SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Duac Once Daily 10 mg/g + 50 mg/g Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains:

10 mg clindamycin as clindamycin phosphate

50 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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Duac Once Daily 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)

Duac Once Daily 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).

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 Duac Once Daily Gel has not been studied beyond 12 weeks in acne vulgaris clinical trials. Treatment with Duac Once Daily Gel should not exceed more than 12 weeks of continuous use.

Paediatric population

The safety and efficacy of Duac Once Daily Gel has not been established in children under 12 years of age, therefore Duac Once Daily Gel is not recommended for use in this population.

Elderly patients

No specific recommendations.

Method of administration

Duac Once Daily 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

Duac Once Daily 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.

Duac Once Daily Gel should be used with caution in patients with a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

Duac Once Daily Gel 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 Duac Once Daily 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, Duac Once Daily 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 Duac Once Daily Gel.

If prolonged or significant diarrhoea occurs or the patient suffers from abdominal cramps, treatment with Duac Once Daily 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 Duac Once Daily 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.

Duac Once Daily Gel 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 Duac Once Daily 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 Duac Once Daily Gel in pregnant women. Animal reproductive/developmental studies have not been conducted with Duac Once Daily 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 Duac Once Daily Gel in human pregnancy is not established. Therefore, Duac Once Daily Gel should only be prescribed to pregnant women after careful risk/benefit assessment by the physician in charge.

Breastfeeding

Use of Duac Once Daily 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 Duac Once Daily Gel. Oral and parenteral administration of clindamycin has been reported to result in the appearance of clindamycin in breast milk. For this reason, Duac Once Daily 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, Duac Once Daily Gel should not be applied to the breast area.

Fertility

There are no data on the effect of Duac Once Daily 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 Duac Once Daily Gel as a combination including any additional ADRs that have been reported for the single topical active ingredients, benzoyl peroxide or clindamycin. 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*			Paraesthesia	
Gastrointestinal disorders				Colitis (including pseudomembranous colitis), haemorrhagic diarrhoea, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders*	Erythema, peeling, dryness *(Generally reported as 'mild' in severity*)	Burning sensation	Dermatitis, pruritus, erythematous rash, worsening of acne	Urticaria
General disorders and Administration site conditions				Application site reactions including skin discoloration

*At site of application. **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 the five clinical trials with Duac Once Daily 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 Duac Once Daily 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 national reporting system listed in Appendix V.

4.9 Overdose

Excessive application of Duac Once Daily 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 Duac Once Daily 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.

Duac Once Daily 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 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.

Clinical efficacy and safety

In five randomised double-blind clinical studies of 1318 patients with facial acne vulgaris with both inflammatory and non-inflammatory lesions, 396 used Duac, 396 used benzoyl peroxide, 349 used clindamycin and 177 used vehicle. Treatment was applied once daily for 11 weeks and patients were evaluated and lesions counted at 2, 5, 8 and 11 weeks.

The mean percentage reduction in the number of lesions after 11 weeks is shown in the table.

Mean percent reduction in number of lesions from baseline after 11 weeks

	Study 150 (n = 120)	**Study 151 (n = 273)**	**Study 152 (n = 280)**	**Study 156 (n = 287)**	**Study 158*** **(n = 358)**
Inflammatory lesions					
Duac Once Daily Gel	65	56	42	57	52
Benzoyl peroxide	**36**	**37**	32	57	**41**
Clindamycin	**34**	**30**	38	**49**	**33**
Vehicle	**19**	**-0.4**	29	-	**29**
Non-inflammatory lesions					
Duac Once Daily Gel	27	37	24	39	25
Benzoyl peroxide	12	30	16	**29**	23

Clindamycin	**-4**	**13**	**11**	**18**	17
Vehicle	**-9**	**-5**	17	-	-7
Total lesions (inflammatory plus non-inflammatory lesions)					
Duac Once Daily Gel	41	45	31	50	41
Benzoyl peroxide	20	35	23	43	34
Clindamycin	**11**	**22**	**22**	**33**	**26**
Vehicle	**1**	**-1**	**22**	-	**16**

[*]**Pivotal study.** Statistically significant differences highlighted in **bold.**

The reduction in total lesions was significantly greater with Duac Once Daily Gel than clindamycin or vehicle in all five studies. The improvement was consistently greater with Duac Once Daily Gel than benzoyl peroxide, but the difference did not achieve statistical significance in individual studies.

Against inflammatory lesions, Duac Once Daily Gel was significantly superior to clindamycin alone in four of five studies and to benzoyl peroxide alone in three of five studies. Against non-inflammatory lesions, Duac Once Daily Gel was significantly better than clindamycin in four of five studies, and tended to be better than benzoyl peroxide alone.

Overall improvement in acne was assessed by the physician and was significantly better with Duac Once Daily Gel than with either benzoyl peroxide or clindamycin alone in three of five studies.

An effect on inflammatory lesions was apparent from week 2 of treatment. The effect on non-inflammatory lesions was more variable, with efficacy generally apparent after 2-5 weeks of treatment.

5.2 Pharmacokinetic properties

In a maximised percutaneous absorption study the mean plasma clindamycin levels during a four-week dosing period for Duac Once Daily 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

Duac Once Daily Gel

In a two year carcinogenicity study in mice, topical administration of Duac Once Daily 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 Duac Once Daily Gel and simulated sunlight. The clinical relevance of the findings in this study is unknown.

Repeat-dose dermal toxicity studies conducted on Duac Once Daily Gel, in two species, for up to 90 days, revealed no toxic effects, apart from minor local irritation.

An ocular irritation study found Duac Once Daily 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 (50000mPa.s)

Dimeticone ($100mm^2.s^{-1}$)

Disodium Lauryl Sulfosuccinate

Edetate Disodium

Glycerol

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

18 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: 5, 6, 15, 25, 30, 50, 55, 60 and 70 grams.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Ltd
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

MA192/02801

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16th November 2005/1st December 2010

10 DATE OF REVISION OF THE TEXT

25th March 2019