

# **EuroGuiDerm Evidence-based Guideline for the Treatment of Acne – long version**

(ICD L70.0, L70.1)

## **Update 2025**

### **Long version**

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## List of abbreviations

ADR	adverse drug reaction
BPO	benzoyl peroxide
CY	cyst
HRQoL	Health Related Quality of Life
IL	inflammatory lesions
IPL	intense pulsed light
LE	level of evidence
ne	no evidence
NIL	non-inflammatory lesions
NO	nodule
PDT	photodynamic therapy
PROMS	Patient Reported Outcome Measures
sys.	systemic
TL	total lesion
top.	topical
UV	ultraviolet
vs.	Versus

## 1 Disclaimer

The EuroGuiDerm guideline was developed in accordance with the EuroGuiDerm Methods Manual v1.3, which can be found on the website of the European Dermatology Forum (EDF), subsection EuroGuiDerm/EDF Guidelines <https://www.guidelines.edf.one/guideline-methods>. This work is licensed under the Creative Commons Attribution-NonCommercial- 4.0. For further information on copyright in case of translation, adaptation, commercial use etcetera, see EDF website. Copyright © European Dermatology Forum.

These evidence- and consensus-based guidelines contain recommendations that were developed to assist clinicians in the care of patients in specific clinical conditions. The recommendations are based on the available evidence and their development followed a pre-specified, standardized process. Nevertheless, guidelines do not replace the clinicians' knowledge and skills, since guidelines never encompass therapy specifications for all medical decision-making situations. Guidelines should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. Deviation from the recommendations may be justified or inevitable in specific situations. The ultimate judgment regarding patient care must be individualized and must be made by the physician and patient in the light of all presenting circumstances.

Safety aspects that were considered within these guidelines do not represent a comprehensive assessment of all available safety information for the included interventions. They are limited to those aspects chosen for evaluation and the information available in the included clinical trials. Readers must carefully check the information in these guidelines and determine whether the recommendations (e.g. regarding dose, dosing regimens, contraindications, or drug interactions) are complete, correct, up-to-date and appropriate.

European guidelines are intended to be adapted to national or regional circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Particularly, the approval situation/availability/reimbursement of the different treatment options has to be adapted to the national situation. Thus, the national medical societies associated adopting European

Guidelines will be responsible for the adoption and implementation of the guidelines on a national level.

## 2 Introduction

Nast

### I. Notes on use

This guideline is an update of the 2016 edition (1). Sections that have been added or modified in response to the prioritized key questions are highlighted in blue text.

### II. Accompanying documents:

The EuroGuiDerm Guideline for the Treatment of Acne Methods report & Evidence tables are available as supplementary files and on the EDF website: <https://www.guidelines.edf.one/guideline-methods>.

### III. Funding

The development of this EuroGuiDerm guideline was funded through the EuroGuiDerm Centre for Guideline Development. The European Dermatology Forum (EDF) is responsible for fundraising and holds all raised funds in one account. The EuroGuiDerm Team is not involved in fundraising or in the decision making on which GL/CS development is funded. The decisions on which GL/CS is funded are made by the EuroGuiDerm Board of Directors independently. The EDF or any other body supporting guideline work is never involved in the development of this guideline and had no say on its content or focus.

## 2.1 Objectives of the guideline

*The general objectives of the acne guidelines are:*

### ***Improvement in the care of acne patients***

The idea behind this guideline is that recommendations based on a systematic review of the literature and a structured consensus process will improve the quality of acne therapy in general. Personal experiences and traditional therapy concepts should be critically evaluated and replaced, if applicable, with the consented therapeutic recommendations. In particular, a correct choice of therapy should be facilitated by presenting the suitable therapy options in a therapy algorithm, taking into account the type of acne and the severity of the disease.

### ***Reduction of serious conditions and scarring***

As a result of the detailed description of systemic therapies for patients with severe acne, reservations about these interventions should be overcome to ensure that patients receive the optimal therapy. With the timely introduction of sufficient therapies, the development of serious post-acne conditions, severe scarring and adverse psychosocial impact should be reduced.

### ***Promotion of adherence***

Good therapeutic adherence is key to treatment success. Adherence is facilitated by knowledge of the product being used, for example treatment duration, the expected onset of effect, the sequence of the healing process, the maximal achievable average effect, expected adverse events, and the benefit to quality of life.

### ***Reduction of antibiotic resistance***

The use of topical and systemic antibiotics should be optimized by using appropriate combinations for a predefined duration, in order to reduce the development of antibiotic resistance.

For this targeted update, the group selected 3 key questions, that were perceived as the most relevant questions to be dealt with in the update:

- 1)
  - a) "For which types of acne and patient groups should isotretinoin be recommended versus systemic antibiotics, and with what strength of recommendation?"
  - b) "For what duration can treatment with systemic antibiotics be administered?"
- 2) "For which types of acne and patient groups should hormonal treatments and spironolactone be recommended, and with what strength of recommendation?"
- 3) "For which types of acne and patient groups should the new acne treatments (trifarotene and clascoterone) be recommended, and with what strength of recommendation?"

## **2.2 Target population**

### **Health care professionals**

This guideline has been developed to help health care professionals provide optimal therapy to patients with mild, moderate or severe acne. The primary target groups are dermatologists and other professionals involved in the treatment of acne, such as paediatricians and general practitioners. The target group may vary with respect to national differences in the distribution of services provided by specialists or general practitioners.

### **Patients**

The recommendations of the guideline refer to patients who suffer from acne. These are mainly adolescents treated in outpatient clinics. The appropriate therapy option is presented according to the type of acne that is present. The primary focus is the induction therapy of facial acne, recommendations also encompass patients with more widespread acne affecting the trunk (see chapter 2.5). Non-primary target groups are patients with special forms of acne, such as, occupational acne, chloracne and acne neonatorum.

## **2.3 Pharmacoeconomic considerations**

European guidelines are intended for adaptation to national conditions. It is beyond the scope of this guideline to take into consideration the specific costs and reimbursement situations in every European country. Differences in prices, reimbursement systems, willingness and ability to pay for medication among patients and the availability of generics are too large. Therefore, pharmacoeconomic considerations will have to be taken into account when guidelines are developed at national and local levels.

The personal financial and health insurance situation of a patient may necessitate amendments to the prioritisation of treatment recommendations. However, if financial resources allow, the suggested ranking in the therapeutic algorithm should be pursued.

## 2.4 Considerations with respect to vehicle for topical treatments

The skin type, the sex, age and stage of disease has to be taken into consideration when choosing the vehicle for topical treatments. The efficacy and safety/tolerability of topical treatments are influenced by the choice of vehicle.

## 2.5 Considerations regarding area of involvement

The face is the primary region of interest for the treatment of acne. Appearance, scarring, quality of life and social stigmatization are important considerations when dealing with facial dermatological diseases.

The recommendations of this guideline apply primarily to the treatment of facial acne. More widespread involvement will certainly favour earlier use of a systemic treatment due to the efficacy and practicability of such treatments.

## 2.6 Clinical features and variants

Layton

Acne (synonym “acne vulgaris”) is a polymorphic chronic inflammatory skin disease nearly always affecting the face (99 %) and clinically presents with open and/or closed comedones and inflammatory lesions including papules, pustules and nodules. Scarring and acne-induced hyperpigmentation are frequently seen clinical sequelae in acne. It also commonly affects the back (up to 60 %) and chest (up to 15 %) (2-4). Seborrhoea is a frequent feature (5).

The clinical picture embraces a spectrum of signs, ranging from mild comedonal acne, with or without sparse inflammatory lesions (IL), to acne conglobata or aggressive fulminant disease with deep-seated inflammation, nodules and in some cases associated systemic symptoms.

### 2.6.1 Comedonal acne

Clinically non-inflamed lesions develop from the subclinical microcomedo which is evident on histological examination early in acne development (2). These lesions encompass both open (blackheads) and closed comedones (whiteheads) (6). Closed comedones are often inconspicuous with no visible follicular opening. Larger closed comedones of greater than 3mm diameter are known as

**macrocomedones**. Longitudinal studies have confirmed that early onset acne with mid-facial comedones as an early feature is associated with a poorer prognosis (7).

### **2.6.2 Papulopustular acne**

Most patients have a mixture of **comedonal** and inflammatory lesions (8). Inflammatory lesions arise from the microcomedo or from **comedonal** lesions and may be either superficial or deep (9). Superficial inflammatory lesions include papules and pustules (5 mm or less in diameter). These may evolve into nodules **defined as >5 mm** in more severe disease (**10 mm has also been suggested as a cut-off**). Inflammatory macules represent **early inflammatory stage of lesions or represent regressing lesions** that may persist for many weeks and contribute markedly to the general inflammatory appearance (8) **and may result in acne-induced atrophic scarring (10)**.

### **2.6.3 Nodular/ conglobate acne**

Nodules are defined as firm, inflamed lesions **>5 mm diameter (10 mm has also been suggested as a cut-off (11)) and are often tender on palpation (11)**. They may extend deeply and over large areas, frequently resulting in painful lesions, exudative sinus tracts and tissue destruction. Conglobate acne is a rare but severe form of acne found most commonly in adult males with few or no systemic symptoms. Lesions usually occur on the trunk and upper limbs and frequently extend to the buttocks. In contrast to ordinary acne, facial lesions are less common. The condition often presents in the second to third decade of life and may persist into the sixth decade. Conglobate acne is characterized by multiple grouped comedones **sometimes with fistular arrangement** amidst inflammatory papules, tender, suppurative nodules which commonly coalesce to form sinus tracts. Extensive and disfiguring scarring is frequently a feature.

### **2.6.4 Other acne variants**

There are several severe and unusual variants or complications of acne as well as other similar diseases. These include acne fulminans, drug induced acne, gram-negative folliculitis, mechanical acne, oil/ tar acne, chloracne, acne in neonates and infants and late onset, persistent acne, sometimes associated with

genetic or iatrogenic endocrinopathies. The current guidelines do not lend themselves to comprehensive management of all of these variants.

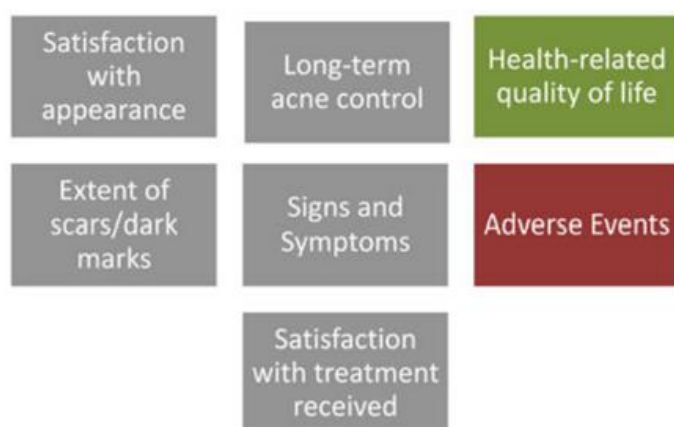
### 3 Assessment, comparability of treatment outcomes

Layton

#### 3.1 Acne grading

Acne can be largely assessed from two perspectives: objective disease activity (based on measurement of visible signs) and quality of life impact. There are other aspects of measurement, such as [site and extent of disease](#), [sebum amount and constituents](#), colonisation by *Cutibacterium acnes* (*C. acnes*) [[previously known as Propionibacterium acnes](#)] and associated microbial dysbiosis, [development of scarring and/](#) or economic impact [which all contribute to overall severity](#).

Accurately assessing outcomes from therapy is notoriously difficult in acne (12). Many different approaches have been adopted but very few are validated. The inconsistent application of a standard method for assessing acne severity challenges interpretation of results from interventional studies. There are detailed reviews and reflections on this subject by Lehmann et al. (13), Barratt et al. (14), Witkowski et al. (15), Thiboutot et al. (16), Gollnick et al. (17) and Tan et al. (18). The Acne Core Outcome Research Network (ACORN) has identified 7 core outcome domains through a Delphi consensus (see Figure 1 below). These are now informing areas for assessment with the potential for development and adoption of future tools for use in clinical practice and trials (19).



**Figure 1:** Core outcome domains in acne (modified after Layton et al. 2017) (19)

Proper lighting, appropriate patient positioning and prior facial skin preparation (gentle shaving for men, removal of make-up for women) are helpful in facilitating accurate assessment. Palpation in addition to visual inspection may also help define lesions more accurately.

Mechanisms to assess acne lesions using digital multimodal imaging are being evaluated but have not yet been accepted or validated for use in clinical practice (20). Patient reported outcomes are now also being considered as an important part of overall assessment (21). However, the most frequently used outcome measures to assess acne involve grading or counting. These evaluations can be further divided into: (i) an evaluation according to the predominant lesion type; (ii) evaluations of separate individual lesions; (iii) overall or ‘global’ assessment. Lesion counts are essential for clinical trials as they offer a reliability not evident in global assessment, however counting remains impractical for use in the day-to-day clinic (22) and does not accurately reflect overall severity (23). In systematic reviews, global grading has been used as an efficacy measure in up to 62% of acne trials (13, 14) and the USA Food and Drug Administration (FDA) has mandated global grading as one of two efficacy measures in which superiority must be demonstrated for approval of acne therapies (23). However, no one global system has been established as a standard: some utilize quantitative measures e. g. lesion counts and numeric ranges and others are based on qualitative descriptions.

### **3.1.1 Acne grading systems**

#### **3.1.1.1 Sign-based methods**

Despite a range of methods being used to measure acne in the 1960’s and 1970’s, it was the Leeds technique (8) that dominated acne measurement for a [long time](#). The Leeds technique included two methods; the grading technique and the counting technique. The grading technique allocated patients a grade from 0 to 10, with seven subgroups between 0 and 2. Photographic guides illustrating each grade are given, but the importance of also palpating lesions is stressed. The experience on which this system was based stemmed from the pre-isotretinoin era, and acne of the severity described by grades above 2 is now rarely seen. The counting technique involves the direct counting of non-inflamed and inflamed lesions, including superficial papules and pustules, deep inflamed

lesions and macules. The revised Leeds acne grading system (24) includes numerical grading systems for the back and chest as well as for the face.

The Echelle de Cotation des Lésions d'Acne (ECLA) or “Acne Lesion Score Scale” system has demonstrated good reliability (25). However, ECLA scores do not correlate with quality of life scores and the use of both disease and quality of life scores is suggested (26).

Persisting hyperpigmentation after active acne has settled is of great concern to many patients. An instrument to measure this has been described, the post acne hyperpigmentation index (PAHPI) (27).

### **3.1.1.2 Global assessment techniques**

Global assessment scales incorporate the entirety of the clinical presentation into a single category of severity. Each category is defined by either photographs with a corresponding numeric scale or by descriptive text. Grading is a subjective task, based on observing dominant lesions, evaluating the presence or absence of inflammation, which is particularly difficult to capture, and estimating the extent of involvement. Global methods are much more practically suited to clinical practice. In clinical investigations, they should be combined with lesion counts as a co-primary endpoint of efficacy (28). A simple photographic standard-based grading method using a 0-8 scale has been successfully employed in several clinical trials (29).

A very simple classification of acne severity was described in the 2003 report from the Global Alliance for better outcome of acne treatment (17). This basic classification was designed to be used in a routine clinic, and its purpose was to map treatment advice onto common clinical presentations. For each acne descriptor a first-choice therapy is advised, with alternatives for females and maintenance therapy. There are five simple descriptors: mild comedonal, mild papulopustular, moderate papulopustular, moderate nodular, and severe nodular/conglobate. A series of eight photographs span and overlap these five descriptors. Different facial views and different magnifications are used, reducing the comparability of the images.

In 2005, the FDA proposed an investigator global assessment (IGA) that represented a static quantitative evaluation of overall acne severity. To accomplish

this, they devised an ordinal scale with five severity grades, each defined by distinct and clinically relevant morphological descriptions that they hoped would minimise inter-observer variability. Indeed, the more detailed descriptive text has resulted in this system being considered to provide even greater reliability than previous global assessments (23).

