The clinical efficacy and safety of Acnatac® in acne was investigated in three multicentre, randomised, double-blind, parallel group 12-week studies involving over **4500 patients** in total, 2915 of whom were adolescents.[11,12] The results from these studies revealed that Acnatac® is highly suited for the treatment of adolescents with acne.

1. *Acnatac® is highly effective at treating acne in adolescents*

A pooled analysis of data from the three pivotal clinical studies of Acnatac® showed that this fixed-dose combination product was **significantly more effective at reducing inflammatory, non-inflammatory and total acne lesions** than its constituent monotherapies and vehicle in adolescents with acne (Figure 2).[12] Twelve weeks of Acnatac® treatment led to a 50–60% reduction in inflammatory and non-inflammatory acne lesions.

Figure 2. Lesion reduction with Acnatac® versus its components in adolescents



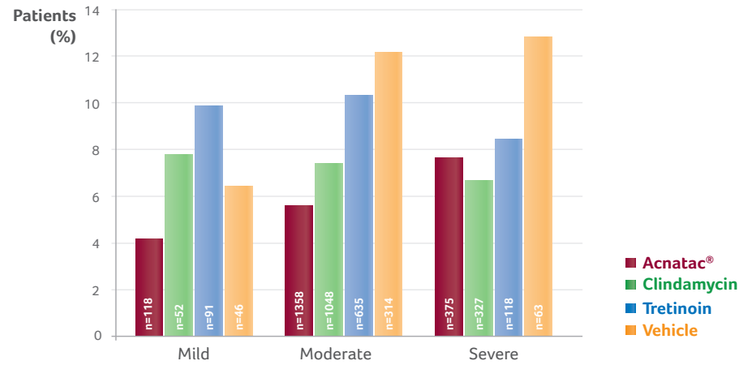
2. *Acnatac® has a rapid onset of action*

Teenagers with acne want to see rapid results when they start treatment for their acne and are typically impatient for results. If treatments are not rapidly effective, adolescents may prematurely discontinue with their treatment regimen. An analysis of data from the Acnatac® pivotal studies showed that Acnatac® has a rapid onset of action in the overall population of patients that was studied. **Acnatac® was shown to be 6 weeks faster than tretinoin at treating inflammatory lesions and 10 weeks faster than clindamycin at treating non-inflammatory lesions.**[13]

3. *Acnatac® does not cause acne flaring*

Adolescents do not want to use acne treatments which exacerbate their skin condition, even if the worsening in acne is only transient. Of note, the results in the overall population of patients investigated in the **clinical studies of Acnatac® showed that this fixed-dose combination treatment is not associated with acne flaring, or a transient increase in the number of inflammatory lesions during the first few weeks of treatment, which can be a particular problem with topical retinoid monotherapy** (Figure 3).[14] In this analysis, acne flaring was defined as a 20% or greater increase in inflammatory lesion count at week 2 of treatment. Tretinoin-induced acne flaring was only observed in the subset of patients with mild acne (i.e., acne flaring in the subgroup of patients with mild acne who were treated with tretinoin was greater than with vehicle).

Figure 3. Acnatac® does not induce acne flaring

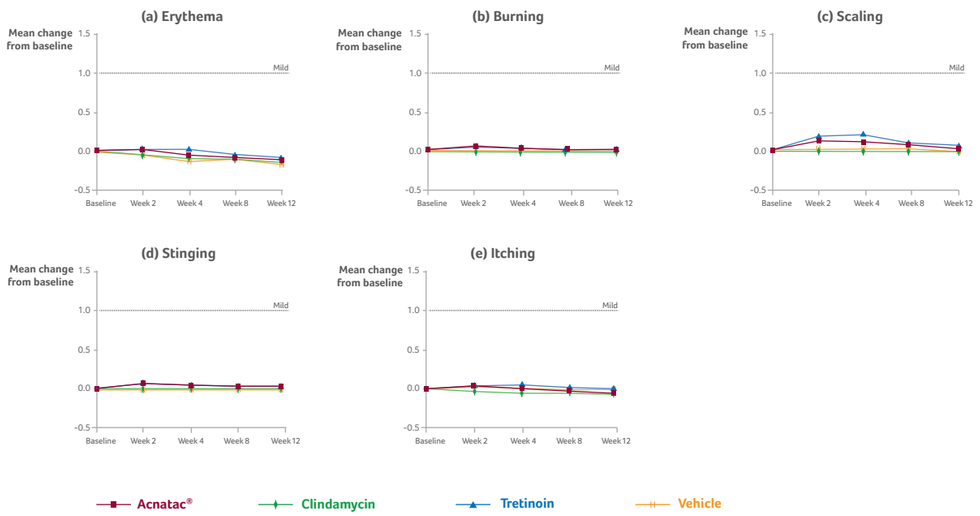


4. *Acnatac® is safe and well tolerated due to its unique formulation*

Adolescents want acne treatments which are safe and well tolerated, and in particular desire treatments which do not cause additional skin irritation or redness. An analysis of the tolerability data from the overall population investigated in the pivotal studies of Acnatac® revealed that this fixed-dose combination has very good tolerability with no new safety concerns compared with its individual constituents. Local skin reactions such as erythema, burning, scaling, stinging and itching were mild and not different between the treatment groups (Figure 4).[12]

