SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains:
10 mg clindamycin as clindamycin phosphate
30 mg anhydrous benzoyl peroxide as hydrous benzoyl peroxide
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel
White to slightly yellow homogeneous gel with visible fine particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clindamycin + Benzoyl Peroxide 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)
Clindamycin + Benzoyl Peroxide Gel 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).

The safety and efficacy of Clindamycin + Benzoyl Peroxide Gel has not been studied beyond 12 weeks in acne vulgaris clinical trials. Treatment with this

medicine should not exceed more than 12 weeks of continuous use.

Paediatric population
The safety and efficacy of Clindamycin + Benzoyl Peroxide Gel has not been established in children under 12 years of age, therefore this medicine is not recommended for use in this population.

Elderly patients
No specific recommendations.

Method of administration
Clindamycin + Benzoyl Peroxide Gel 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

Clindamycin + Benzoyl Peroxide Gel must not be administered to patients with known hypersensitivity to:

- clindamycin
- lincomycin
- benzoyl peroxide
- any of the excipients in the formulation 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.

Clindamycin + Benzoyl Peroxide Gel should be used with caution in patients with a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

This medicine 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 Clindamycin + Benzoyl Peroxide Gel 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, Clindamycin + Benzoyl Peroxide Gel 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 this medicine.

If prolonged or significant diarrhoea occurs or the patient suffers from abdominal cramps, treatment with Clindamycin + Benzoyl Peroxide Gel 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 + Benzoyl Peroxide 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.

This medicine 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 Clindamycin + Benzoyl Peroxide Gel 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 this medicine in pregnant women. Animal reproductive/developmental studies have not been conducted with Clindamycin + Benzoyl Peroxide 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 foetus/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 foetus due to clindamycin.

The safety of Clindamycin + Benzoyl Peroxide Gel in human pregnancy is not established. Therefore, this medicine should only be prescribed to pregnant women after careful risk/benefit assessment by the physician in charge.

Breastfeeding

Use of Clindamycin + Benzoyl Peroxide 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 this medicine. Oral and parenteral administration of clindamycin has been reported to result in the appearance of clindamycin in breast milk. For this reason, Clindamycin + Benzoyl Peroxide Gel 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, this medicine should not be applied to the breast area.

Fertility

There are no data on the effect of Clindamycin + Benzoyl Peroxide 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 Clindamycin + Benzoyl Peroxide Gel 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 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000) and not known (cannot be estimated from the available data).

MedDRA SOC	Very Common	Common	Uncommon	Not known**
Immune system disorders				Allergic reactions including hypersensitivity and anaphylaxis
Nervous system disorders*		Headache[4]	Paraesthesia[1]	
Gastrointestinal disorders				Colitis (including pseudomembranous colitis), haemorrhagic diarrhoea, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders*	Pruritus, burning sensation, dryness, erythema, peeling *(Generally reported as 'slight' in severity. Frequency relates to data from solicited tolerability assessments during the clinical trial)*	Dermatitis, photosensitivity reaction	Erythematous rash, worsening of acne	Urticaria
General disorders and Administration site conditions		Application site pain[4]		Application site reactions including skin discoloration

[1]At site of application. [2]Based on post-marketing reports with topical clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel. 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. [3]Reported from studies conducted with topical clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel. [4]Reported from studies conducted with topical clindamycin 10 mg/g foam.

Local Tolerability

During the pivotal clinical trial with a Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel, patients were assessed for local cutaneous signs and symptoms of erythema, dryness, peeling, itching, and burning/stinging. The percentage of patients that had symptoms present before treatment, during treatment, and present at week 12 are shown in the next two tables:

Percentage of Subjects in the Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel Group (N=327) with Symptoms of Burning/Stinging and Itching (patient assessed)

	Before Treatment (Baseline)			Maximum During Treatment			End of Treatment (Week 12)		
	Slight	Mod	Strong	Slight	Mod	Strong	Slight	Mod	Strong
Burning/ Stinging	15%	4%	0	20%	6%	1%	8%	2%	<1%
Itching	28%	6%	1%	29%	9%	1%	17%	2%	0

Percentage of Subjects in the Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel Group (N=327) with Signs of Dryness, Erythema and Peeling (investigator assessed)

	Before Treatment (Baseline)				Maximum During Treatment				End of Treatment (Week 12)			
	Slight	Mild	Mod	Severe	Slight	Mild	Mod	Severe	Slight	Mild	Mod	Severe
Dryness	15%	2%	1%	0	24%	7%	2%	0	9%	1%	1%	0
Erythema	19%	11%	5%	0	26%	13%	5%	<1%	19%	4%	2%	0
Peeling	10%	2%	0	0	17%	3%	1%	0	4%	<1%	0	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 Clindamycin + Benzoyl Peroxide Gel 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 Clindamycin + Benzoyl Peroxide Gel, 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 0.4mcg/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.

Clindamycin + Benzoyl Peroxide Gel 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 in clindamycin 10 mg/g + benzoyl peroxide 50 mg/g gel reduces the potential for the emergence of organisms resistant to clindamycin. This has not been studied in Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel.