The Comprehensive Acne Severity System (CASS) was developed by extending a pre-existing 6-category facial IGA scale, ranging from clear through to very severe grading, to include the chest and back (30). This has been validated and provides a global system that includes a restricted number of categories to allow for a practical and comprehensive approach when assessing treatment outcomes.

In order to give treatment recommendations based on disease activity, the EU Guideline group has considered how best to classify acne patients. It has used the following simple clinical classification:

1. Comedonal acne
2. Mild - moderate papulopustular acne
3. Severe papulopustular acne, moderate nodular acne
4. Severe nodular acne, conglobate acne

Other already existing systems are very difficult to compare with one another. The group has tried to map the existing systems to the guidelines' clinical classification. However, in many cases the systems do not include corresponding categories and often it has to be considered an approximated attempt rather than a precise mapping (Table 1).

**Table 1:** Comparison of different acne assessment scales. This is an attempt to approximately map the various published acne classifications to the simple four group classification used in this guideline.

Publication	Comedonal acne	Mild-moderate papulo-pustular acne	Severe papulopustular acne, moderate nodular acne	Severe nodular acne, conglobate acne
Pillsbury 1956 (31)	-	1 - 4	2 - 4	2 - 4
Kligman 1976 (32)	1 = < 10 2 = 10-25 3 = > 25-50 4 = > 50	-	-	-

Publication	Comedonal acne	Mild-moderate papulo-pustular acne	Severe papulopustular acne, moderate nodular acne	Severe nodular acne, conglobate acne
	(facial comedones)			
Michaelsson 1977 (33)	-	0 - 30	20 - 30	20 - >30
Cook 1979 (29)	0 - 1	2 - 4	6	8
Wilson 1980 (34)	0	2 - 4	6 - 8	8
Allen 1982 (35)	0 - 2	2 - 6	6	8
Burke (Leeds) 1984 (8)	0.5	0.75 - 2	2 - 3	3 - 8
Pochi 1991 (28)	Mild	Mild/moderate	Moderate	Severe
O'Brien (Leeds) 1998 (face) (24)	1 - 3	4 - 7	8 - 10	11 - 12, nodulocystic
Dreno 1999 (25)	F1R1 - 5	F1Is1 - 4	F1Is4 - 5, F1Ip 1 - 4	F1Ip 4 - 5
Lehmann 2002 (13)	Mild	Mild/moderate	Severe	Severe
Gollnick 2003 (17)	Mild comedonal	Mild papular-pustular, moderate papular-pustular	Moderate nodular	Severe nodular/conglobate
FDA's IGA for acne vulgaris (2005) (23)	1 Almost clear: rare NIL with no more than 1 papule	2 Mild: some NIL but no more than a few papule/pustule	3 Moderate: many NIL, some IL no more than 1 nodule	4 Severe: up to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions
Del Rosso 2007 (3)	-	Mild	Moderate	Severe
Tan 2007 (30)	-	Mild: 0-5 papules-pustules	Moderate: 6-20 papules - pustules	Severe: 21-50 papules - pustules, Very severe: >50 IL Severe
Hayashi 2008 (36)	-	Mild 0-5 Papules and pustules	Moderate 6-20 Papules and pustules	Severe 21-50 papules and pustules >50 very severe
Layton 2010 (37)	-	Mild	Moderate	Severe
Dreno 2011 (38)	0-5	Mild 1-2	Moderate 2-4	Severe 5

### 3.1.1.3 Quality of life methods

The use of Patient Reported Outcome Measures (PROMS) and Health Related Quality of Life (HRQoL) tools to capture the impact of acne as well as the impact of treatment on the patient's life as a means of supporting the identification of those vulnerable to psychological complications is of great importance. Adopting a HRQoL measure as an integral part of acne management is now routinely recommended. In order for quality of life measures to be used more frequently in routine clinical work, they need to be easy to use, the scores need to be

meaningful, and they need to be readily accessible. It is possible to measure the impact of acne on quality of life using several questionnaires. There are acne-specific, dermatology-specific and generic measures, which can be used across all diseases.

Acne specific measures include [ComPAQ and ComPAQ-SF \(39\)](#) and the “Assessments of the Psychological and Social Effects of Acne” (APSEA) questionnaire (40, 41), [both of which capture facial and truncal acne](#), the Cardiff Acne Disability Index (42, 43) the Acne Quality of Life Scale (AQOL) (44), the Acne-specific Quality of Life Questionnaire (Acne-QoL) (45) and the short version of this, the Acne-Q4 (46). A recent novel patient reported outcome measure, the Acne Symptom and Impact Scale (ASIS) seeks to capture both symptoms and impacts of facial acne (47, 48).

[Of measures available it has been suggested that 2 PROMs can currently be recommended for use in acne clinical studies: The Acne-Q and CompAQ. Evidence on content validity and other measurement properties were lacking for all PROMs; further research investigating the quality of remaining acne-specific, dermatology-specific, and generic HRQoL PROMs is required to recommend their use \(49\).](#)

[Another study suggested high internal consistency \(Cronbach's alpha 0.74-0.96\) and reliability \(intraclass correlation coefficient values 0.88-0.97\) for both Skindex-16 and CompAQ and better construct validity when compared with Acne-QoL. However, qualitative data uncovered wide-ranging views regarding usability and acceptability with no PROM showing superior usability and acceptability. The authors confirmed that any PROM should be acceptable for further research in adult acne but researchers should consider the different domains and whether they will measure only facial or facial and truncal acne before making a selection \(50\).](#)

Dermatology specific measures used in acne include the Dermatology Life Quality Index (DLQI) (51-53), the Children’s Dermatology Life Quality Index (CDLQI) (54) and Skindex-29, -16 (55). Generic measures used in acne include the SF-36 (56) and the General Health Questionnaire (56). [The Skindex-16 has recently been shown to be reliable and a valid instrument for measuring quality of life among patients with acne. Some floor and ceiling effects were noted for the](#)

symptoms and functioning domain, therefore the authors concluded that it is also possible that items in these domains may have less relevance for patients with acne or may be less sensitive among those with milder severity (57). Further validation work is on-going with other measures.

In addition, it is possible to measure the secondary impact of acne on the lives of partners and other family members, using a dermatology specific measure, the Family Dermatology Life Quality Index (58) and a generic measure, the Family Reported Outcome Measure (FROM-16) (59).

Patient satisfaction with treatment is also an important aspect to consider. ACORN have recently assessed the adapted use of DermSat-7 in acne and it to be an effective tool in a cross-sectional study for measuring treatment satisfaction, particularly effectiveness and overall satisfaction domains, among patients with acne. Further research is needed to examine additional measurement properties of the DermSat-7, such as content validity and interpretability, as well as to validate the DermSat-7 in other populations of patients with acne as this was a single centre study (60).

Acne also affects functional abilities. Patients are prone to embarrassment and social withdrawal, depression, anxiety and anger. The combined use of QoL and psychosocial questionnaires is essential to adequately understand just how severely the disease is affecting a patient, and can aid in assessing the efficacy of therapy and justifying clinical decisions. In patients with a severe impact on their quality of life, a more aggressive therapy may be justified.

## **3.2 Prognostic factors that should influence treatment choice**

### **3.2.1 Prognostic factors of disease severity**

A number of prognostic factors relating to more severe disease should be considered when assessing and managing acne. These are outlined and evidenced in review papers published by Holland and Jeremy 2005 (61) and Dréno et al. 2006 (62) and include family history, course of inflammation, persistent or late-onset disease, hyperseborrhoea, androgenic triggers, truncal acne and/ or psychological sequelae. Reported risks include family history, course of inflammation, persistent or late-onset disease, hyperseborrhoea, androgenic triggers, truncal acne and/ or psychological sequelae and in some cases certain foods, alcohol

and smoking have shown a positive correlation. Previous infantile acne may also correlate with resurgence of acne at puberty and early age of onset with mid-facial comedones, early and more severe seborrhoea and earlier presentation relative to the menarche are all factors that should alert the clinician to increased likelihood of more severe acne.

### **3.2.2 The influence of the assessment of scarring/ potential for scarring on disease management**

Acne scarring, albeit mild, has been identified in up to 95 % of patients attending a dermatology clinic (63). [Scarring usually follows deep-seated inflammatory lesions, but may also occur as a result of more superficial inflamed lesions in scar-prone patients.](#) Scars may show increased collagen (hypertrophic and keloid scars) or be associated with collagen loss (atrophic scars: more frequent) (64). The duration of inflammation relates to scar production hence a delay in appropriate management is more likely to result in significant scarring (30, 63).

Acne scarring should always be included in the assessment of acne severity. Scars can produce significant disfigurement and psychosocial impairment in their own right with increased negative psychosocial impact (65, 66) and stigmatization (67). The difficulty in evaluation of acne scars is manifold and clinical assessment of scars demonstrates significant variation between assessors (68). Several different systems have been described to evaluate acne scars (see Table 2). Other techniques have been employed in an attempt to quantify scarring at specified time points in relation to treatment. These include ultrasound (69) surface profilometry using silicone imprints (70), standardized photography (71), and three dimensional in vivo microtopography measurements (72), dermoscopy, reflectance confocal microscopy and optical coherence tomography and optical coherence tomography (73).

A recent COSMIN review identified 3 PROMS to assess acne scarring (74).

However, to date no single validated method to evaluate the extent or volume deficiency of acne scars has been uniformly adopted for use in routine clinical practice.

The presence of scarring should support aggressive management and therapy should be commenced early in the disease process.

**Table 2:** Acne scar severity grading systems, \*PROMs for acne scarring assessment

Acne Scar System	Severity Scheme	Regional Relevance
Leeds (63)	Numeric (Maximum 30 for each region)	Face, chest and back
Echelle d'Evaluation Clinique des Cicatrices d'Acne (75)	Numeric (maximum 540)	Face
Qualitative Global Acne Scarring Grading System (76)	Four descriptive grades	Face, chest and back
Quantitative Global Acne Scarring Grading System (77)	Numeric (maximum 84)	Face
Patient and Observer Scar Assessment Scale (POSAS) (78)	Numeric (maximum 50 observer/maximum 60 patient)	Face
New evidence-based facial acne scar evaluation tool (FASET) to assess atrophic scars (79)	Global, Dispersion, Numeric	Face
*Acne-Q Scar Subscale (PROM)	10-item scale	Face
*Facial Acne Scar Quality of Life Scale (FASQoL) (PROM)	10-item scale	Face
*Self-assessment Acne Related Scars (SCARS) (PROM)	5-item scale	Face

Of the three PROMS identified in the recent review (74), each PROM was found to have adequate development and sufficient content validity. The Acne-Q Scar subscale was also found to have sufficient structural validity, internal consistency, reliability, and construct validity. The FASQoL was also found to have sufficient construct validity. No studies evaluated responsiveness or measurement invariance.

## 4 Epidemiology and pathophysiology

### 4.1 Epidemiology

Degitz/ Ochsendorf

Acne is regarded as one of the most frequent skin diseases [worldwide \(80\)](#). Epidemiologic studies in Western industrialized countries estimated the prevalence of acne in adolescents to be between 50% and 95%. If mild manifestations were excluded and only moderate or severe manifestations were considered, the frequency was still 20% - 35% (81-84). Acne [involves the sebaceous follicle](#). It is a disease primarily of adolescence (80). It is triggered in children by the initiation of androgen production by the adrenal glands and gonads. It may begin as early as age 7-9 (85) and usually subsides after the end of growth. However, to some degree, acne may persist beyond teen age in a significant proportion of individuals (86). Acne scars and hyper- or hypopigmentation are not uncommon long-lasting negative outcomes [of acne \(16, 87\)](#). Genetic factors have been recognized. There is a high concordance among identical twins, and [a family history of acne strongly correlates with the likelihood of developing acne and also with disease severity \(88, 89\)](#). Multiple genes [appear to be](#) involved in acne predisposition. [Genome-wide association studies have identified susceptibility loci associated with inflammation, androgen metabolism, or tissue remodelling \(90\)](#). Environmental factors also appear to be of relevance for acne prevalence. [A high glycemic load diet and dairy products are associated with worsening the development of acne \(91\)](#). However, at present there is not enough evidence to support specific diets for treating acne beyond recommending a “balanced diet” (92, 93).

### 4.2 Pathophysiology

Dréno/ Gollnick

Acne is an androgen-dependent disorder of pilosebaceous follicles (or pilosebaceous unit). There are four primary pathogenic factors, which interact to produce acne lesions: 1) increased sebum production by the sebaceous gland, 2) alteration in the follicular keratinization process, 3) [skin microbiome dysbiosis involving](#)

the bacterium *C. acnes*, with a shift toward the more inflammatory IA1 phylotype, and 4) release of inflammatory mediators.

Patients with seborrhoea and acne have a significantly greater number of lobules per gland compared with unaffected individuals (the so-called genetically prone “Anlage”). Inflammatory responses occur prior to the hyperproliferation of keratinocytes. [By cyanoacrylate strips and confocal microscopy, it was demonstrated that there is a significant higher number of microcomedones in clinically normal skin of acne patients compared to healthy subjects \(94-96\).](#) Interleukin-1 $\alpha$  up-regulation contributes to the development of comedones independent of the colonization with *C. acnes*. A relative linoleic acid deficiency has also been described [\(97-102\).](#)

Sebaceous lipids are regulated by peroxisome proliferator-activated receptors which act in concert with retinoid X receptors to regulate epidermal growth and differentiation as well as lipid metabolism. Sterol response element binding proteins mediate the increase in sebaceous lipid formation induced by insulin-like growth factor-1. Substance P receptors, neuropeptidases,  $\alpha$ -melanocyte stimulating hormone and corticotrophin-releasing hormone (CRH)-R1 are also involved in regulating sebocyte activity as are the ectopeptidases, such as dipeptidylpeptidase IV and aminopeptidase N. The sebaceous gland in particular acts as an endocrine organ in response to changes in androgens and other hormones with [a start at puberty.](#) Dihydrotestosterone is the most potent hormone to stimulate sebocytes in acne prone areas. The critical enzyme in the metabolic pathway is 5- $\alpha$  Reductase isoenzyme 1. Adrenal DHEA-S is hormonal active but can also be a stimulator of IL-2 driven T-cells and, therefore, driving the inflammatory process (103). Oxidized squalene can stimulate hyperproliferative behaviour of keratinocytes, and lipoperoxides produce leukotriene B<sub>4</sub>, a powerful chemoattractant. [Mature sebocytes release their lipid content through a programmed cell death process mediated by the active DNase 2 enzyme, delivering the lipids programmed cell death process via the sebaceous duct into the infrainfundibulum \(104\).](#)

Microcomedones, macules and further developed visible lesions of acne produce chemotactic factors and promote the synthesis of tumour necrosis factor- $\alpha$  and interleukin-1 $\beta$ . Another cytokine, IL-17 has been identified as potentially playing

an important role in addition to IL-1 $\beta$  in acne (105). Cytokine induction by *C. acnes* occurs through Toll-like receptor (TLR) 2 activation via activation of nuclear factor- $\kappa$ B and activator protein 1 (AP-1) transcription factor. *C. acnes* activates also Protease activated Receptor (PAR) 2. (106) Both TLR and PAR belong to the innate immune system and play a crucial role in the modulation and duration of inflammation of acne lesions in association with antimicrobial peptides (107). Activation of AP-1 induces matrix metalloproteinase genes, the products of which degrade and alter the dermal matrix and could be a central factor in the development of acne scars.

The skin microbiome is also involved: a dysbiosis of the *C. acnes* population is seen. Data suggest a shift in *C. acnes* phylotypes and a reduction in *C. acnes* diversity in acne patients compared to healthy individuals. This shift is characterized by an absolute decrease in phylotypes IB and II and a relative increase in phylotype IA1 among acne patients. Such changes promote the presence of strains with higher pro-inflammatory activity, thereby exerting a stronger impact on innate immunity (108-113). *C. acnes* as a therapeutic target has become questionable following studies showing that not all follicles are colonized by *C. acnes*. While *C. acnes* cell numbers are not increased in acne compared to healthy skin, the *C. acnes* phylotype shift correlates with the severity and progression of the condition (114). Recently, it could be shown that *C. acnes* induces the activation of the inflammasome, resulting in IL-1 $\beta$  secretion (115).

