SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acnecutan 10 mg/g + 50 mg/g Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g gel contains:
10 mg (1 % w/w) clindamycin as clindamycin phosphate
50 mg (5 % w/w) anhydrous benzoyl peroxide as hydrous benzoyl peroxide
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel
White gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acnecutan 10 mg/g + 50 mg/g Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions, in adults and adolescents aged 12 years and above
(see sections 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

For cutaneous use only.

Posology

Adults and Adolescents (aged 12 years and above)
Acnecutan 10 mg/g + 50 mg/g Gel (in this SmPC referred to as Acnecutan) should be applied once daily in the evening, to the entire affected area.
Patients should be advised that excessive application will not improve efficacy, but may increase the risk of skin irritation. If excessive dryness or peeling occurs,

frequency of application should be reduced or application temporarily interrupted (see section 4.4).
An effect on inflammatory and non-inflammatory lesions may be seen as early as week 2-5 of
treatment (see section 5.1).
The safety and efficacy of Acnecutan has not been studied beyond 12 weeks in acne vulgaris clinical trials. Treatment with Acnecutan should not exceed more than 12 weeks of continuous use.
Paediatric population
The safety and efficacy of Acnecutan in children under 12 years of age has not been established. Therefore, Acnecutan is not recommended for use in this population.

Elderly patients
No specific recommendations.

Method of administration
Acnecutan should be applied in a thin film after washing gently with a mild cleanser and fully drying. If the gel does not rub into the skin easily, too much is being applied.

Hands should be washed after application.

4.3 Contraindications

Hypersensitivity to clindamycin, lincomycin, benzoyl peroxide or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated or broken skin should be avoided. Application to sensitive areas of skin should be made with caution. In case of accidental contact, rinse well with water.
Acnecutan should be used with caution in patients with a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.
Acnecutan should be used with caution in atopic patients, in whom further skin drying may occur.
During the first weeks of treatment, an increase in peeling and reddening will occur in most patients. Depending upon the severity of these side effects, patients can use a non-comedogenic moisturiser, temporarily reduce the frequency of application of Acnecutan or temporarily discontinue use; however, efficacy has not been established for less than once daily dosing frequencies.
Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy may occur, which sometimes may be severe, especially with the use of peeling, desquamating, or abrasive agents.
If severe local irritancy (e.g. severe erythema, severe dryness and itching, severe stinging/burning) occurs, Acnecutan should be discontinued.
As benzoyl peroxide may cause increased sensitivity to sunlight, sunlamps should not be used and deliberate or prolonged exposure to sun should be avoided or minimised. When exposure to strong sunlight cannot be avoided, patients should be advised to use a sunscreen product and wear protective clothing.
If a patient has sunburn, this should be resolved before using Acnecutan.

If prolonged or significant diarrhoea occurs or the patient suffers from abdominal cramps, treatment with Acnecutan should be discontinued immediately, as the symptoms may indicate antibiotic-associated colitis. Suitable diagnostic methods, such as the determination of *Clostridium difficile* and toxin and, if necessary, colonoscopy should be employed and treatment options for colitis considered.
The product may bleach hair or coloured fabrics. Avoid contact with hair, fabrics, furniture or carpeting.

Resistance to clindamycin
Patients with a recent history of systemic or topical clindamycin or erythromycin use are more likely to have pre-existing anti-microbial resistant *Propionibacterium acnes* and commensal flora (see section 5.1).

Cross-resistance
Cross-resistance may occur with other antibiotics such as lincomycin and erythromycin when using antibiotic monotherapy (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug-drug interaction studies have been performed with clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel.
Concomitant topical antibiotics, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol and/or astringents, should be used with caution as a cumulative irritant effect may occur.
Acnecutan should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component.
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore caution should be exercised with concomitant use.
Concomitant application of Acnecutan with tretinoin, isotretinoin and tazarotene should be avoided since benzoyl peroxide may reduce their efficacy and increase irritation. If combination treatment is required, the products should be applied at different times of the day (e.g. one in the morning and the other in the evening).
Using topical benzoyl peroxide-containing preparations at the same time as topical sulfonamide-containing products may cause skin and facial hair to temporarily change colour (yellow/orange).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel in pregnant women. Animal reproductive/developmental studies have not been conducted with clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel or benzoyl peroxide. There are limited data on the use of clindamycin and benzoyl peroxide alone in pregnant women. Data from a limited number of pregnancies exposed in the first trimester to clindamycin indicate no adverse effects of clindamycin on pregnancy or on the health of the fetus/new-born child.
Reproduction studies in rats and mice, using subcutaneous and oral doses of clindamycin, revealed no evidence of impaired fertility or harm to the fetus due to clindamycin.