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 a Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel applied once daily were evaluated in a 12-week multicentre, randomised, double-blind phase III study in 1315 subjects with acne vulgaris, aged 12 to 45 years. Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel was compared with

clindamycin 1 % in vehicle gel, benzoyl peroxide 3 % in vehicle gel, and vehicle gel alone. The primary efficacy measures for acne severity were evaluated using lesion counts and the 6-point Investigator's Static Global Assessment (ISGA) scale. The ISGA scoring scale used in the clinical trial was as follows:

Grade/ Score	Description
0	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost clear: rare non-inflammatory lesions present, with no more than rare papules.
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, many non-inflammatory lesions and may have some inflammatory lesions, but no more than 1 small nodular lesion.
4	Severe: greater than Grade 3, up to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions.
5	Very severe: many non-inflammatory and inflammatory lesions and more than a few nodular lesions. May have cystic lesions.

The mean age of subjects was 20.4 years old and 60 % were females and 79 % were Caucasian. At baseline, the mean number of acne lesions per subject was 72 total lesions, with 45.3 non-inflammatory lesions and 26.6 inflammatory lesions. The majority of subjects (62 %) enrolled with a baseline ISGA score of 3 (range 2 to 4). The efficacy results at week 12 are presented in the following table.

Efficacy Results at Week 12

	Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel (N=327)	**Clindamycin 1% gel (N=328)**	**Benzoyl Peroxide 3% gel (N=328)**	**Vehicle gel (N=332)**
Inflammatory Lesions				
Mean absolute reduction*	18.2	**15.6**	**16.8**	**13.1**
Mean percentage reduction	68.9 %	**58.1 %**	**61.8 %**	**48.8 %**
Non-inflammatory Lesions				
Mean absolute reduction*	24.8	**19.8**	22.2	**14.8**
Mean percentage reduction	53.9 %	**43.3 %**	50.8 %	**34.0 %**
Total Lesions				
Mean absolute reduction*	43.0	**35.5**	**39.0**	**27.8**
Mean percentage reduction	59.8 %	**49.2 %**	55.5 %	**40.4 %**
Investigator's Global Assessment				
Percentage of subjects with minimum 2-grade improvement in ISGA from baseline to week 12*	39 %	**25 %**	**30 %**	**18 %**
Percentage of subjects with ISGA of clear or almost clear skin at week 12	45 %	**28 %**	**35 %**	**24 %**

*Primary endpoints. Statistically significant differences from Clindamycin + Benzoyl Peroxide10mg/g + 30mg/g Gel highlighted in bold.

The Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel was superior to clindamycin gel, benzoyl peroxide 3% gel, and vehicle gel in the proportion of subjects who had at least a 2-grade improvement in ISGA. Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel was superior to clindamycin gel and vehicle gel in the absolute reduction of inflammatory, non-inflammatory, and total lesions, and was superior to benzoyl peroxide 3 % gel in the absolute reduction of inflammatory and total lesions.

Secondary endpoints showed that the percentage reduction in all lesion counts from baseline to week 12 for Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel was superior to clindamycin 1 % gel and vehicle gel and the percentage reduction in inflammatory lesions was superior to benzoyl peroxide 3 % gel. The percentage of subjects with ISGA score of 0 (clear) or 1 (almost clear) at week 12 was significantly greater for Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel relative to its active constituents and the vehicle gel.

In a separate analysis of the data it was observed that a greater proportion of subjects in the Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel group had a 2-grade improvement in ISGA from baseline to week 12 together with an ISGA score of 0 (clear) or 1 (almost clear) at week 12 compared with clindamycin gel ($P<0.001$), benzoyl peroxide gel ($P=0.003$), and vehicle gel ($P<0.001$).

Other Endpoints

In an assessment of other endpoints, improvement versus vehicle or clindamycin gel on inflammatory and non-inflammatory lesions was apparent from week 2 of treatment ($P<0.05$). Lesion count continued to decrease throughout the 12 week course of the study.

5.2 Pharmacokinetic properties

In an open-label study of 24 patients with moderate-to-severe acne vulgaris, approximately 4 grams of a Clindamycin + Benzoyl Peroxide 10 mg/g + 30 mg/g Gel was applied once daily for 5 days to the face, upper chest, upper back, and shoulders. Geometric mean maximal plasma clindamycin exposure (Cmax) on Day 5 was 0.961 ng/mL with an AUC_{∞} of 12.9 ng*hr/mL.

In a maximised 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 + Benzoyl Peroxide Gel
In a two year carcinogenicity study in mice, topical administration of a 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 + Benzoyl Peroxide 10 mg/g + 30 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 co-carcinogenicity 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 980
Dimeticone
Disodium Lauryl Sulfosuccinate
Edetate Disodium
Glycerol (E 422)
Silica, Colloidal Hydrated

Poloxamer 182
Purified Water
Sodium Hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life of medicinal product as packaged for sale
24 months

Shelf life of medicinal product after dispensing
2 months

6.4 Special precautions for storage

Store in a refrigerator (2□C to 8□C)
Do not freeze

Storage conditions after dispensing
Do not store above 25□C

6.5 Nature and contents of container

Internally lacquered membrane-sealed aluminium tubes fitted with a polyethylene screw-cap, packed into a carton.

Pack sizes: 30 and 60 grams.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aspire Pharma Limited
Unit 4, Rotherbrook Court
Bedford Road
Petersfield
Hampshire
GU32 3QG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL35533/0212

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/12/2024

10 DATE OF REVISION OF THE TEXT

30/12/2024