Furthermore, new findings on the role of growth factors such as IGF-1 in the regulation of sebocytes have demonstrated that transcriptional factors such as FOXO1 can interact with PPAR gamma and sebocyte differentiation and proliferation and may give some hint to a possible role of diets in the daily practice of acne patients. However, it could be shown that those growth factors also upregulate TLR 2 and 4. This means that not only *C. acnes* is a key for upregulating TLR's (116). Finally, GATA6, which is expressed in the upper pilosebaceous unit of normal human skin, is down-regulated in acne. GATA6 controls keratinocyte proliferation and differentiation to prevent hyperkeratinisation of the infundibulum, which is the primary pathological event in acne (117).

The improved understanding of acne development on a molecular level suggests that acne is a disease that involves the androgen hormone and growth hormone

axis, and, to some degree, the closely interacting innate and adaptive immune systems with a predominant role for innate immunity in the regulation of inflammatory events.

## 5 Methods - Assessment of evidence

For further details please see methods report.

Many different grading systems for assessing the quality of evidence are available in the field of guideline development. The EuroGuiDerm methods manual suggests the use of the GRADE approach (118-120). However, as this guideline is an update of an already existing guideline (1, 121) not developed with GRADE so far, a complete switch to the GRADE system was not possible due the limitation of funding. The previous methodological approach was refined whenever necessary, with new and more appropriate methodological tools being incorporated (for example Cochrane Risk of Bias tool 2, AMSTAR 2 tool)..

### 5.1 Risk of bias and methodological quality (update 2025)

The authors used the Cochrane Risk of Bias tool 2 (122) to assess risk of bias in randomized controlled trials. For evaluating the methodological quality of systematic reviews, the authors used the AMSTAR 2 tool (123).

### 5.2 Grade of evidence (quality of individual trial) (update 2016)

The available literature was evaluated with respect to the methodological quality of each single trial. A grade of evidence was given to every individual trial included:

- A Randomized, double-blind clinical trial of high quality (e. g. sample-size calculation, flow chart of patient inclusion, intention-to-treat [ITT] analysis, sufficient sample size)
- B Randomized clinical trial of lesser quality (e. g. only single-blind, no ITT)
- C Comparative trial with severe methodological limitations (e. g. not blinded, very small sample size)

### 5.3 Level of evidence (quality of body of evidence to answer a specific question) (update 2016)

When looking at a specific question (e. g. efficacy of BPO relative to adapalene) the available evidence was summarized by aligning a level of evidence (LE), as

our criteria were combined with the definition of GRADE (124) as used in the 2011 acne guideline version:

1	<b>Further research is very unlikely to change our confidence in the estimate of effect.</b> At least two trials are available that were assigned a grade of evidence A and the results are predominantly consistent with the results of additional grade B or C studies.
2	<b>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</b> At least three trials are available that were assigned a grade of evidence B and the results are predominantly consistent with respect to additional grade C trials.
3	<b>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</b> Conflicting evidence or limited amount of trials, mostly with a grade of evidence of B or C.
4	<b>Any estimate of effect is very uncertain.</b> Little or no systematic empirical evidence; included trials are extremely limited in number and/ or quality.

#### 5.4 Consensus process (update 2025)

All recommendations were agreed on in an online consensus conference using a formal and structured consensus methodology. The consensus conference was moderated by Prof. Dr. med. Alexander Nast. All nominated experts were entitled to vote in the consensus conference, but the votes of experts with relevant conflicts of interest were deducted.

In order to weigh the different recommendations, the group assigned a “strength of recommendation” grade (see box below). The strength of recommendation considered all aspects of the treatment decision, such as efficacy, safety, patient preference, and the reliability of the existing body of evidence (level of evidence).

##### **Strength of recommendation**

In order to grade the recommendation a “standardized guideline language” was used:

- 1) High strength of recommendation: is strongly recommended
- 2) Medium strength of recommendation: can be recommended
- 3) Low strength of recommendation: can be considered
- 4) Open recommendation: a recommendation for or against treatment X cannot be made at the present time.
- 5) Negative recommendation: is not recommended

## **6 Induction therapy**

### **Summary of therapeutic recommendations <sup>1</sup> for induction therapy**

Recommendations are based on available evidence and expert consensus. Available evidence and expert voting led to classification of strength of recommendation.

Overview of Recommended Treatments by Acne Type				
Acne Type	Comedonal <sup>3</sup>	Mild to moderate papulopustular	Severe papulopustular/ moderate nodular	Severe nodular/ conglobate <sup>13</sup>
<b>High strength of recommendation<sup>1</sup></b> “is strongly recommended”	-	Top. Adapalene + BPO (f.c.) <i>or</i> BPO + Clindamycin (f.c.) <sup>5</sup>	Syst. Isotretinoin	Syst. Isotretinoin
<b>Medium strength of recommendation<sup>1</sup></b> “can be recommended”	Topical retinoid <sup>4</sup>	Top. Azelaic acid <i>or</i> top. BPO <i>or</i> top. Retinoid <sup>4</sup> <i>or</i> top. Clindamycin + Tretinoin (f.c.) <sup>5,6</sup> <i>or</i> Systemic Antibiotic <sup>5,7,8</sup> + top. Adapalene <sup>9</sup>	Systemic Antibiotic <sup>5,8</sup> + top. Adapalene <sup>9</sup> <i>or</i> Systemic Antibiotic <sup>5,8</sup> + top. Trifarotene <sup>9</sup> <i>or</i> Systemic Antibiotic <sup>5,8</sup> + top. Azelaic acid <sup>10</sup> <i>or</i> Systemic Antibiotic <sup>5,8</sup> + top. Adapalene + BPO (f.c.)	Systemic Antibiotic <sup>5,8</sup> + top. Azelaic Acid <i>or</i> Systemic Antibiotic <sup>5,8</sup> + top. Adapalene + BPO (f.c.)
<b>Low strength of recommendation<sup>1</sup></b> “can be considered”	Top. Azelaic acid <i>or</i> top. BPO	Blue Light <i>or</i> oral Zinc <sup>17</sup> <i>or</i> Systemic Antibiotic <sup>5,7,8</sup> + top. Azelaic Acid <sup>10</sup> <i>or</i> Systemic Antibiotic <sup>5,7,8</sup> + top. Adapalene + BPO (f.c.) <sup>11</sup> <i>or</i> Systemic Antibiotic <sup>5,7,8</sup> + top. BPO <sup>12</sup> <i>or</i> Topical Erythromycin + Isotretinoin (f.c.) <sup>5</sup> <i>or</i> Topical Erythromycin + Tretinoin (f.c.) <sup>5</sup>	Systemic Antibiotic <sup>5,8</sup> + top. BPO <sup>12</sup>	Systemic Antibiotic <sup>5,8</sup> + top. Adapalene <sup>9,11</sup> <i>or</i> Systemic Antibiotic <sup>5,8</sup> + top. Trifarotene <sup>9</sup> <i>or</i> Systemic Antibiotics <sup>5,8</sup> + top. BPO <sup>11</sup>
<b>Alternatives for females<sup>2</sup></b>	-	Syst. Spironolactone <sup>14</sup> + other systemic <sup>16</sup> and/or + topical treatment as indicated	Hormonal antiandrogenic contraceptives or other hormonal combined contraceptives (see Table 21) <sup>15</sup> + other systemic and/or + topical treatment as indicated <i>or</i> Spironolactone <sup>14</sup> + other systemic <sup>16</sup> and/or + topical treatment as indicated	Hormonal antiandrogenic contraceptives or other hormonal combined contraceptives (see Table 21) <sup>15</sup> + other systemic and/or topical treatment as indicated <i>or</i> Spironolactone <sup>14</sup> + other systemic <sup>16</sup> and/or + topical treatment as indicated
<p><sup>1</sup> Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e. g. financial resources/ reimbursement limitations, legal restrictions, availability, drug licensing).</p> <p><sup>2</sup> Low strength of recommendation</p> <p><sup>3</sup> The recommendation for comedonal treatment passed with vote of 60% agreement only, see chapter 3 for more details.</p> <p><sup>4</sup> Adapalene to be preferred over tretinoin/ isotretinoin (see chapter 6.1), trifarotene is also recommended with a medium strength of recommendation, however, there is insufficient head-to-head trial data to clearly assess its position among the other topical retinoids.</p>				

- 5 Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.
- 6 The fixed combination (f.c.) of clindamycin/tretinoin shows comparable efficacy and safety to the fixed combination (f.c.) BPO/clindamycin, downgrading to a medium strength of recommendation was done based on general concerns with respect to the development of antibiotic resistance
- 7 In case of more widespread disease/ moderate severity, initiation of a systemic treatment can be recommended.
- 8 Doxycycline and lymecycline (see chapter 6.4)
- 9 Only studies found on systemic AB + adapalene or antibiotic (AB) + trifarotene; topical isotretinoin and tretinoin can be considered for combination treatment based on expert opinion
- 10 Indirect evidence from nodular and conglobate acne and expert opinion
- 11 Indirect evidence from severe papulopustular acne
- 12 Indirect evidence from a study also including chlorhexidine, recommendation is additionally based on expert opinion
- 13 Systemic treatment with corticosteroids can be considered
- 14 Off-label treatment
- 15 Partially off-label treatment for acne, as approval varies by region and specific intervention
- 16 Caution is advised when combining spironolactone and other systemic treatments
- 17 in the included clinical trials, dosages of 60-200 mg zinc gluconate or 220-411 mg zinc sulphate 1x/day for 3 months were used.

Abbreviations: BPO: Benzoyl peroxide, IPL: Intense Pulsed Light, PDT: Photodynamic Therapy, UV: Ultraviolet, f.c.: fixed combination, top.: topical use, syst.: systemic use

For the definition of strength of recommendation and approval rates during voting see methods report.

## 6.1 Treatment of comedonal acne

### 6.1.1 Recommendations for comedonal acne<sup>1</sup>

Treatment recommendations for comedonal acne					
High strength of recommendation <sup>1</sup> : <i>"is strongly recommended"</i>	Medium strength of recommendation <sup>1</sup> : <i>"can be recommended"</i>	Low strength of recommendation <sup>1</sup> : <i>"can be considered"</i>	Open recommendation: <i>"a recommendation for or against can not be made at the present time"</i>	Negative recommendation: <i>"is not recommended"</i>	Alternatives for females:
<p>Because of the general lack of direct evidence for the treatment of comedonal acne, the strength of recommendation was downgraded for all considered treatment options, starting with medium strength of recommendation as a maximum.</p>	Top. retinoid <sup>2</sup>	Top. Azelaic acid	IPL	Top./syst. antibiotics	<p>"a recommendation for or against Spironolactone<sup>4</sup> can not be made at the present time"</p>
		Top. BPO	Laser	Syst. isotretinoin <sup>3</sup>	
			PDT	Artificial ultraviolet (UV) radiation	
			Visible light	Syst. hormonal antiandrogenic contraceptives or other combined hormonal contraceptives <sup>5,6</sup>	

<sup>1</sup> Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e. g. financial resources/ reimbursement limitations, legal restrictions, availability, drug licensing).  
<sup>2</sup> Adapalene to be preferred over tretinoin/ isotretinoin, Trifarotene is also recommended with a medium strength of recommendation, however, there is insufficient head-to-head trial data to clearly assess its position among the other topical retinoids.  
<sup>3</sup> In rare cases of severe comedonal acne ("sand paper acne") that is resistant to standard therapy, systemic isotretinoin may be considered (note: this is an off-label use concerning acne severity).  
<sup>4</sup> Off-label treatment  
<sup>5</sup> Partially off-label treatment for acne, as approval varies by region and specific intervention  
<sup>6</sup> Except when the primary intent is contraception or other gynaecological indications, such as symptomatic menstrual irregularities or other endocrinological indications  
 Abbreviations: BPO: Benzoyl peroxide, IPL: Intense Pulsed Light, PDT: Photodynamic Therapy, UV: Ultraviolet, top.: topical use, syst.: systemic use  
 The recommendation for comedonal treatment passed with vote of 60% agreement only, see background text and methods report for more details.

### 6.1.2 Reasoning

**General comment:** Only one trial looks specifically at patients with comedonal acne. As a source of indirect evidence, trials including patients with papulopustular acne were used and the percentage in the reduction of non-inflammatory lesions was considered as the relevant outcome parameter. Because of the general lack of direct evidence for the treatment of comedonal acne, the strength of recommendation was downgraded for all considered treatment options, starting with medium strength of recommendation as a maximum.

Due to the usually mild to moderate severity of comedonal acne, generally a topical therapy is recommended. [In rare cases of severe comedonal acne \(for example “sand paper acne”\) that is resistant to standard therapy, systemic isotretinoin may be considered \(note: this is an off-label use concerning acne severity in this case\).](#)

The best efficacy was shown for topical retinoids, BPO and azelaic acid.

The tolerability of topical retinoids and BPO is comparable; there is a trend towards azelaic acid having a better safety/ tolerability profile than BPO and a comparable profile to adapalene (indirect evidence, see Table 15).

The fixed dose combination of adapalene with BPO shows a trend towards better efficacy against non-inflammatory lesions (NIL) when compared to BPO and a comparable efficacy when compared to adapalene (see Table 4). However, there is also a trend towards inferiority of the fixed combination with respect to the safety/ tolerability profile (indirect evidence, see Table 17).

The fixed dose combinations of [topical](#) clindamycin with BPO showed a trend towards better efficacy against NIL versus [topical](#) clindamycin and comparable efficacy versus BPO (see Table 5). With respect to the safety/ tolerability profile, the combination is comparable to its single components (indirect evidence, see Table 17).

Few and only indirect data on patient preference are available. They indicate patient preference for adapalene over other topical retinoids.

Additional pathophysiological considerations favour the use of topical retinoids (reduction of microcomedones).

### 6.1.2.1 Efficacy

See Table 3 to Table 7 for summary of efficacy data. Please see methods report for explanation of assessment strategy.