The safety of clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel in human pregnancy is not established. Therefore, Acnecutan should only be prescribed to pregnant women after careful risk/benefit assessment by the physician in charge.

Breastfeeding

Use of clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel has not been studied during breastfeeding. Percutaneous absorption of clindamycin and benzoyl peroxide is low however; it is not known whether clindamycin or benzoyl peroxide is excreted in human milk following the use of clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel. Oral and parenteral administration of clindamycin has been reported to result in the appearance of clindamycin in breast milk. For this reason, Acnecutan should be used during lactation only if the expected benefit justifies the potential risk to the infant.

To avoid accidental ingestion by the infant if used during lactation, Acnecutan should not be applied to the breast area.

Fertility

There are no data on the effect of clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel on fertility in humans.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse drug reactions (ADRs) are summarised below for Acnecutan as a combination, including any additional ADRs that have been reported for the single topical active ingredients, benzoyl peroxide or clindamycin, that occurred either during clinical studies or that were spontaneously reported. Adverse drug reactions are listed by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000) and not known (cannot be estimated from the available data).

MedDRA SOC	Very Common	Common	Uncommon	Not known[2]
Immune system disorders				Allergic reactions including hypersensitivity and anaphylaxis
Nervous system disorders			Paraesthesia[1]	
Gastrointestinal disorders				Colitis (including pseudomembranous colitis), haemorrhagic diarrhoea, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders[1]	Erythema, peeling, dryness	Burning sensation	Dermatitis, pruritus, erythematous	Urticaria

	(Generally reported as 'mild' in severity)		rash, worsening of acne	
General disorders and Administration site conditions				Application site reactions including skin discolouration

[1]At site of application. [2]Based on post-marketing reports. Since these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency however, systemic reactions are rarely seen.

In addition to the ADRs reported in the table above, in the pivotal trial conducted with topical clindamycin 1%/benzoyl peroxide 3% gel, application site photosensitivity reaction was also reported commonly.

Also in addition to the ADRs reported above, in studies conducted with topical clindamycin alone, headache and application site pain were reported commonly.

Local Tolerability
During five clinical trials with clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

Local Tolerability Assessments for Subjects (N=397) in the clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel Group during the Phase 3 Studies

	Before Treatment (Baseline)			**During Treatment**		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Excessive application of Acnecutan may result in severe irritation. In this event, discontinue use and wait until the skin has recovered.
Topically applied benzoyl peroxide is not generally absorbed in sufficient amounts to produce systemic effects.
Excessive application of topically applied clindamycin may result in absorption of sufficient amounts to produce systemic effects.
In the event of accidental ingestion of Acnecutan, gastrointestinal adverse reactions similar to those seen with systemically administered clindamycin may be seen.

Appropriate symptomatic measures should be taken to provide relief from irritation due to excessive application.
Accidental ingestion should be managed clinically or as recommended by the National Poisons Centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Clindamycin, combinations, ATC code: D10AF51

Clindamycin is a lincosamide antibiotic with bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin bind to the 23S subunit of the bacterial ribosome and inhibit the early stages of protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.Although clindamycin phosphate is inactive *in-vitro*, rapid *in-vivo* hydrolysis converts this compound to the antibacterial active clindamycin. Clindamycin activity has been demonstrated clinically in comedones from acne patients at sufficient levels to be active against most strains of *Propionibacterium acnes*. Clindamycin *in-vitro* inhibits all *Propionibacterium acnes* cultures tested (MIC 0.4 mcg/ml). Free fatty acids on the skin surface have been decreased from approximately 14 % to 2 % following application of clindamycin.
Benzoyl peroxide is mildly keratolytic acting against comedones at all stages of their development. It is an oxidising agent with bactericidal activity against *Propionibacterium acnes*, the organism implicated in acne vulgaris. Furthermore, it is sebostatic, counteracting the excessive sebum production associated with acne.
Acnecutan has a combination of mild keratolytic and antibacterial properties providing activity particularly against inflamed lesions of mild to moderate acne vulgaris.
The prevalence of acquired resistance may vary geographically and with time for selected species. Local information of resistance is desirable, particularly when treating severe infections.
The inclusion of benzoyl peroxide reduces the potential for the emergence of organisms resistant to clindamycin.
The presentation of both active ingredients in one product is more convenient and ensures patient compliance.

<u>Clinical efficacy and safety</u>

The safety and efficacy of <Invented name> applied once daily were evaluated in a 12-week multicentre, randomised, double-blind phase III study in 680 subjects with papulopustular acne, aged 12 to 61 years. The two primary efficacy variables were the percentage change in number of inflammatory lesions and the percentage change in total number of lesions between start and end of treatment (week 12). The safety and efficacy were compared between the <Invented name> group, the clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel reference group (originator) and the Vehicle group.