The low levels of cutaneous irritation associated with Acnatac® are due to its unique formulation. This formulation is a water-based gel, which is less irritating than an alcohol-based gel. In addition, **Acnatac® contains two forms of tretinoin: a solubilised** form which is immediately available on the skin, and a **crystalline** form which is delivered into the skin in a slow and sustained fashion.[15] Furthermore, the anti-inflammatory properties of clindamycin may also contribute to the low irritative potential of Acnatac®.[16]

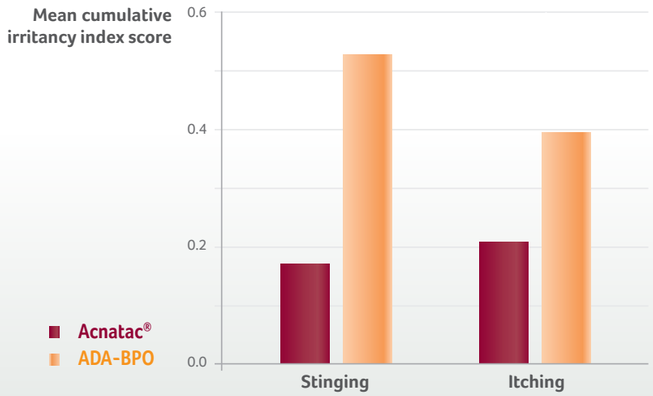
Figure 4. Tolerability profile of Acnatac®



Tolerability rated as none (0), mild (1), moderate (2) or servere (3).

The unique formulation of Acnatac® also accounts for its more favourable tolerability profile compared with other retinoid-based acne treatments. For example, **a recent head-to-head study in 24 patients over 3 weeks showed that Acnatac® leads to significantly less stinging/burning and itching compared with a fixed-dose combination of topical adapalene 0.1%/benzoyl peroxide (BPO) 2.5%** (Figure 5).[17]

Figure 5. Skin irritation with Acnatac® and adapalene 0.1% / BPO 2.5%



5. *Acnatac® has a skin-friendly formulation and is easy to handle and apply*

As mentioned above, the skin-friendly formulation of Acnatac® is well tolerated and associated with only very low levels of skin irritation. Several other features of this formulation mean that it **is likely to be preferred by adolescents to other acne treatments,** and together these characteristics may improve the adherence of adolescents to this treatment:

- The water-based gel can be **easily applied** to the skin with the fingers
- Acnatac® contains two active ingredients and is applied **once-daily** to the skin. This is likely to be **more convenient for teenagers** than having to apply two separate medications to their skin at different times of the day
- Unlike several other acne treatments, **Acnatac® does not contain BPO** which can cause a problem for many teenagers since it bleaches their hair and clothes
- Acnatac® can be **stored at room temperature,** unlike certain other acne medications which have to be stored in the fridge
- The tretinoin component of Acnatac® is **not degraded by sunlight or BPO** in contrast to other retinoid formulations

"Acnatac® is an effective fixed combination product for our acne patients. It is as effective as other fixed combinations with improved tolerability, and is easy to handle. These characteristics of this new drug improve the adherence of our patients to the treatment." Prof Estebaranz

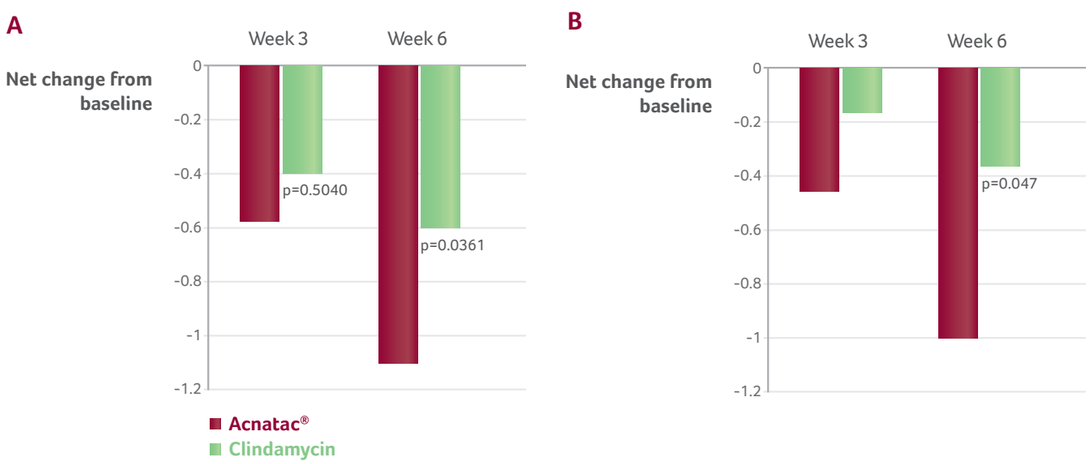
SPOTLIGHT ON ANTIBIOTIC RESISTANCE

Antimicrobial resistance due to antibiotic monotherapy for acne is a significant and growing global problem. Antibiotic resistant strains of *P. acnes* have been isolated from over 90% of acne patients.[18,19] The presence or development of antibiotic resistant bacteria can substantially reduce the efficacy of topical antibiotics for acne and may lead to a disease relapse.[1]