**Table 3:** Efficacy: Comedonal acne – top. therapy vs. vehicle/ top. therapy

	Vehicle (v)	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
BPO	BPO > v LE 1	BPO > aa LE 4	BPO = a LE 1	BPO = i LE 3	t ≥ BPO LE 4*
Azelaic acid (aa)	aa > v LE 1	X	a > aa LE 4	ne	t > aa LE 4
Adapalene (a)	a > v LE 1	X	X	a = i LE 4	a = t LE 1**
Isotretinoin (i)	i > v LE 1	X	X	X	i > t LE 4
Tretinoin (t)	t > v LE 1	X	X	X	X

LE=level of evidence; ne=no evidence; top.=topical

\* BPO 5% = tretinoin 0.1% (LE 4); tretinoin 0.025% > BPO 5% (LE 4)

\*\* adapalene 0.1% = tretinoin 0.025% (LE 1); tretinoin 0.05% ≥ adapalene 0.1% (LE 4); TMG 0.1% ≥ adapalene 0.1% (LE 4)

**Table 4:** Efficacy: Comedonal acne – top. antibiotics vs. vehicle/ BPO/ azelaic acid/ top. retinoids

	Vehicle (v)	BPO	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
Clindamycin (c)	c > v LE 2	BPO ≥ c LE 1	aa ≥ c LE 4*	ne	ne	t = c LE 3
Erythromycin (e)	e ≥ v LE 1	ne	aa = e LE 4	ne	e = i LE 3	ne
Nadifloxacin (n)	n > v LE 4	ne	ne	ne	ne	ne
Tetracycline (t)	ne	BPO > t LE 3	ne	ne	ne	ne

LE=level of evidence; ne=no evidence; top.=topical

\* azelaic acid 15% > clindamycin 1% (LE 4); clindamycin 1% = azelaic acid 5% (LE 4)

**Table 5:** Efficacy: Comedonal acne – top. combination therapy vs. top. therapy/ combinations

	Vehicle (v)	BPO	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)	Clin-damycin (c)	Erythromycin (e)	Adapalene-BPO (a-BPO)	BPO-clindamycin (BPO-c)	Clindamycin-tretinoin (ct)
Adapalene-BPO (a-BPO)	a-BPO > v LE 1	a-BPO > BPO LE 3	a-BPO = a LE 3	ne	ne	ne	ne	X	X	ne
BPO-clindamycin (BPO-c)	BPO-c > v LE 1	BPO-c = BPO LE 1	a = BPO-c LE 3	ne	ne	BPO-c > c LE 1	ne	BPO-c = a-BPO LE 4	X	BPO-c = ct LE 4
Clindamycin-tretinoin (ct)	ct > v LE 1	ne	ne	ne	ct = t LE 1	ct > c LE 4	ne	ne	X	X
Clindamycin-zinc (cz)	ne	ne	ne	ne	ne	cz = c LE 3	ne	ne	ne	ne
Erythromycin-isotretinoin (ei)	ei > v LE 3	ne	ne	ei = i LE 3	ne	ne	ei = e LE 3	ne	ne	ne
Erythromycin-tretinoin (et)	ne	ne	ne	ne	ne	ne	ne	ne	ne	ne
Erythromycin-zinc (ez)	ez > v LE 1	ne	ne	ne	ne	ez > c LE 4	ez ≥ e LE 3	ne	BPO-c > ez LE 4	ne

LE=level of evidence; ne=no evidence; top.=topical

**Update 2025:****Table 6:** Efficacy: Comedonal acne – top. combination therapy vs. top. therapy

NIL reduction	Vehicle (v)	Azelaic acid (aa)	Adapalene (a)	Clascoterone (cl)	Isotretinoin (i)	Tretinoin (t)	Trifarotene (tri)
Trifarotene (tr)	tri > v (see evidence report)	ne	ne	ne	ne	ne	X
Clascoterone (c)	cl > v (see methods + evidence report)	ne	ne	x	ne	ne	ne

Ne=no evidence; top.=topical

**Table 7:** Efficacy: Comedonal acne – top. combination therapy vs. top. therapy/ combinations

NIL reduction	Vehicle + placebo	Trifarotene (tri) + placebo	Vehicle (v) + system. Doxy (sDox)
Trifarotene (tri) + system. Doxycycline (sDox)	ne	ne	tri + sDox > v + sDox

NIL reduction	Vehicle + placebo	Trifarotene (tri) + placebo	Vehicle (v) + system. Doxy (sDox)
			(see methods + evidence report)

Ne=no evidence; top.=topical

## Light sources

Although in the literature search for the first version of this guideline, there were some studies for the treatment of NIL with laser and light sources, no clear recommendations could be drawn. The published evidence was very scarce.

### 6.1.2.2 Safety/ tolerability

Only one trial looked specifically at comedonal acne. It showed a superior safety/ tolerability profile for azelaic acid compared with tretinoin (LE 4) (125).

As a source of further indirect evidence, trials in patients with papulopustular acne were considered to evaluate the safety and tolerability profile of the included treatments. For a summary of the data, see chapter 6.2.3.2.

### 6.1.2.3 Patient preference

Based on a systematic review by Dressler et al. (126) there is only indirect evidence from trials including patients with mild to moderate papulopustular acne, see chapter 6.2.3.3.

### 6.1.2.4 Other considerations

Animal experiments, in the rhino mouse model in particular, have shown for decades that retinoids have a strong anti-comedonal efficacy. Clinical trials on the microcomedo, the natural precursor of comedones, have shown that retinoids significantly reduce microcomedo counts. [Additionally, study data](#) provide pathophysiological support for the use of topical retinoids for comedonal acne (127, 128).

## 6.2 Treatment of papulopustular acne

### 6.2.1 Recommendations for mild to moderate papulopustular acne<sup>1</sup>

Treatment recommendations for mild to moderate papulopustular acne					
High strength of recommendation <sup>1</sup> : “is strongly recommended”	Medium strength of recommendation <sup>1</sup> : “can be recommended”	Low strength of recommendation <sup>1</sup> : “can be considered”	Open recommendation: “a recommendation for or against can not be made at the present time”	Negative recommendation: “is not recommended”	Alternatives for females: “can be considered”
Top. Adapalene + BPO (f.c.)	Top. Azelaic acid	Blue Light	IPL	Top. antibiotics (as a monotherapy)	Syst. Spironolactone <sup>11</sup> + other syst. <sup>13</sup> and/or + top. treatment as indicated (low strength recommendation)
Top. BPO + Clindamycin (f.c.) <sup>2</sup>	Top. BPO	Oral Zinc <sup>14</sup>	Laser	Top. Erythromycin/ + zinc (f.c.)	
	Top. Retinoid <sup>7</sup>	Syst. Antibiotic <sup>2,3,4</sup> + top. Azelaic Acid <sup>8</sup>	PDT	For mild acne only: Syst. Antibiotic or syst. Isotretinoin or syst. hormonal antiandrogenic contraceptives or other combined hormonal contraceptives <sup>12</sup>	
	Top. Clindamycin + Tretinoin (f.c.) <sup>2, 6</sup>	Syst. Antibiotic <sup>2,3,4</sup> + top. Adapalene + BPO <sup>9</sup> (f.c.)	Red light		
	Syst. Antibiotic <sup>2,3,4</sup> + top. Adapalene <sup>5,6</sup>	Syst. Antibiotic <sup>2,3,4</sup> + top. BPO <sup>10</sup>			
	Syst. Antibiotic <sup>2,3,4</sup> + top. Trifaroten <sup>5,6,14</sup>	Top. Erythromycin + Isotretinoin (f.c.) <sup>2</sup>			
		Top. Erythromycin + Tretinoin (f.c.) <sup>2</sup>			

<sup>1</sup> Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e. g. financial resources/ reimbursement limitations, legal restrictions, availability, drug licensing).  
<sup>2</sup> Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.  
<sup>3</sup> Doxycycline and lymecycline (see chapter 6.4), limited to a treatment period of three months.  
<sup>4</sup> In case of more widespread disease/ moderate severity, initiation of a systemic treatment can be recommended.  
<sup>5</sup> Only studies found on systemic AB + adapalene or + trifarotene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion.  
<sup>6</sup> The f.c. of clindamycin/tretinoin shows comparable efficacy and safety to the f.c. of BPO/clindamycin; downgrading to a medium strength of recommendation was done based on general concerns with respect to the development of antibiotic resistance.  
<sup>7</sup> Adapalene to be preferred over tretinoin/ isotretinoin (see chapter 6.1). Trifarotene is also recommended with a medium strength of recommendation, however, there is insufficient head-to-head trial data to clearly assess its position among the other topical retinoids.  
<sup>8</sup> Indirect evidence from nodular and conglobate acne and expert opinion.  
<sup>9</sup> Indirect evidence from severe papulopustular acne.  
<sup>10</sup> Indirect evidence from a study also including chlorhexidine, recommendation is additionally based on expert opinion.  
<sup>11</sup> Off-label treatment  
<sup>12</sup> Partially off-label treatment for acne, as approval varies by region and specific intervention  
<sup>13</sup> Caution is advised when combining spironolactone and other systemic treatments  
<sup>14</sup> In the included clinical trials, dosages of 60-200 mg zinc gluconate or 220-411 mg zinc sulfate 1x/day for 3 months were used.  
Abbreviations: BPO: Benzoyl peroxide, IPL: Intense Pulsed Light, PDT: Photodynamic Therapy, UV: Ultraviolet, f.c.: fixed combination, top.: topical use, syst.: systemic use

### 6.2.2 Recommendations for severe papulopustular/ moderate nodular acne<sup>1</sup>

Treatment recommendations for severe papulopustular/ moderate nodular acne					
High strength of recommendation <sup>1</sup> : <i>"is strongly recommended"</i>	Medium strength of recommendation <sup>1</sup> : <i>"can be recommended"</i>	Low strength of recommendation <sup>1</sup> : <i>"can be considered"</i>	Open recommendation: <i>"a recommendation for or against can not be made at the present time"</i>	Negative recommendation: <i>"is not recommended"</i>	Alternatives for females: <i>"can be considered"</i>
Syst. Isotretinoin	Syst. Antibiotic <sup>2,3</sup> + top. Adapalene <sup>4</sup>	Syst. Antibiotic <sup>2,3</sup> + top. BPO <sup>5</sup>	IPL	Single or combined top. monotherapy	Hormonal antiandrogenic contraceptives or other hormonal combined contraceptives + other syst. and/or + top. treatment as indicated <sup>8</sup>
	Syst. Antibiotic <sup>2,3</sup> + top. Trifarotene <sup>4</sup>		Laser	Syst. antibiotics as monotherapy	
	Syst. Antibiotic <sup>2,3</sup> + top. Azelaic Acid <sup>5</sup>		PDT	Hormonal antiandrogenic contraceptives or other hormonal combined contraceptives	Syst. Spironolactone <sup>7</sup> + other syst. <sup>9</sup> and/or top. treatment as indicated
	Syst. Antibiotic <sup>2,3</sup> + top. Adapalene + BPO (f.c.)		Red light		
				Artificial UV radiation sources	

<sup>1</sup> Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e. g. financial resources/ reimbursement limitations, legal restrictions, availability, drug licensing).

<sup>2</sup> Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.

<sup>3</sup> Doxycycline and lymecycline (see chapter 6.4), limited to a treatment period of three months.

<sup>4</sup> Only studies found on systemic AB + adapalene or + trifarotene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion.

<sup>5</sup> Indirect evidence from nodular and conglobate acne and expert opinion.

<sup>6</sup> Indirect evidence from a study also including chlorhexidine, recommendation additionally based on expert opinion.

<sup>7</sup> Off-label treatment

<sup>8</sup> Partially off-label treatment for acne, as their approval varies by region and specific intervention

<sup>9</sup> Caution is advised when combining spironolactone and other systemic treatments

Abbreviations: BPO: Benzoyl peroxide, IPL: Intense Pulsed Light, PDT: Photodynamic Therapy, UV: Ultraviolet, f.c.: fixed combination, top.: topical use, syst.: systemic use

### 6.2.3 Reasoning

Monotherapy with azelaic acid, BPO or topical retinoids showed superior efficacy when compared with vehicle.

Adapalene, azelaic acid and BPO showed comparable efficacy when compared with each other. When comparing the topical retinoids (adapalene, isotretinoin and tretinoin) directly against each other, no relevant difference with respect to efficacy was seen. Some conflicting evidence to the comparability of the efficacy of the treatment options above arises, when looking at the other head to head comparisons indicating superiority of BPO over isotretinoin and tretinoin over azelaic acid.

With respect to the **topical** fixed combinations, BPO/ clindamycin shows superiority over both single components.

The three **topical** fixed combinations of adapalene/ BPO, clindamycin/ tretinoin as well as erythromycin/ isotretinoin show superiority to one of the components but not to both of the components when compared individually.

Head to head comparisons of the **topical** fixed combinations of adapalene/ BPO versus BPO/ clindamycin as well as head to head comparisons of clindamycin/ tretinoin versus BPO/ clindamycin show comparable efficacy.

Due to the serious concerns regarding the risk of developing antibiotic resistance, topical monotherapy with antibiotics is generally not recommended. The potential risk of developing antibiotic resistance was taken into consideration by the expert group. It led to a medium strength of recommendation for the **topical** fixed combination of clindamycin/ tretinoin despite comparable efficacy and safety when compared to the **topical** fixed combination of BPO/ clindamycin. The differentiation between **topical** clindamycin/ tretinoin (medium strength of recommendation) and **topical** erythromycin/ isotretinoin (low strength of recommendation) was based on evidence showing the lack of development of antibiotic resistance after 16 weeks of treatment with **topical** clindamycin/ tretinoin (129) as well as indirect evidence on stronger development of antibiotic resistance to **topical** erythromycin (130) and expert opinion on better follicular penetration and galenic of the **topical** clindamycin/ tretinoin f.c. formulation.

Monotherapy with azelaic acid, BPO, or topical retinoids showed comparable efficacy when compared with each other.

Spironolactone is an off-label treatment option used for acne in females. Depending on the selected outcome, it has been shown to have superior or comparable efficacy compared to placebo. A head-to-head trial against doxycycline showed no statistically significant difference after 4 months with regard to the Adult Female Acne Scoring Tool (AFAST) [OR 1.37 (95% CI 0.60–3.12)]. After 6 months, spironolactone showed better improvement with regard to AFAST [OR 2.87 (95% CI 1.38–5.99)], however, spironolactone was given for 6 months while doxycycline was stopped after 3 months. Both groups received topical BPO throughout the 6-month period. Adverse events were more frequent in the spironolactone group; however, these were mostly mild or moderate in severity (see also chapter 6.4.13).

For hormonal antiandrogenic contraceptives or other combined hormonal contraceptives see chapter 6.4.12 and Table 21) (note: hormonal antiandrogenic contraceptives and other combined hormonal contraceptives are partially off-label for acne, as approval varies by region and specific intervention).

For severe cases, systemic treatment with isotretinoin is recommended based on the very good efficacy seen in clinical practice.

The available evidence on safety and tolerability is extremely scarce and was considered insufficient to be used as a primary basis to formulate treatment recommendations.

The lack of standardized protocols, experience and clinical trial data mean there is insufficient evidence to recommend the treatment of papulopustular acne with laser and light sources other than blue light.

### **Choice of topical versus systemic treatment**

There are limited data comparing topical treatments with a systemic treatment or the additional effect of a combination of a topical plus systemic versus topical treatment only. Most of the available trials compare a topical antibiotic monotherapy with a systemic antibiotic monotherapy.

Issues of practicability between topical and systemic treatments must also be taken into consideration in cases of severe, and often widespread, disease.

The consensus within the expert group was that most cases of severe papulopustular acne or moderate nodular acne, will achieve better efficacy when a systemic antibiotic treatment in combination with a topical treatment or if systemic isotretinoin is used. Involvement of the trunk areas play an important role. In addition, better adherence and patient satisfaction is anticipated for systemic treatments.

### 6.2.3.1 Efficacy

See Table 8 to [Table 14](#) for summary of efficacy data. Please see methods report for explanation of assessment strategy.