The overall median age of subjects was 19 years with 41.8 % below the age of 18 years. 65.6 % of the participants were females and 98.8% were Caucasian. At

baseline, the mean number of inflammatory lesions per subject was 29.7 for the test product, 29.8 for the reference product and 29.7 for the vehicle. The mean number of total lesions per subject was 78.4 for the test product, 72.5 for the reference product and 76.8 for the vehicle. At baseline the majority of the patients had “moderate” acne (76.9%), 8.5% had “mild” and 14.6% “severe” acne. Efficacy results at week 12 are presented in the table below:

Efficacy results in week 12

	<Invented name> (n = 221)	clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel reference product (n = 223)	Vehicle (n = 228)
Inflammatory lesions			
Mean absolute change	24.3	22.9	14.1
Mean percent change	84.6 %	81.8%	50.7%
Total lesions (inflammatory lesions plus non-inflammatory lesions)			
Mean absolute change	60.4	51.8	34.2
Mean percent change	80.2 %	77.3 %	50.1 %

The **mean percent change** in number of inflammatory lesion was 84.6% for the test product, 81.8% for the reference and 50.7% for vehicle. The percent change in total number of lesions was 80.2% for the test product, 77.3% for the reference and 50.1% for the vehicle. For both primary efficacy variables, therapeutic equivalence of <Invented name> in comparison to clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel reference product was statistically proven, and both active preparations were statistically superior to vehicle.

The results of the secondary efficacy variables were consistent with the results of the primary efficacy variables:
The clinical success at the end of the treatment, defined as decrease of at least 2 points in the Investigator`s Global assessment score, was achieved in 51.6% of patients for the test product, 49.3% for the reference and 21.5% for vehicle. The following IGA scoring scale was used in the clinical trial:

Score	Description
0	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions).
3	Moderate severity; greater than Grade 2, up to many non-inflammatory lesions and may

	have some inflammatory lesions. But no more than one small nodular lesion.
4	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions.

All three treatments were tolerated well according to the tolerability ratings of the investigators. That is, for nearly all patients in each treatment group, tolerability was reported as *very good* or *good* for all visits (test product 91.4%, reference product: 93.3%, vehicle: 92.5%).

5.2 Pharmacokinetic properties

In a maximal percutaneous absorption study the mean plasma clindamycin levels during a four-week dosing period for clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel were negligible (0.043% of applied dose).

The presence of benzoyl peroxide in the formulation did not have an effect on the percutaneous absorption of clindamycin.

Radio-label studies have shown that absorption of benzoyl peroxide through the skin can only occur following its conversion to benzoic acid. Benzoic acid is mostly conjugated to form hippuric acid, which is excreted via the kidneys.

5.3 Preclinical safety data

Clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel
In a two year carcinogenicity study in mice, topical administration of clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel showed no evidence of increased carcinogenic risk, compared with controls.
In a photococarcinogenicity study in mice, a slight reduction in the median time to tumour formation was observed relative to controls following concurrent exposure to clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel and simulated sunlight. The clinical relevance of the findings in this study is unknown.
Repeat-dose dermal toxicity studies conducted on clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel, in two species, for up to 90 days, revealed no toxic effects, apart from minor local irritation.
An ocular irritation study found clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel to be only very slightly irritant.
Benzoyl peroxide
In animal toxicity studies, benzoyl peroxide was well tolerated when applied topically.
Although high doses of benzoyl peroxide have been shown to induce DNA strand breaks, the available data from other mutagenicity studies, carcinogenicity studies and a photo cocarcinogenicity study indicate that benzoyl peroxide is not a carcinogen or a photocarcinogen.
No reproductive toxicity data are available.
Clindamycin
In-vitro and *in-vivo* studies did not reveal any mutagenic potential of clindamycin. No long-term animal studies investigating the tumorigenic potential of clindamycin have

been conducted. Otherwise, preclinical data reveal no special hazard for humans based on conventional studies of single and repeat-dose toxicity and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer
Dimeticone
Disodium lauryl sulfosuccinate
Disodium edetate
Glycerol 85 %
Silica, colloidal hydrated
Poloxamer 182
Purified water
Sodium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Shelf life of medicinal product after first opening:
2 months

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.

Storage conditions after first opening:
Do not store above 25°C.

6.5 Nature and contents of container

Aluminium tube with internal protective lacquer (epoxy phenolic resin combination) and a HDPE screw cap with piercing device.

Before using the gel for the first time, the aluminium membrane has to be pierced by the spike on the outer side of the screw cap.

Pack sizes: 30 g, 50 g and 60 g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mibe Pharma UK Ltd
4 Coleman Street, 6th Floor
London
EC2R 5AR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 49452/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/09/2025

10 DATE OF REVISION OF THE TEXT

02/09/2025