The Global Alliance to Improve Outcomes in Acne Group has issued several recommendations to limit the development of antibiotic resistance. These include **avoiding the use of antibiotic monotherapy, and instead using combinations of topical retinoids together with topical antimicrobial agents to treat acne patients.**[1]

A recent study demonstrated that **Acnatac® is more effective against clindamycin-resistant *P. acnes* than clindamycin monotherapy** (Figure 6A), and was also more effective against highly-resistant *P. acnes* (Figure 6B). This study was an open-label, split-face, 6-week investigation in which 22 patients with clindamycin-resistant *P. acnes* applied Acnatac® or clindamycin 1% once-daily to either the left or right-side of their face.[20]

Figure 6. Effect of Acnatac® and clindamycin against (A) all clindamycin-resistant *P. acnes* and (B) highly-resistant *P. acnes (log/cm²)**



*Minimum inhibitory concentration ≥ 512 µg/mL.

Since tretinoin is not known to have an antimicrobial effect, these results suggest that the topical retinoid in Acnatac® increases the concentration of clindamycin within the subcutaneous follicles.

References:

1. Thiboutot D, Gollnick H, Bettoli V, *et al.* New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. J Am Acad Dermatol. 2009;60:S1-50.
2. 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;86:103-108.
3. Dreno B, Thiboutot D, Gollnick H, *et al.* Large-scale worldwide observational study of adherence with acne therapy. Int J Dermatol. 2010;49:448-456.
4. Baldwin HE. Tricks for improving compliance with acne therapy. Dermatol Ther. 2006;19:224-236.
5. Nast A, Dreno B, Bettoli V, *et al.* European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol. 2012;26 Suppl 1:1-29.
6. Acnatac®. Summary of Product Characteristics.
7. Rademaker M, Garioch JJ, Simpson NB. Acne in schoolchildren: no longer a concern for dermatologists. BMJ. 1989;298:1217-1219.
8. Kubota Y, Shirahige Y, Nakai K, Katsuura J, Moriue T, Yoneda K. Community-based epidemiological study of psychosocial effects of acne in Japanese adolescents. J Dermatol. 2010;37:617-622.
9. Klassen AF, Newton JN, Mallon E. Measuring quality of life in people referred for specialist care of acne: comparing generic and disease-specific measures. J Am Acad Dermatol. 2000;43:229-233.
10. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet. 2012;379:361-372.
11. Schlessinger J, Menter A, Gold M, *et al.* Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. J Drugs Dermatol. 2007;6:607-615.
12. Dreno B, Bettoli V, Ochsendorf F, *et al.* Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies. Eur J Dermatol. 2014;24:201-209.
13. Dreno B, Layton A. Onset of action and efficacy of novel clindamycin 1% / tretinoin 0.025% formulation for acne vulgaris. Presented at AAD 2013 Poster 6406.
14. Leyden JJ, Wortzman M. A novel gel formulation of clindamycin phosphate-tretinoin is not associated with acne flaring. Cutis. 2008;82:151-156.
15. Del Rosso JQ, Jitpraphai W, Bhambri S, Momin S. Clindamycin phosphate 1.2%- tretinoin 0.025% gel: vehicle characteristics, stability, and tolerability. Cutis. 2008;81:405-408.
16. Del Rosso JQ, Schmidt NF. A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. Cutis. 2010;85:15-24.
17. Goreshi R, Samrao A, Ehst BD. A double-blind, randomized, bilateral comparison of skin irritancy following application of the combination acne products clindamycin/tretinoin and benzoyl peroxide/adapalene. J Drugs Dermatol. 2012;11:1422-1426.
18. Ross JI, Snelling AM, Carnegie E, *et al.* Antibiotic-resistant acne: lessons from Europe. Br J Dermatol. 2003;148:467-478.
19. Dumont-Wallon G, Moyse D, Blouin E, Dreno B. Bacterial resistance in French acne patients. Int J Dermatol. 2010;49:283-288.
20. Leyden JJ. In vivo antibacterial effects of tretinoin-clindamycin and clindamycin alone on Propionibacterium acnes with varying clindamycin minimum inhibitory. J Drugs Dermatol. 2012;11:1434-1438.

Acnatac®

clindamycin 1% and tretinoin 0.025%

MEDA