**Table 8:** Efficacy: Papulopustular acne - top. therapy vs. vehicle/ top. therapy

	Vehicle (v)	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
BPO	BPO > v LE 1	BPO = aa LE 2	BPO = a LE 1	BPO > i LE 3	conflicting LE 4*
Azelaic acid (aa)	aa > v LE 1	X	aa = a LE 4	ne	t > aa LE 4
Adapalene (a)	a > v LE 1**	X	X	i = a LE 4	a = t LE 2-4***
Isotretinoin (i)	i > v LE 1	X	X	X	i = t LE 4
Tretinoin (t)	t > v LE 1	X	X	X	X

LE=level of evidence; ne=no evidence; top.=topical

\* tretinoin 0.025% > BPO 5% (LE 4); BPO 5% > tretinoin 0.1% (LE 4); BPO 5-10% = tretinoin 0.05% (LE 4)

\*\* adapalene 0.1% > placebo/vehicle (LE 1); adapalene 0.3% > placebo/vehicle (LE 1)

\*\*\* adapalene 0.1% = tretinoin 0.025% (LE 2); tretinoin 0.05% > adapalene 0.1% (LE 4); TMG 0.1% = adapalene 0.1% (LE 3)

**Table 9:** Efficacy: Papulopustular acne - top. combination therapy vs. top. therapy/ combinations

	Vehicle (v)	BPO	Adapalene (a)	Iso-tretinoin (i)	Tretinoin (t)	Clindamycin (c)	Erythromycin (e)	Adapalene-BPO (a-BPO)	BPO-clindamycin (c-BPO)	Clindamycin-tretinoin (ct)
Adapalene-BPO (a-BPO)	a-BPO > v LE 1	a-BPO = BPO LE 3	a-BPO > a LE 1	ne	ne	ne	ne	X	X	X
BPO-clindamycin (BPO-c)	BPO-c > v LE 1	BPO-c > BPO LE 4	BPO-c > a LE 3	ne	ne	BPO-c > c LE 1	ne	BPO-c = a-BPO LE 4*	X	X
Clindamycin-tretinoin (ct)	ct > v LE 1	ne	ne	ne	ct > t LE 1	ct = c LE 2	ne	ne	BPO-c = ct LE 4	X
Clindamycin-zinc (cz)	ne	ne	ne	ne	ne	cz = c LE 3	ne	ne	ne	ne
Erythromycin-isotretinoin (ei)	ei > v LE 3	ne	ne	ei > i LE 3	ne	ne	ei = e LE 3	ne	ne	ne
Erythromycin-tretinoin (et)	ne	ne	ne	ne	ne	ne	ne	ne	ne	ne
Erythromycin-zinc (ez)	ez > v LE 1	ne	ne	ne	ne	ez > c LE 4	ez ≥ e LE 3	ne	BPO-c = ez LE 4	ne

LE=level of evidence; ne=no evidence; top.=topical

\* clindamycin-BPO = adapalene-BPO after 12 weeks of treatment (LE 4); clindamycin-BPO = adapalene-BPO after 2 weeks of treatment (LE 4)

**Table 10:** Efficacy: Papulopustular acne - top. therapy vs. sys. therapy

	Isotretinoin	Clindamycin/ erythromycin/ lymecycline	Tetracycline (t)	Doxycycline (d)	Minocycline (m)
Azelaic acid (aa)	ne	ne	ne	ne	ne
BPO	ne	ne	ne	ne	BPO = m LE 3
Clindamycin (c)	ne	ne	c = t LE 1	ne	c > m LE 4
Erythromycin (e)	ne	ne	e > t LE 3	ne	ne
Erythromycin+ zinc (ez)	ne	ne	ez ≥ t LE 3*	ne	ez > m LE 4
Tetracycline (t)	ne	ne	ne	ne	ne

LE=level of evidence; ne=no evidence; sys.=systemic; top.=topical

\* erythromycin + zinc liquid &gt; sys. tetracycline (LE 3); erythromycin + zinc gel &gt; sys. tetracycline (LE 3)

**Table 11:** Efficacy: Papulopustular acne - sys. monotherapy vs. antibiotics/ isotretinoin/ zinc

	Placebo/ vehicle (v)	Doxycycline (d)	Erythromycin (e)	Lymecycline (l)	Minocycline (m)	Tetracycline (t)	Isotretinoin (i)	Zinc (z)
Clindamycin (c)	c > v LE 3	ne	ne	ne	ne	t > c LE 3	ne	ne
Doxycycline (d)	conflicting LE 3*	X	e = d LE 3	ne	m = d LE 3	ne	ne	ne
Erythromycin (e)	ne	X	X	ne	ne	e = t LE 3	ne	ne
Lymecycline (l)	l > v LE 3	X	X	X	m = l LE 4	ne	ne	ne
Minocycline (m)	m > v LE 1	X	X	X	X	m = t LE 2	ne	m > z LE 3
Tetracycline (t)	t > v LE 1	X	X	X	X	X	ne	t > z LE 3
Isotretinoin (i)	i > v LE 4	X	X	X	X	X	X	ne
Zinc (z)	z > v LE 1	X	X	X	X	X	X	X

LE=level of evidence; ne=no evidence; sys.=systemic

\* doxycycline 20mg BID or 0.6mg/kg QD = placebo (LE 3); doxycycline 1.2mg/kg or 100mg QD ≥ placebo (LE 3); doxycycline 2.4mg/kg &gt; placebo (LE 3)

\* doxycycline 20mg BID or 0.6mg/kg QD = placebo (LE 3); doxycycline 1.2mg/kg or 100mg QD = placebo (LE 1); doxycycline 2.4mg/kg &gt; placebo (LE 3)

**Table 12:** Efficacy: Papulopustular acne - sys. therapy vs. sys.-top. combination

	Isotretinoin (i)	Clindamycin (c)	Doxycycline (d)	Lymecycline (l)	Tetracycline (t)
Top. adapalene + sys. doxycycline (a-d)	ne	ne	a-d = d LE 4	ne	ne
Top. adapalene + BPO (f.c.) + sys. doxycycline (a-BPO-d)	a-BPO-d = i LE 4	ne	d-a-BPO > d LE 3	ne	ne
Top. adapalene + sys. tetracycline (ta-t)	i > ta-t LE 4	ne	ne	ne	ne
Top. adapalene + sys. lymecycline (a-l)	ne	ne	ne	a-l > l LE 4	ne
Top. azelaic acid + sys. minocycline (aa-m)	aa-m = i LE 4	ne	ne	ne	ne
Top. tetracycline + sys. tetracycline (t-t)	ne	ne	ne	ne	ne

f.c.=fixed combination, LE=level of evidence; ne=no evidence; sys.=systemic; top.=topical

**Update 2025:****Table 13:** Efficacy: Papulopustular acne - top. therapy vs. vehicle/ top. therapy

IL reduction	Vehicle (v)	Azelaic acid (aa)	Adapalene (a)	Clascoterone (cl)	Isotretinoin (i)	Tretinoin (t)	Trifarotene (tri)
Trifarotene (tr)	tri > v (see methods report)	ne	ne	ne	ne	ne	X
Clascoterone (c)	cl > v	ne	ne	x	ne	c>t	ne

	(see evidence report)					(see methods report)	
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Ne=no evidence; top.=topical

**Table 14: Efficacy: Papulopustular acne - sys. therapy vs. sys.-top. combination**

IL reduction	Vehicle + placebo	Trifarotene (tri) + placebo	sDox	Vehicle (v) + system. Doxy (sDox)
Trifarotene (tri) + system. Doxycycline (sDox)	ne	ne	ne	tri + sDox > v + sDox (see method report)
Spirolonactone (Sp)	(see evidence report)	x	(see evidence report)	x

Ne=no evidence; top.=topical

\* the difference in the mean absolute change of IL was 9.9, the methods group decided to accept this a sufficient to be in line with the 10% rule of clinical relevance (see methods report)

## Light sources

Due to the still very limited evidence, the open recommendation for IPL, laser and PDT were maintained in the update. The low strength of recommendation for a treatment with blue light was kept based on the evidence identified in the 2011 version of the guideline and confirmed by expert voting.

### 6.2.3.2 Safety/ tolerability

See Table 15 to Table 19 for summary of safety/ tolerability data.

**Table 15: Safety/ tolerability: Papulopustular acne - top. therapy vs. top. therapy**

	Azelaic acid (aa)	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)
BPO	aa > BPO LE 4	BPO = a LE 4	BPO = i LE 4	BPO = t LE 4 / insufficient data*
Azelaic acid (aa)	X	aa > a LE 4	ne	aa > t LE 4
Adapalene (a)	X	X	a > i LE 4	a > t LE 4**
Isotretinoin (i)	X	X	X	insufficient data

LE=level of evidence; ne=no evidence; top.=topical

\* tretinoin 0.025% = BPO 5% (LE 4); BPO 5% vs. tretinoin 0.1% (insufficient data); BPO 5-10% vs. tretinoin 0.05% (insufficient data)

\*\* adapalene 0.1% > tretinoin 0.025% (LE 4); adapalene 0.1% > tretinoin 0.05% (LE 4); adapalene 0.1% > TMG 0.1% (LE 4)

## Update 2025:

**Table 16: Safety/ tolerability: Papulopustular acne - top. therapy vs. top. therapy**

	Azelaic acid (aa)	Adapalene (a)	Clascoterone (cla)	Isotretinoin (i)	Tretinoin (t)	Trifarotene (tri)
Clascoterone 1%	ne	ne	x	ne	insufficient data (see methods report)	ne
Trifarotene (tri)	ne	ne	ne	ne	ne	x

ne=no evidence

**Table 17:** Safety/ tolerability: Papulopustular acne - top. combinations vs. top. therapy/ combinations

	BPO	Adapalene (a)	Isotretinoin (i)	Tretinoin (t)	Clindamycin (c)	Erythromycin (e)	Adapalene-BPO (a-BPO)	BPO-clindamycin (BPO-c)	Clindamycin-tretinoin (ct)
Adapalene-BPO (a-BPO)	BPO > a-BPO LE 1	a > a-BPO LE 4	ne	ne	ne	ne	X	X	X
BPO-clindamycin (BPO-c)	BPO-c = BPO LE 1	BPO-c > a LE 4	ne	ne	BPO-c = c LE 1	ne	BPO-c > a-BPO LE 4*	X	X
Clindamycin-tretinoin (ct)	ne	ne	ne	t = ct LE 4	c > ct LE 1	ne	ne	BPO-c = ct LE 4	X
Clindamycin-zinc (cz)	ne	ne	ne	ne	cz = c LE 4	ne	ne	ne	ne
Erythromycin-isotretinoin (ei)	ne	ne	ei = i LE 4	ne	ne	ei = e LE 4	ne	ne	ne
Erythromycin-tretinoin (et)	ne	ne	ne	ne	ne	ne	ne	ne	ne
Erythromycin-zinc (ez)	ne	ne	ne	ne	ez = c LE 4	e > ez LE 4	ne	BPO-c = ez LE 4	ne

LE=level of evidence; ne=no evidence; top.=topical

\* clindamycin-BPO &gt; adapalene-BPO after 12 weeks of treatment (LE 4); clindamycin-BPO &gt; adapalene-BPO after 2 weeks of treatment (LE 4)

## Topical monotherapy versus systemic monotherapy

Topical treatments usually result in local side effects whereas systemic treatments cause, among others, mostly gastrointestinal effects. It is therefore difficult to accurately compare topical and systemic treatments in terms of safety/ tolerability.

## Systemic antibiotics

From the included trials, no clear conclusion can be drawn as to which antibiotic treatment has the best safety/ tolerability profile.

**Table 18:** Safety/ tolerability: Papulopustular acne - sys. monotherapy vs. sys. antibiotics/ isotretinoin/ zinc

	Doxycycline (d)	Erythromycin (e)	Lymecycline (l)	Minocycline (m)	Tetracycline (t)	Isotretinoin (i)	Zinc (z)
Clindamycin (c)	ne	ne	ne	ne	t = c LE 4	ne	ne
Doxycycline (d)	X	insufficient data	ne	m = d LE 4	ne	ne	ne
Erythromycin (e)	X	X	ne	ne	t > e LE 4	ne	ne
Lymecycline (l)	X	X	X	l > m LE 4	ne	ne	ne
Minocycline (m)	X	X	X	X	m = t LE 4	ne	m > z LE 4
Tetracycline (t)	X	X	X	X	X	ne	insufficient data
Isotretinoin (i)	X	X	X	X	X	X	ne

LE=level of evidence; ne=no evidence; sys.=systemic

Smith and Leyden (131) performed a systemic review analysing case reports on adverse events with minocycline and doxycycline between 1966 and 2003. As a result, they suggest that adverse events may be less likely with doxycycline than with minocycline. More severe adverse events seem to appear during treatments with minocycline. Doxycycline however, leads to photosensitivity, which is not seen with minocycline.

See also chapter 6.4.4 Choice of type of systemic antibiotic.

See also chapter 6.4.12 Use of hormonal antiandrogenic contraceptives or other combined hormonal contraceptives and 6.4.13 Use of spironolactone.

### Systemic treatments with isotretinoin

From the included trials, no clear comparison of the safety/ tolerability profiles of isotretinoin with other systemic treatments can be made. (For a discussion of isotretinoin depression, see chapter 6.4.10).

**Table 19:** Safety/ tolerability: Papulopustular acne - sys.-top. combination vs. sys. therapy

	Isotretinoin (i)	Clindamycin (c)	Doxycycline (d)	Lymecycline (l)	Tetracycline (t)
Top. adapalene + sys. doxycycline (a-d)	ne	ne	a-d = d LE 4	ne	ne
Top. adapalene + BPO (f.c.) + sys. doxycycline (a-BPO-d)	a-BPO-d = i LE 4	ne	a-BPO-d = d LE 4	ne	ne

	Isotretinoin (i)	Clindamycin (c)	Doxycycline (d)	Lymecycline (l)	Tetracycline (t)
Top. adapalene + sys. tetracycline (ta-t)	not comparable	ne	ne	ne	ne
Top. adapalene + sys. lymecycline (a-l)	ne	ne	ne	l > a-l LE 4	ne
Top. azelaic acid + sys. minocycline (aa-m)	aa-m > i LE 4	ne	ne	ne	ne
Top. tetracycline + sys. tetracycline (t-t)	ne	ne	ne	ne	ne

f.c.=fixed combination, LE=level of evidence; ne=no evidence; sys.=systemic; top.=topical

## Light sources

Although in the literature search for the first version of this guideline, there were some studies for the treatment of severe nodular / conglobate acne with laser and light sources, no clear recommendations could be drawn. The published evidence was very scarce.

### 6.2.3.3 Patient preference

The systematic review by Dressler et al. (126) includes two split-face studies reporting patient preferences for adapalene over tretinoin (low risk of bias).

Two cross-over trials evaluated **topical** erythromycin versus **topical** clindamycin but only one RCT found a statistically significant difference for patient preferences for **topical** erythromycin (unclear risk of bias).

Two split-face studies reported patient preferences for clindamycin 1%/BPO 5%/2.5% over adapalene 0.1%/BPO 2.5% (descriptive data only; unclear risk of bias).

### 6.2.3.4 Other considerations

For further discussion on the use of isotretinoin as a first-line treatment for severe papulopustular acne, see chapter 6.4.7.

The expert group feels strongly that the effectiveness seen in clinical practice is highest with systemic isotretinoin, although this can only be partly supported by published evidence. Strong expert voting also took perceived lower relapse rates after treatment with isotretinoin into consideration.

## 6.3 Treatment of severe nodular/ conglobate acne

### 6.3.1 Recommendations for severe nodular/ conglobate acne <sup>1</sup>

Treatment recommendations for severe nodular/ conglobate acne					
High strength of recommendation <sup>1</sup> : "is strongly recommended"	Medium strength of recommendation <sup>1</sup> : "can be recommended"	Low strength of recommendation <sup>1</sup> : "can be considered"	Open recommendation: "a recommendation for or against can not be made at the present time"	negative recommendation: "is not recommended"	Alternatives for females: "can be considered"
Syst. Isotretinoin	Syst. Antibiotic <sup>2,3</sup> + top. Azelaic Acid	Syst. Antibiotic <sup>2,3</sup> + top. Adapalene <sup>4,5</sup>	IPL	Top. monotherapy	Hormonal antiandrogenic contraceptives or other hormonal combined contraceptives + other syst. and/or + top. treatment as indicated <sup>7</sup>
	Syst. Antibiotic <sup>2,3</sup> + top. Adapalene + BPO (f.c.)	Syst. Antibiotic <sup>2,3</sup> + top. BPO <sup>5</sup>	Laser	Syst. antibiotics as monotherapy	
			PDT	Hormonal antiandrogenic contraceptives or other hormonal combined contraceptives as a monotherapy	Spirolactone <sup>6</sup> + other syst. <sup>8</sup> and/or top. treatment as indicated
				Artificial UV radiation sources	
				Visible light as monotherapy	

<sup>1</sup> Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e. g. financial resources/ reimbursement limitations, legal restrictions, availability, drug licensing).

<sup>2</sup> Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.

<sup>3</sup> Doxycycline and lymecycline (see chapter 6.4), limited to a treatment period of three months.

<sup>4</sup> Only studies found on systemic AB + adapalene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion.

<sup>5</sup> Indirect evidence from severe papulopustular acne.

<sup>6</sup> Off-label treatment

<sup>7</sup> Partially off-label treatment for acne, as approval varies by region and specific intervention

<sup>8</sup> Caution is advised when combining spironolactone and other systemic treatments

Abbreviations: BPO: Benzoyl peroxide, IPL: Intense Pulsed Light, PDT: Photodynamic Therapy, UV: Ultraviolet, f.c.: fixed combination, top.: topical use, syst.: systemic use

### 6.3.2 Reasoning

**General comment:** Very few of the included trials (described below) looked specifically at patients with nodular or conglobate acne. As a source of indirect evidence, studies of patients with severe papulopustular acne were used and the percentage in the reduction of nodules (NO) and cysts (CY) in these studies was used. In case of use of such indirect evidence, the strength of recommendation was downgraded for the considered treatment options.

Systemic isotretinoin shows superior efficacy in the treatment of severe nodular/ conglobate acne when compared with systemic antibiotics or topical therapy only.

The expert group considered that the greatest effectiveness in the treatment of severe nodular/ conglobate acne in clinical practice is seen with systemic isotretinoin. This can only be partly supported by published evidence, due to the scarcity of clinical trials in conglobate acne.

In the experts' opinion, safety concerns with isotretinoin are manageable if treatment is properly initiated and monitored. Patient benefit with respect to treatment effect, improvement in quality of life and avoidance of scarring outweigh the side effects.

Indirect evidence from clinical trials with patients with papulopustular acne was taken into consideration for the recommendation on spironolactone (off-label treatment).

#### 6.3.2.1 Efficacy

See Table 20 for summary of efficacy data. Please see methods report for explanation of assessment strategy.

#### **Systemic monotherapy versus placebo**

Systemic isotretinoin has superior efficacy compared with placebo (132) (LE 4\*).

\* There is only one trial comparing systemic isotretinoin with placebo in nodular/ conglobate acne resulting only in LE 4. However, there are multiple trials comparing different dosage without a placebo group and following expert opinion, there is no doubt about its superior efficacy.

## Systemic monotherapy versus systemic monotherapy or combination

See Table 20 for summary of efficacy data.

**Table 20:** Efficacy: Nodular/ conglobate acne

	Sys. isotretinoin (si)	Sys. tetracycline (st)
Adapalene + tetracycline (a-t)	si = a-t LE 4	ne
Adapalene/BPO + doxycycline (ab-d)	ab-d =si LE 4	ne
Azelaic acid + minocycline (aa-m)	si = aa-m LE 4	ne
Sys. tetracycline (st)	si > st LE 3	X
Top. clindamycin (tc)	ne	st > tc LE 3

LE=level of evidence; ne=no evidence; sys.=systemic; top.=topical

### Light sources

Due to insufficient evidence, it is not currently possible to make a recommendation for or against treatment with IPL, laser or PDT in conglobate acne. See also 5.2.3.1.

#### 6.3.2.2 Safety/ tolerability

See also chapter 6.2.3.2 on the tolerability/ safety of papulopustular acne treatments.

From the trials specifically investigating severe nodular/ conglobate acne, very little information is available to compare the different treatment options. Almost all patients suffer from xerosis and cheilitis during treatment with isotretinoin, whereas systemic antibiotics more commonly cause gastrointestinal adverse events.

#### 6.3.2.3 Patient preference

The systematic review by Dressler et al. (126) did not identify any evidence on the treatment preferences of patients suffering from conglobate acne.

#### 6.3.2.4 Other considerations

For comment on EMA directive see also chapter 6.4.8.

## 6.4 General considerations

### 6.4.1 Choice of type of topical retinoid

Adapalene should be selected in preference to tretinoin and isotretinoin.

There is currently not enough evidence to compare trifarotene against adapalene, tretinoin or topical isotretinoin, as no head-to-head trials are available.

Studies on trifarotene focussed on truncal acne, where it was shown to be effective compared to placebo.

#### 6.4.1.1 Reasoning

All topical retinoids show comparable efficacy against IL (see chapter 6.2.3.1), whereas against NIL the evidence is conflicting (see chapter 6.1.2.1).

Among the topical retinoids, adapalene shows the best tolerability/ safety profile followed by isotretinoin and tretinoin (see chapter 6.2.3.2).

Patient preference favours adapalene over tretinoin (see chapter 6.2.3.3).

Head to head trials to position trifarotene among the other topical retinoids have not been identified.

### 6.4.2 Considerations on the safety of benzoyl peroxide (BPO)

Dréno

Could benzoyl peroxide (BPO) be carcinogenic and induce leukaemia in particular? This question is obviously very important in the context of a molecule that has been used very frequently since the beginning of the 20th century as a basic treatment for acne.

The starting point is information that has appeared on several over-the-counter BPO products degrading into benzene at high temperatures (37° to 70°) and that can emit substantial amounts of benzene into the air from a closed package. Benzene is a well-known carcinogen, and chronic exposure to low doses can induce leukaemia, the most common form being acute myeloid leukaemia (AML). To date, it has not been shown that the use of BPO in acne patients is associated with an increased risk of developing AML: 2 studies try to answer to the questions. The 1st one (1) using Cosmos, a community health systems network representing more than 243 million patients from more than 1,400 hospitals and 32,500

clinics in the United States, estimated the prevalence of AML in more than 2.3 million acne patients with or without BPO between March 8, 2010 and March 7, 2024. Acne patients prescribed BPO had a 0.012% prevalence of AML, compared to 0.017% of patients with no recorded prescription (OR, 0.70; 95%CI, 0.55-0.90). The 2nd study (2) with the same objectives was carried out using a different method. The authors used TriNetX US Collaborative Network (63 healthcare organizations) to assess whether the use of BPO for acne is associated with the development of lymphoma or internal cancers. This cohort of acne patients treated with PBO was compared with a control cohort matched for age, basic demographic data and confounding comorbidities, in patients seen for a diagnosis of nevus or actinic keratosis. No significant difference was found in terms of risk of lymphoma (hazard ratio (HR) [95% CI] = 1.00 [0.68, 1.47]), leukaemia (HR [95% CI] 66 = 0.91 [0.51, 1.65]), or both combined (HR [95% CI] = 1.04 [0.74, 1.45]), and an increased risk of internal cancer (HR [95% CI] = 1.00 [0.68, 1.47]) (133, 134).

Although further studies are needed to reproduce these results and to ensure their generalization, these two studies support the safety of the standard use of benzoyl peroxide in the treatment of acne.

#### **6.4.3 Considerations regarding clascoterone**

Clascoterone was part of the evidence assessment and all extracted data can be found in the full version and evidence report. For clascoterone, a marketing-authorization application was submitted to the European Medicines Agency (EMA) in October 2023. In April 2025, the EMA's Committee for Medicinal Products for Human Use (CHMP) initially rejected the application, stating that the benefit-risk ratio in adolescents (12-17 years) was not sufficiently demonstrated. After a re-examination, the CHMP changed its position and on 25 August 2025 adopted a positive recommendation for the approval of Winlevi for the treatment of acne vulgaris in adults and for facial acne in adolescents from 12 to <18 years. On 21 October 2025, the European Commission granted the marketing authorization in the EU with those indications. As it was not yet approved at the time of the consensus conference and clinical experience was lacking, the group decided to not yet integrate it into the treatment algorithm and the recommendations.

#### **6.4.4 Choice of type of systemic antibiotic**

Doxycycline and lymecycline [can be recommended](#) in preference to minocycline and tetracycline.

[Azithromycin has been considered as an alternative antibiotic; however, at the time of guideline development, a recommendation by the EMA committee was published advising against its use for the treatment of acne, as current evidence does not sufficiently support its efficacy, and the “benefits do not outweigh the risks”, particularly with regard to antimicrobial resistance \(135\).](#)

##### **6.4.4.1 Reasoning**

##### **6.4.4.2 Efficacy**

Doxycycline, lymecycline, minocycline and tetracycline all seem to have a comparable efficacy against IL (see chapter 6.2.3.1).

Tetracycline showed better efficacy compared to clindamycin and comparable efficacy with erythromycin.

[Azithromycin has superior efficacy against IL compared to placebo. Azithromycin seems to have a comparable efficacy compared to doxycycline with regard to IL reduction \(136-138\), however, head-to-head trials only included a small number of patients \(see evidence report\) \(note: off-label, note: EMA recommendation \(135\)\).](#)

##### **6.4.4.3 Safety/ tolerability**

From the included trials, no clear results can be drawn as to which antibiotic treatment has the best safety/ tolerability profile.

Smith and Leyden (131) performed a systemic review analysing case reports on adverse events with minocycline and doxycycline between 1966 and 2003. As a result, they suggest that adverse events may be less likely with doxycycline than with minocycline. More severe adverse events seem to appear during treatments with minocycline. Doxycycline however, leads to photosensitivity, which is not seen with minocycline.

The most frequent ADRs for doxycycline are manageable (sun protection for photosensitivity and water intake for oesophagitis), whereas the most relevant side

effects of minocycline (hypersensitivity, hepatic dysfunction, lupus like syndrome) are not easily managed (139).

The phototoxicity of doxycycline is dependent on dosage and the amount of sun light (140-143).

There is little information on the frequency of ADRs with lymecycline. Its phototoxicity has been reported to be lower than with doxycycline and its safety profile is comparable to that of tetracycline (139, 144).

More severe drug reactions are experienced during treatment with minocycline compared with doxycycline, lymecycline and tetracycline.

Frequent ADRs of azithromycin are diarrhoea, nausea and vomiting (142, 145-148).

For further information, see chapters 6.4.5 Recommended treatment duration with systemic antibiotics and 6.4.11 Risk of antibiotic resistance.


#### 6.4.4.4 Patient preference/ practicability

Doxycycline, lymecycline and minocycline have superior practicability compared with tetracycline due to their requirement for less frequent administration.

#### 6.4.4.5 Other considerations

The use of systemic clindamycin for the treatment of acne is generally not recommended as this treatment option should be kept for severe infections.

### 6.4.5 Recommended treatment duration with systemic antibiotics

<p><b>It can be recommended</b> to limit the use of systemic antibiotics for the treatment of acne to a period of three months.</p> <p>If treatment beyond three months is necessary, and topical treatments are insufficient, while systemic isotretinoin or systemic hormonal treatments are not a suitable option, then a course of systemic antibiotics for more than three months <b>can be considered</b>.</p>	<p>Strong consensus</p>  <p>Evidence and consensus based</p>
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#### 6.4.5.1 Reasoning


It is emphasized that systemic antibiotic treatment beyond three months should remain exceptional and should be carefully weighed against the risk of resistance. Most of the included trials on the systemic AB treatment of acne have a treatment duration of 12 weeks, with some extending up to 16 or 18 weeks.

A duration of three months may be too short for the treatment of severe acne or in case of truncal involvement, hence treatment continuation may be advisable to continue a treatment with partial response and continuing improvement. In addition, a prolonged treatment may be necessary in case of recurrence after previous successful treatment cycles, if other treatments are not a suitable alternative.

Indirect evidence from other indications such as chronic obstructive pulmonary disease (COPD), asthma, schizophrenia, bronchiectasis or cystic fibrosis is available, with treatment durations of more than three months (149-153). Examining the evidence table with the long-term safety results in these other indications, the group did not identify AEs of particular relevance that may arise especially when systemic antibiotics are used for more than three months (see evidence report). However, the development of antibiotic resistance is a major concern that should limit the prolonged use of systemic antibiotics. Treatment of acne with longer courses of topical or systemic antibiotics may lead to the induction of antibiotic resistance. This may contribute to increased healthcare burden and the development of antibiotic-resistant bacteria, which is an ongoing public health concern. For further information, see chapter 6.4.11 **Risk of antibiotic resistance**.

#### 6.4.6 Treatment during pregnancy

This chapter is based on expert opinion / existing narrative reviews (154) and national databases on drug safety during pregnancy.

<p>Among the treatment options discussed in the guideline, the following treatment options <b>can be considered</b> for the use during pregnancy:</p> <p>Topical therapy: Azelaic acid, BPO (if needed in combination with a topical antibiotic: clindamycin, erythromycin)</p> <p>Systemic therapy: Zinc, Azithromycin*</p>	<p>Strong consensus</p>  <p>Consensus based</p>
<p>*At the time of guideline development, an EMA recommendation was published advising against the use of azithromycin for the treatment of acne as current evidence does not sufficiently support its efficacy, and the “benefits do not outweigh the risks”, particularly with regard to antimicrobial resistance (135). However, as no other systemic treatment options are available during pregnancy, the use of azithromycin may be considered following a careful risk-benefit assessment in this clinical situation.</p>	

Erythromycin has not been included as a recommended treatment option in the guideline for the general acne patient population due to the high rates of antibiotic resistances, however, it can be considered as an additional option specifically for pregnant women, where other choices are limited.

Systemic corticosteroids can be considered in cases of conglobate acne with very strong inflammation, high pain levels, systemic symptoms, or fulminant progression. For possible harm see respective assessments.

There is a strong contraindication for systemic isotretinoin during pregnancy and in women trying to conceive a child due to a high teratogenic risk. Effective contraception is mandatory (155, 156).

#### **6.4.7 Considerations on isotretinoin and dosage**

Layton / Nast

Dosing regimens


Identifying the optimal dosing regimen of isotretinoin in the management of acne is challenging. Isotretinoin is highly lipophilic and most dosing studies including those assessing cumulative dosing have been conducted retrospectively and failed to control for fat intake. As isotretinoin has been used more frequently off license to treat more moderate acne this too has challenged interpretation of study results relating to dosing.

A systematic review (157) examined studies using various doses and regimes of isotretinoin in different severities of acne and provided the following conclusions:

1. Patients with more severe acne respond better to conventional or high fixed-dose regimens of isotretinoin and daily dosing results in better efficacy than intermittent dosing regimens in this cohort of patients.
2. The severity of common adverse effects, particularly mucocutaneous side effects are dose-dependent and adopting a low-dose regimen will avoid some of the mucocutaneous side effects associated with standard or high-dose isotretinoin
3. Relapse rates are higher in patients assigned to low-dose and intermittent-dosing regimens when compared with those on high-dose and conventional regimens
4. Low dose extended courses of isotretinoin, providing they are continued until clearance or near clearance, appear to have a similar efficacy to conventional doses of isotretinoin

5. Higher cumulative doses were not associated with increased efficacy in studies of mild to moderate acne in which isotretinoin was being used off-license. Therefore, attempts to determine the cumulative dose necessary to obtain an optimal treatment response and low relapse rate have not yet yielded sufficient evidence for a strong recommendation.

A study using data from the Market Scan commercial claims database published after the systematic review described above found that female sex (hazard ratio [HR], 1.43; 95% CI, 1.35-1.52) was significantly associated with increased rates of acne relapse, and isotretinoin cumulative dosage (mg/kg) was associated with a decreased rate of acne relapse (HR, 0.996; 95% CI, 0.995-0.997) (158).

<p>For severe papulopustular acne/ moderate nodular acne, a dosage of systemic isotretinoin of 0.3 - 0.5 mg/kg per day <b>can be recommended</b>.</p> <p>For <b>severe nodular/</b> conglobate acne a dosage of systemic isotretinoin of <math>\geq 0.5</math> mg/kg per day <b>can be recommended</b>.</p> <p>In case of refractory cases or poor response, an increase in the dosage (max 1mg/kg per day) <b>can be considered</b>.</p> <p>The duration of the therapy should be at least 6 months. In case of insufficient response, the treatment period <b>can be prolonged</b>.</p>	<p>Strong consensus</p>  <p>Consensus based</p>
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An evidence-based recommendation regarding a cumulative dose required to prevent relapse or the need for an isotretinoin retrial cannot be provided at this time.

Based on clinical experience, most members of the guideline group treat with isotretinoin for at least 6 months, whereas the patient should be clear of inflammatory lesions for at least 1-2 months depending on the severity.

As differences in pharmacokinetics between different brands of isotretinoin cannot be ruled out it is advisable to prescribe a certain product and to use this same preparation throughout a treatment period (159).

In clinical practice, initial “flare up” of acne has been observed after the initiation of isotretinoin.

In cases of conglobate acne with very strong inflammation, high pain level, systemic symptoms, or fulminant progression, the combination of isotretinoin and systemic glucocorticosteroids can be considered to gain clinical control to reduce

strong inflammation. Suggestions on glucocorticosteroid dosing (0,5-1 mg/kg prednisone daily for 4-5 weeks) have been published as expert opinion-based recommendations by Greywal et al (160).

#### **6.4.8 Isotretinoin considerations with respect to EMA directive and selection of systemic antibiotics versus systemic isotretinoin**

Layton/ Ochsendorf/ Bukvić Mokos

Oral isotretinoin is licensed for severe acne. The current European Medicine Agency (EMA) Directive for prescribing oral isotretinoin states: “oral isotretinoin should only be used in severe acne, nodular and conglobate acne, that has or is not responding to appropriate antibiotics and topical therapy” (161). The inference of this being that isotretinoin should not be used as first-line therapy for severe disease.

After four decades of experience with oral isotretinoin, there has been extensive data published and significant experience and opinion gleaned by many experts and prescribers including members of the European Guideline group, which supports the notion of systemic isotretinoin being considered as the first-choice treatment for many cases of severe papulopustular, moderate nodular, and severe nodular/ conglobate acne (17, 162-164)

It is recognized that reduction in inflammatory acne may prevent the occurrence of clinical and psychological scarring, improve quality of life and in some cases reduce depression (165-167).

As a result of these findings recent guidelines (168-170) advocate the use of isotretinoin sooner rather than later as there is a clear correlation between acne severity and duration of acne before adequate treatment and scarring (171), and the negative psychosocial impact of scarring can be long lasting and worse than that caused by clinical acne alone (66).

Delaying the use of oral isotretinoin for severe acne therefore has potential to pose a significant ethical problem.

Comparative trials are lacking. However, clinical experience confirms that the relapse rates after treatment with isotretinoin are the lowest among all the available therapies and a meta-analysis demonstrated the superior effect of oral

isotretinoin when compared to all other therapies for acne (172). This systematic review was identified by hand search.

Although there is acknowledgement that the decision is not supported by robust evidence-based data, not only the EMA Directive but other regulatory bodies such as the MHRA (Medicines and Healthcare Products Regulatory Agency) recommend that oral isotretinoin should only be used after failure to respond to good combination treatment regimes in severe disease (173).

Clinicians are generally free to prescribe drugs, such as oral isotretinoin, off license according to their professional experience and clinical judgment. However, in the event of any medical problems, prescribers could be deemed liable if they have failed to follow recommended prescribing practice and to ensure patients and carers are fully informed (174).

The EMA recommendations include the following suggestions:

1. To start at the dosage of 0.5 mg/kg daily.
2. To avoid isotretinoin in patients under 12 years of age.
3. To monitor laboratory parameters, primarily liver enzymes and lipids, before treatment, 1 month after starting and every 3 months thereafter.
4. To adopt a pregnancy prevention programme.
5. To avoid laser treatment, peeling and wax epilation for at least 6 months after stopping therapy.

The European Guideline group supports these EMA recommendations, although expert opinion suggests that being less than 12 years old (point 2) is not necessarily a contraindication for the off license use of isotretinoin and in some cases regardless of age it may be appropriate to commence therapy at a lower dose than 0.5 mg/kg/day (see chapter 6.4.7).

Areas which remain under review include dosing regimens, abnormal wound healing described whilst on oral isotretinoin. Recent studies and consensus statements suggest that even less laboratory monitoring is necessary (175-177).

#### **6.4.9 Isotretinoin and risk of abnormal wound healing**

Layton

Current recommendations to **delay** acne scar repair procedures **for** 6 months post oral isotretinoin arose from **case** reports in the mid 1980's of delayed wound healing and hypertrophic scarring **following** conventional and argon laser dermabrasion. There are also reports of impaired wound healing following liposuction (178).

However, **more recent** critical appraisals and systematic reviews have challenged this recommendation (179-185).

One retrospective observational study also demonstrated no tendency to develop or get worsening keloid or hypertrophic scarring among acne patients who took oral isotretinoin (186).

This recent evidence therefore suggests that the recommendation to avoid acne scar repair procedures within 6 months of taking oral isotretinoin should be re-considered.

The guideline authors **conclude** that oral isotretinoin could interfere with wound healing albeit relatively rare, **however**, the guideline group also appreciates that earlier treatment of scarring may provide more effective management by addressing the scars in a timely fashion. As such the guideline group recommend that patients should be offered superficial procedural treatments earlier than the 6 months post isotretinoin therapy which is currently recommended but with the caveat patients are fully informed of the available evidence and the risks and benefits.

#### **6.4.10 Consideration on isotretinoin and the risk of depression**

##### **Nast**

It is recommended to assess prior symptoms of depression as part of the medical history of any patient before the initiation of isotretinoin and during the course of the treatment.

It is recommended to inform patients about a possible risk of depression and suicidal behaviour (156).

Published studies and previous systematic reviews have come to different conclusions with regard to the risk of depression during isotretinoin treatment (187, 188).

Previously examined systematic reviews all have methodological limitations with respect to their stringency of inclusion and exclusion criteria and systematic reporting of identified studies.

For the update of the guideline a new search for the most recent systemic review was performed to reassess the risk of depression during the treatment with isotretinoin.

The Review by Tan et al. was identified as the most recent systematic review. The review's findings "indicate that there is no epidemiological evidence to suggest an increased relative risk of suicide or psychiatric conditions among isotretinoin users at a population level" (189).

Although the most recent systematic review included did not find evidence suggesting an increased relative risk of suicide or psychiatric conditions among isotretinoin users at a population level, more data on the impact of isotretinoin, specifically on patients with pre-existing psychological comorbidity, is desirable.

Considering the numerous studies and reviews with varying results, as well as their clinical experiences, the guideline group continues to recommend caution in the use of isotretinoin in patients with a history of depression and suicidal ideation.

#### **6.4.11 Risk of antibiotic resistance**

Brüggemann/ Lambert/ Ochsendorf

As outlined in chapter 6.5, systemic antibiotics should generally be limited to a maximum of three months, with longer use considered only in exceptional cases when alternatives are unsuitable. Treatment of acne with longer courses of topical or systemic antibiotics may increase the likelihood of inducing antibiotic resistance. Such resistance contributes to increased mortality and extended hospitalizations attributable to antibiotic-resistant pathogens, representing a critical public health challenge worldwide, including across Europe. It is well known that one broad spectrum antibiotic can select for multi-resistance against a number of different antibiotics (190). Furthermore, it has been shown, that even low concentrations of antibiotics, well below the MIC value, may select for even high-level resistance (191, 192). The use of antibiotics to treat acne may lead to resistance in local *C. acnes* and other local cutaneous bacteria including staphylococci, and

importantly, also in species of the patients' total microbiome on skin and mucosal surfaces. Resistance may spread from non-pathogenic/commensal to pathogenic species.

The first relevant changes in *C. acnes* antibiotic sensitivity were found in the USA shortly after the introduction of the topical formulations of erythromycin and clindamycin. The molecular basis of resistance, via mutations in genes encoding 23S and 16S rRNA, are widely distributed (193). In Japan, the acquisition of resistance genes, i.e. *erm(X)*, *erm(50)* and *tet(W)*, via horizontal gene transfer has been reported. The gene *erm(X)* is located on the transposon Tn5432, while *erm(50)* and *tet(W)* are found on the multidrug resistance plasmid pTZC1 (194-196). The gene *erm(X)* is frequently found also in Europe, the others were not reported yet.

Combined resistance to clindamycin and erythromycin is much more common (highest prevalence 91% in Spain) than resistance to the tetracyclines (highest prevalence 26% in the UK) (197). Use of topical antibiotics can lead to resistance largely confined to the skin of treated sites, whereas oral antibiotics can lead to resistance in commensal microbiota at all body sites (198). Resistance is more common in patients with moderate-to-severe acne and in countries with high out-patient antibiotic sales (199). Resistance is disseminated primarily by person-to-person contact, and so the spread of resistant strains by the treating physicians and by family and friends occurs frequently (16, 193, 197). Although some data suggest that resistant isolates disappear after antibiotic treatment is stopped (200, 201), other data suggest that resistance persists and can be reactivated rapidly (202).

There has been an increasing number of reports of systemic infections caused by resistant *C. acnes* in non-acne patients, e. g. post-surgery (199). In addition, a transmission of factors conferring resistance to bacteria other than *C. acnes* is described (203, 204).

Although antibiotic use in acne patients has been shown to be associated with an increased risk of upper respiratory tract infection and with an increased carriage of *S. aureus* (205), the true clinical importance of these findings requires further investigation.

It has been argued that the most likely effect of resistance is to reduce the clinical efficacy of antibiotic-based treatment regimens to a level below that which would occur in patients with fully susceptible microbiota (197, 206). Some trials have suggested a clear association between *C. acnes* resistance to the appropriate antibiotic and poor therapeutic response (197, 206). There is a gradual decrease in the efficacy of topical erythromycin in clinical trials of therapeutic intervention for acne, which is probably related to the development of antibiotic-resistant cuti-bacteria (130). In contrast, there is so far no evidence that the efficacy of oral tetracycline or topical clindamycin has decreased in the last decades (130, 207, 208). However, studies show a complex population of *C. acnes* with diverse virulence potential and antibiotic resistance patterns. This may explain the difficulties in predicting the clinical effects of antibiotic treatment of acne (209).

Since *C. acnes* is the major skin commensal bacterium found in both acne and healthy skin, the strain-level analysis is important to help understand the role of *C. acnes* in acne pathogenesis and in skin health. It has been demonstrated that the *C. acnes* population [on the phylotype level](#) were significantly different in acne patients and healthy controls (109, 113, 114).

This data could help [determine whether therapeutic modulation of the local \*C. acnes\* community can restore the host to a healthy state, which potentially leads to new treatment options.](#)

Studies on *C. acnes* resistance have highlighted the need for treatment guidelines to restrict the use of antibiotics in order to limit the emergence of resistant *C. acnes* strains. Data indicate that the combination of topical antibiotics with BPO may prevent the development of resistance in local *C. acnes* and staphylococci (129, 210-214). However, it is not known if resistance may develop in the periphery or outside the treatment zone due to antibiotic gradients or if a low level of systemic absorption can lead to resistance on mucosal surfaces (215, 216). There is not good evidence that the combination of local antibiotics with retinoids or zinc is efficient to prevent local resistance in *C. acnes* and no data is available on the effect on other cutaneous or mucosal bacteria (129, 217-220).

[A systematic search identified six systematic reviews on microbiological resistance when applying systemic antibiotics for a period of more than 12 weeks in patients with different health conditions \(149, 151-153, 221, 222\). For details](#)

of underlying health conditions and results see evidence report. The guideline group considers the findings in the literature as partially conflicting and insufficient to rule out the risk of development of clinically relevant antibiotic resistance.

It is currently unclear whether low-dose systemic doxycycline treatment for acne contributes to the development of antibiotic resistance. Studies, identified in a hand search, have shown that bacteria exposed to sub-MIC levels of antibiotics can develop high-level resistance through successive mutations (223). In particular one study showed development of resistance in subgingival plaques during low dose doxycycline treatment of periodontitis (224). Whether this phenomenon also applies to *C. acnes* remains to be investigated.

As a consequence, the use of systemic antibiotics and topical antibiotics should be limited (both indication and duration) and topical antibiotics should preferably be used in combination with BPO and avoided as monotherapy. Other recommendations include stricter cross-infection control measures when assessing acne in the clinic and combining systemic antibiotic therapy with topical broad-spectrum antibacterial agents, such as BPO (16, 62, 197).

#### **6.4.12 Use of hormonal antiandrogenic contraceptives or other combined hormonal contraceptives**

Pennitz / Nast / Layton / Al Wattar / Thozhukat

For treatment recommendations with respect to specific acne subtype, see chapter 6 “Induction therapy”. Combined oral hormonal contraceptives, are widely used for pregnancy prevention and other health benefits, such as acne treatment. These contraceptives contain a combination of oestrogen and progestin, which work together to inhibit ovulation and regulate menstrual cycles. The oestrogen component is usually ethinyl estradiol (EE), a synthetic form of oestrogen, though some newer formulations use alternatives such as 17 $\beta$ -estradiol, which closely resembles natural human oestrogen, as well as oestradiol valerate or oestetrol. Progestins, synthetic forms of progesterone, are designed to enhance contraceptive efficacy by preventing excessive endometrial growth and suppressing ovulation and are categorized by generations (136, 225).

Early-generation progestins (first, second, and third) are derived from testosterone and can have androgenic effects when used alone and therefore may

worsen acne. Newer generations of progestins have been developed to minimize androgenic effects and may offer additional benefits like antiandrogenic and anti-mineralocorticoid properties. Therefore, these newer progestins lead to fewer issues like acne and excessive hair growth (hirsutism), but may carry increased risks of venous thromboembolism (VTE) (136, 225).

Several COCs are licensed for the treatment of acne and patients should be counselled on their risks and benefits relevant to the primary treatment objective, individualised risk factors, and local regulatory practice. The use of COCs to treat acne outside their licenced indications could carry additional risks and patients should be counselled on potential side effects and long-term health impact as per the Summary of product characteristics (SmPC) and national regulatory guidance.

Hormonal antiandrogenic contraceptives or combined oral contraceptives (COCs) can be considered as adjunctive therapy in female patients with moderate to severe papulopustular, nodular or conglobate acne, particularly when contraception is desired or when acne is associated with hormonal influences or androgen excess. Systemic therapy with hormonal antiandrogenic contraceptives or other combined hormonal contraceptives (see Table 21) is not recommended for the treatment of comedonal or mild to moderate papulopustular acne, except when the primary intent is contraception or the management of concurrent gynaecological conditions, such as menstrual irregularities or other endocrinological conditions.

Table 21 gives an overview of the different generations of contraceptives and their possible impact on acne.

Table 21 is based on consensus and based on mechanistic considerations only. The table focuses solely on the efficacy in treating acne, while safety aspects are not addressed. Please note, that when choosing a hormonal treatment, more aspects than only their impact on the acne need to be considered, such as safety aspects, contraindications and individual patient characteristics. Please note that the use of hormonal treatments for acne is partly off-label, as approvals vary by region and product; prescribing COCs outside their licensed indications may carry additional risks, and patients should be counselled on potential side effects and long-term health impacts according to the SmPC and national regulatory

guidance. While some hormonal antiandrogenic or combined hormonal contraceptives are primarily used for contraception, their anti-acne efficacy differs by formulation and is mainly associated with progestins exhibiting anti-androgenic activity.

**Table 21:** Different contraceptives and their possible impact on acne

All information given in this table is based on consensus and on mechanistic considerations. Not all of the substances are licensed for acne and approval varies by region.		
The table focuses solely on the efficacy in treating acne, while safety aspects are not addressed.		
Please note, that when choosing a hormonal treatment, more aspects than only their impact on the acne need to be considered, such as individual patient characteristics.		
	Potential benefit for acne	
<b>Co-cyprindiol (ethinyloestradiol + cyproterone acetate)</b>	Co-cyprindiol (ethinyloestradiol + cyproterone acetate <sup>1</sup> )	
<b>Combined oral contraceptives</b>	<b>Examples include:</b> <ul style="list-style-type: none"> <li>• 1st generation (oestrogen<sup>2</sup> combined with chlormadinone acetate<sup>3</sup>)</li> <li>• 2nd generation (oestrogen<sup>2</sup> combined with levonorgestrel or norethisterone / norethindrone)</li> <li>• 3rd generation (oestrogen<sup>2</sup> combined with desogestrel or gestodene or norgestimate)</li> <li>• 4th generation (oestrogen<sup>2</sup> combined with dienogest or drospirenone or nomegestrol acetate<sup>3</sup>)</li> </ul>	
	Less likely to worsen acne / possibly beneficial	May worsen acne
<b>Progestin-only oral contraceptives</b>	<ul style="list-style-type: none"> <li>• 3rd generation (desogestrel)</li> <li>• 4th generation (dienogest, drospirenone)</li> </ul>	<ul style="list-style-type: none"> <li>• 1st generation (medroxyprogesterone acetate)</li> <li>• 2nd generation (levonorgestrel, norethisterone/ norethindrone)</li> <li>• 3rd generation (norgestimate, gestodene)</li> <li>• 4th generation (nomegestrol acetate<sup>3</sup>)</li> </ul>
<b>Other non-oral contraceptives</b>		<ul style="list-style-type: none"> <li>• Etonogestrel: implant</li> <li>• Norelgestromin: transdermal patch</li> <li>• Levonorgestrel: hormonal intra-uterine device (IUD)</li> <li>• Ethinyloestradiol/etonogestrel: vaginal ring</li> </ul>
<sup>1</sup> for safety concerns regarding meningioma, please see: <a href="https://www.ema.europa.eu/en/documents/press-release/restrictions-use-cyproterone-due-meningioma-risk_en.pdf">https://www.ema.europa.eu/en/documents/press-release/restrictions-use-cyproterone-due-meningioma-risk_en.pdf</a> <sup>2</sup> Oestrogen: for example, ethinyloestradiol or oestradiol or oestradiol valerate or oestetrol or mestranol <sup>3</sup> for safety concerns regarding meningioma, please see: <a href="https://www.ema.europa.eu/en/documents/referral/new-measures-minimise-risk-meningioma-medicines-containing-nomegestrol-or-chlormadinone_en.pdf">https://www.ema.europa.eu/en/documents/referral/new-measures-minimise-risk-meningioma-medicines-containing-nomegestrol-or-chlormadinone_en.pdf</a> and <a href="https://www.ema.europa.eu/en/medicines/human/referrals/nomegestrol-chlormadinone">https://www.ema.europa.eu/en/medicines/human/referrals/nomegestrol-chlormadinone</a>		

#### **6.4.12.1 Efficacy**

For this update of the EuroGuiDerm Acne Guideline, we used the data summary from the Cochrane Review by Arowojolu et al. (226) and the American Academy of Dermatology (AAD) Guidelines on the treatment of acne vulgaris (136) to evaluate the efficacy and safety of hormonal treatments, including combined oral contraceptives (COCs). Following the guideline's search period, we conducted a systematic search across two databases to identify randomized controlled trials investigating the use of hormonal interventions for acne treatment. However, no new studies on oral hormonal contraceptives were found.

For detailed information on the efficacy data see evidence report.

#### **6.4.12.2 Safety**

Combined oral contraceptives (COCs) can cause adverse events, such as venous thromboembolism (VTE), myocardial infarction, stroke, depression, breast and cervical cancer, and an increased risk of meningiomas. The risk of VTE is lower in COCs containing less than 50 µg of ethinyl estradiol (EE), although further reductions in EE dose have not significantly impacted VTE risk. The absolute risk of VTE is small compared to pregnancy or postpartum, with slightly higher risks in drospirenone-containing COCs. Additionally, COCs may slightly increase the risk of heart attack and stroke, especially in women over 35 who smoke or have conditions like hypertension, diabetes, or migraines (136, 225).

While COCs show a slight increase in breast and cervical cancer risks, they reduce the risks of endometrial, ovarian, and colorectal cancers. A long-term UK study observed a neutral balance between cancer risks and benefits in past COC users after 30 years (136, 225).

Beyond contraception, COCs offer other benefits, such as regulating menstrual cycles, treating acne, preventing menstrual migraines, and managing conditions like dysmenorrhea, endometriosis, and premenstrual syndrome. Given the range of benefits and risks, patient-centered counselling that considers individual preferences is essential in making informed decisions about contraceptive use (136, 225).

For detailed information on the safety data see evidence report and international guidelines on safety aspects of COCs (225, 227-229).

### **6.4.13 Use of spironolactone**

Nast / Pennitz

Due to its antiandrogenic properties, spironolactone is used off-label to treat acne in women. This treatment is particularly beneficial for women with acne linked to hormonal imbalances, such as those associated with polycystic ovary syndrome (PCOS). As new evidence on spironolactone's efficacy has been published and as the guideline group perceived a need for additional systemic treatment options, it decided to include spironolactone into the guideline despite the fact that it is not licenced for acne in Europe.

For treatment recommendations with respect to specific acne subtype, see chapter 6 "Induction therapy".

#### **6.4.13.1 Safety**

Patients taking spironolactone may experience side effects such as menstrual irregularities, breast tenderness, fatigue, headache, and dizziness. Menstrual irregularities can often be managed with the addition of combined oral contraceptives (COCs). Although animal studies have indicated a tumorigenicity warning, human studies have not shown a significant association between spironolactone use and cancer risk (136).

Regarding the risk for electrolyte disbalances, the AAD guidelines found that routine potassium monitoring is of limited value unless patients have risk factors for hyperkalaemia, such as older age, underlying medical conditions, or use of certain medications. This conclusion is mostly based on observational studies (136). Potassium monitoring should be considered for older adults, those with medical conditions like hypertension, diabetes, or chronic kidney disease, and those taking medications that affect renal, adrenal, or liver function (such as ACE inhibitors, ARBs, NSAIDs, and digoxin). (136).

A literature review, identified via hand search, did not find evidence for feminization of males exposed to spironolactone in utero (230).

### **Reasoning for recommendations**

The use of spironolactone is limited by its off-label status, which, depending on the national regulations of the individual countries, usually makes it a second line treatment in case of failure of the standard of care.

Spironolactone shows superior efficacy compared to placebo for some comparisons and outcomes, but not for all. The comparison to doxycycline is limited due to the shorter treatment duration in the doxycycline treatment arm (see evidence report).

### **Dosing recommendation and treatment duration**

Start with 50 mg, increasing to 100 mg after four weeks if well tolerated (e.g. no breast tenderness, fatigue, headache, dizziness/hypotension).

Patients should be informed about the gradual onset of effectiveness; continued improvement has been observed in clinical trials over 6 months duration.

### **Monitoring**

No laboratory monitoring is needed for healthy patients under 45; individual factors may warrant exceptions (136).

## 7 Maintenance therapy (last update 2016)

### Summary of therapeutic recommendations for maintenance therapy with respect to acne type before induction therapy

Recommendations are based on available evidence and expert consensus. Available evidence and expert voting lead to classification of strength of recommendation.

A maintenance treatment, especially for the patients with “particular need for a maintenance treatment” as defined below, is recommended.

The low strength of recommendation provided below reflects primarily the lack of good evidence as to which is the best treatment and does not put into question the need for maintenance therapy in general.

	Comedonal acne	Mild to moderate papulopustular acne	Severe papulopustular/ moderate nodular acne	Severe nodular/ conglobate acne
<b>High strength of recommendation</b>	-	-	-	-
<b>Medium strength of recommendation</b>	-	-	-	-
<b>Low strength of recommendation</b>	Azelaic Acid or Topical Retinoid <sup>2</sup>	Azelaic Acid or BPO or Topical Retinoid <sup>2</sup>	Adapalene + BPO (f.c.) <sup>3</sup> or Azelaic Acid or BPO <sup>3</sup> or Low Dose Systemic Isotretinoin (max. 0.3mg/kg/d) or Topical Retinoid <sup>2</sup>	Adapalene + BPO (f.c.) <sup>3</sup> or Azelaic Acid or BPO <sup>3</sup> or Low Dose Systemic Isotretinoin (max. 0.3mg/kg/d) or Topical Retinoid <sup>2</sup>
<b>Alternatives for females <sup>1</sup></b>	-	-	Continued Hormonal Antiandrogens <sup>4</sup> + Topical Treatment (apart from antibiotics)	Continued Hormonal Antiandrogens <sup>4</sup> + Topical Treatment (apart from antibiotics)

<sup>1</sup> low strength of recommendation

<sup>2</sup> preference for adapalene over isotretinoin / tretinoin

<sup>3</sup> in case of continuing inflammatory lesions

<sup>4</sup> refer to national guidelines and EMA recommendations for precautions with respect to risk and duration of hormonal antiandrogens/combined oral contraceptives

### 7.1 Recommendations for maintenance therapy

**Recommendations for maintenance therapy**

High strength of recommendation

None

Medium strength of recommendation

None

Low strength of recommendation

**Comedonal acne**

Azelaic acid **can be considered** for the maintenance treatment of comedonal acne.

Topical retinoid<sup>1</sup> **can be considered** for the maintenance treatment of comedonal acne.

**Mild to moderate papulopustular acne**

Azelaic acid **can be considered** for the maintenance treatment of mild to moderate papulopustular acne.

Topical retinoid<sup>1</sup> **can be considered** for the maintenance treatment of mild to moderate papulopustular acne.

**Severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne**

The fixed-dose combination adapalene and BPO<sup>2</sup> **can be considered** for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.

Azelaic acid **can be considered** for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.

BPO<sup>2</sup> **can be considered** for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.

Low dose systemic isotretinoin (max. 0.3 mg/kg/d) **can be considered** for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.

Topical retinoid<sup>1</sup> **can be considered** for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.

For females: Continued hormonal antiandrogens<sup>3</sup> and topical treatment (apart from antibiotics) **can be considered** for the maintenance treatment of severe papulopustular/ moderate nodular acne and severe nodular/ conglobate acne.

Open recommendation

Due to a lack of sufficient evidence, **it is currently not possible** to make a recommendation for or against maintenance treatment with red light, blue light, IPL, Laser, PDT or oral zinc.

Negative recommendation

Topical and/or systemic antibiotics as monotherapy or combination therapy **are not recommended** for maintenance treatment of acne.

Artificial UV radiation **is not recommended** for maintenance treatment of acne.

<sup>1</sup> preference for adapalene over isotretinoin / tretinoin

<sup>2</sup> in case of continuing inflammatory lesions

<sup>3</sup> refer to national guidelines and EMA recommendations for precautions with respect to risk and duration of hormonal antiandrogens/combined oral contraceptives

## 7.2 Background

### Gollnick/ Dréno

Acne is a chronic inflammatory disease that can persist for a number of years, and is known to have a negative impact on the patients' quality of life. Scarring is the most difficult sequela of the disease and has therefore to be avoided by appropriate early intervention using an evidence-based treatment strategy. Acne has the general tendency to relapse; however, very little data exists regarding the frequency and/or severity and/or velocity of relapses.

The strategy for treating acne today includes an induction phase followed by a maintenance phase, and is further supported by adjunctive treatments (light, peeling) and/or cosmetic treatments (231).

Education about the physiopathology and the treatment procedures of acne can enhance patient adherence to maintenance therapy. However, the psychosocial benefits of further reconstituting the skin may be the most compelling reason for consistent maintenance therapy. It may also be helpful to explain to patients that acne is often a chronic disease running over years that requires acute and maintenance therapy for sustained remission.

### **Definition of maintenance treatment / goals of maintenance treatment**

No standard definition for maintenance treatment exists/is used.

The European acne guideline version 2011 stated: 'Maintenance therapy can be defined as the regular use of appropriate therapeutic agents to ensure that acne remains in remission'.

Dressler et al. (232) defined 'maintenance is the treatment period that follows a successful induction therapy at the end of which patients had achieved a pre-defined treatment goal'.

The Board of the Global Alliance for better Outcome of Acne (GA) consented the following treatment goals:

- prevention of relapse of more than 10-20% of inflammatory lesions
- preventing recurrence of microcomedones
- further improvement of postinflammatory hyperpigmentation and atrophic scarring

### **Identification of patients with particular need for maintenance treatment**

Adapted from a consensus from the Board of the Global Alliance for better Outcome of Acne (GA) the following predictive factors for relapse may serve as criteria to identify patients with particular need for maintenance therapy:

- history of severe of acne
- family history of chronicity of acne/ persisting acne courses
- tendency for scarring
- time until clearance during interventional treatment
- severe seborrhea
- early and fast onset courses in young adolescents
- early and fast onset of conglobate acne in young adolescents
- patients already having the course of acne tarda or persisting adult acne
- female patients with endocrinological disturbances (clinical or/and serological).
- repeated relapse in medical history after previous therapy

### **Pathophysiological considerations for the maintenance phase**

It has been shown that microcomedones significantly decrease during the active treatment phase but rebound almost immediately after discontinuation of a topical retinoid (128).

Therefore, a maintenance therapy to reduce the potential of reoccurring visible lesions should be considered as part of routine care today. In particular, inflammatory lesions are the prominent marker to be suppressed by topical or combined topical and systemic treatment as soon as possible. They almost develop from the recurrence of microcomedones.

### **Efficacy and safety during maintenance therapies**

A systematic review by Dressler et al. (232) identified four randomized controlled trials and three non-randomized intervention studies on acne maintenance treatment.

Three RCTs (233-235) evaluated adapalene 0.1% gel QD maintenance treatment compared to placebo over the course of 12, 16 and 24 weeks each. The pooled effect of two RCTs evaluating adapalene versus vehicle on 'number of patients maintaining at least 50% improvement achieved in the initial study' was statistically significant based on inflammatory and non-inflammatory lesion count

(233, 234). The 24-week open RCT by Zang et al. (235) also reported a higher mean percentage reduction in total lesion count in the adapalene than in the placebo arm. Adapalene showed superior efficacy in maintaining response on NIL and IL compared to placebo/ vehicle.

Poulin et al. (236) assessed the fixed combination adapalene 0.1%/ BPO 2.5% gel QD compared to vehicle QD as maintenance treatment. A statistically significant difference was found at 12 and 24 weeks based on inflammatory and non-inflammatory lesion count: adapalene/ BPO fixed combination showed superior efficacy on NIL and IL compared to placebo.

Reported data on tolerability and safety was limited. Tolerability was reported by all authors with mild but mostly no burning / stinging, erythema or dryness (232).

There is a strong need to develop more standardized study designs to systematically assess maintenance therapy for acne. Due to the set inclusion and exclusion criteria, many trials reporting on long maintenance treatment could not be included, mostly due to the lack of a clearly defined minimum treatment goal which defines responders to enter into a maintenance phase.

### **Additional clinical trials**

Recent clinical trials have in particular looked for the effect of maintenance therapy on microcomedones. In one of those controlled trials it could be shown that adapalene and azelaic acid have been equivalent in preventing relapse and suppressing microcomedone recurrence (128, 237).

Some other trials which further confirm maintenance therapy to prevent relapse but could not be included because of the guideline rules and less defined maintenance treatment inclusion criteria in the past (see above) should be mentioned here. In a vehicle controlled study by Vender et al. (238) prevention with tretinoin 0.04% gel (microsphere) against relapse was shown in patients having been before successfully treated by oral isotretinoin. In another prospective, randomized, double-blind and vehicle-controlled study of 30 patients with acne previously treated with isotretinoin a retinoid combination (retinsphere technology Bi-retix) was applied to one side of the face and vehicle was applied to the other, once daily, for 3 months. The relapse rate was significantly lower on the retinoid-treated side compared to the vehicle-treated side.

### **7.3 Reasoning**

Available evidence indicates efficacy of azelaic acid, topical retinoids and adapalene/ BPO over vehicle during maintenance treatment.

Pathophysiological data supports use of azelaic acid, topical retinoids and adapalene based on their demonstrated efficacy on microcomedones.

Any use of topical or systemic antibiotics is not recommended on a long-term base / during maintenance therapy.

#### **Duration of long term-treatment**

The following maintenance treatment periods can be considered:

- 3 to 6 months following clearing after interventional treatment phase can be recommended
- patients with conglobate acne may need long-term maintenance over 6 to 12 months
- acne tarda patients may need individual long-term maintenance over years.

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## 9 Supporting information

The EuroGuiDerm Guideline for the Treatment of Acne Methods report & Evidence tables and report are available as supplementary files and on the EDF website: <https://www.guidelines.edf.one/edf-guidelines-and-consensus-state-ments>

**Appendix:** Included studies

**Appendix:** List of abbreviations

### Methods report

**Table S1:** Comedonal acne

**Table S2:** Papulopustular acne

**Table S3:** Conglobate acne

### Evidence report – update 2025