For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

ACNETOR AD

(Clindamycin & Adapalene Gel)

COMPOSITION

Clindamycin Phosphate I.P.	
equivalent to Clindamycin	1.00% W/W
Adapalene B.P.	0.1% W/W
Preservatives	
Methyl Parahydroxybenzoate I.P.	0.1% W/W
Phenoxyethanol I.P.	0.25% W/W
In gel base	q.s.

DOSAGE FORM

Topical gel

INDICATION

ACNETOR AD is indicated for treatment of Acne vulgaris.

DOSE AND METHOD OF ADMINISTRATION

ACNETOR AD should be applied to the acne affected areas once a day before retiring and after washing. A thin film of gel should be applied, with the fingertips, avoiding the eyes and lips. Ensure that the affected areas are dry before application.

Since it is customary to alternate therapies in the treatment of acne, it is recommended that the physician assess the continued improvement of the patient after three months of treatment with ACNETOR AD Gel.

With patients for whom it is necessary to reduce the frequency of application or to temporarily discontinue treatment, frequency of application may be restored or therapy resumed once it is judged that the patient can again tolerate the treatment.

If patients use cosmetics, these should be non-comedogenic and non-astringent.

Paediatric population: The safety and effectiveness of ACNETOR AD Gel have not been studied in children below 12 years of age. ACNETOR AD gel should not be used in patients with severe acne.

USE IN SPECIAL POPULATIONS

Fertility, pregnancy and lactation

Pregnancy:

Clindamycin

There are no adequate and well-controlled studies in pregnant women during the first trimester. A moderate amount of data from clinical trials in pregnant women (between 300-1000 pregnancy outcomes) during the second and third trimesters indicates systemic administration of

clindamycin has not been associated with an increased frequency of congenital abnormalities or feto/neonatal toxicity. Animal reproductive toxicity studies revealed no evidence of impaired fertility or harm to the foetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response. Clindamycin topical gel should be used during pregnancy only if clearly needed.

Adapalene
Animal studies by the oral route have shown reproductive toxicity at high systemic exposure. Clinical experience with locally applied adapalene in pregnancy is limited but the few available data do not indicate harmful effects on pregnancy or on the health of the foetus exposed in early pregnancy. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, adapalene should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued.

Breast-feeding
Clindamycin
It is not known whether clindamycin is excreted in human milk following use of Acnetor AD Topical gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. As a general rule, breast-feeding should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Adapalene
No study on animal or human milk transfer was conducted after cutaneous application of adapalene. No effects on the suckling child are anticipated since the systemic exposure of the breast-feeding woman to adapalene is negligible.

Adapalene can be used during breastfeeding. To avoid contact exposure of the infant, application of adapalene to the chest should be avoided when used during breast-feeding.

CONTRAINDICATIONS
ACNETOR AD is contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin , adapalene or to any of the excipients. Clindamycin topical is contraindicated in individuals with a history of inflammatory bowel disease or a history of antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS
Adapalene
If a reaction suggesting sensitivity or severe irritation occurs, use of the medication should be discontinued. If the degree of local irritation warrants, patients should be directed to use the medication less frequently, to discontinue use temporarily, or to discontinue use altogether. Adapalene Gel should not come into contact with the eyes, mouth, nostrils or mucous membranes.

If product enters the eye, wash immediately with warm water. The product should not be applied to either broken (cut and abrasions) or eczematous skin, nor should it be used in patients with severe acne involving large areas of the body.

Clindamycin
Products containing benzoyl peroxide should not be used concurrently with clindamycin topical gel.

Oral and parenteral clindamycin, as well as most other antibiotics, have been associated with severe pseudomembranous colitis. Post-marketing studies, however, have indicated a very low incidence of colitis with clindamycin topical solution. The physician should, none the less, be alert to the development of antibiotic associated diarrhoea or colitis. If significant or prolonged diarrhoea occurs, the product should be discontinued immediately.

Diarrhoea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

Studies indicate a toxin(s) produced by *Clostridium difficile* is the major cause of antibiotic associated colitis. Colitis is usually characterised by persistent, severe diarrhoea and abdominal cramps. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *C. difficile* and/or assay for *C. difficile* toxin may be helpful to diagnosis.

Vancomycin is effective in the treatment of antibiotic-associated colitis produced by *C. difficile*. The usual dose is 125-500 mg orally every 6 hours for 7-10 days. Additional supportive medical care may be necessary.

Mild cases of colitis may respond to discontinuance of clindamycin alone. Colestyramine and colestipol resins havebeen shown to bind *C. difficile* toxin *in vitro*, and colestyramine has been effective in the treatment of some mild casesof antibiotic-associated colitis. Colestyramine resins have been shown to bind vancomycin; therefore, when bothcolestyramine and vancomycin are used concurrently, their administration should be separated by at least two hours.

Topical clindamycin should be prescribed with caution to atopic individuals.

DRUG INTERACTIONS
Clindamycin
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently monitored in patients treated with vitamin K antagonists.

Adapalene

There are no known interactions with other medications which might be used cutaneously and concurrently with adapalene gel, however, other retinoids or drugs with a similar mode of action should not be used concurrently with adapalene.

Adapalene is essentially stable to oxygen and light and is chemically non-reactive. Whilst extensive studies in animals and man have shown neither phototoxic nor photoallergic potential for adapalene, the safety of using adapalene during repeated exposure to sunlight or UV irradiation has not been established in either animals or man. Exposure to excessive sunlight or UV irradiation should be avoided.

Absorption of adapalene through human skin is low and therefore interaction with systemic medications is unlikely. There is no evidence that the efficacy of oral drugs such as contraceptives and antibiotics is influenced by the cutaneous use of adapalene gel.

UNDESIRABLE EFFECTS

Clindamycin

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000) and Not known (frequency cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions possibly or probably related to Clindamycin Phosphate Topical Solution based on clinical trial experience and post-marketing surveillance:

	Very Common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon ≥1/1,000 to <1/100**	**Frequency Not Known**
Infections and Infestations				Gram-negative Folliculitis
Eye Disorders				Stinging of the eye
Gastrointestinal Disorders			Gastrointestinal Disturbances	Abdominal pain
Skin and Subcutaneous Tissue Disorders	Skin dryness Skin irritation Urticaria	Skin oiliness		Contact dermatitis

Adapalene

Adapalene

Adapalene may cause the following adverse drug reactions:

Body System (MeDRA)	**Frequency**	**Adverse Drug Reaction**
Skin and subcutaneous tissue disorders	Common (≥1/100 to <1/10)	Dry skin, skin irritation, skin burning sensation, erythema
	Uncommon (≥1/1000 to	Dermatitis contact, skin discomfort, sunburn, pruritus, skin

	<1/100)	exfoliation, acne
	Unknown*	Dermatitis allergic (allergic contact dermatitis), pain of skin, skin swelling, eyelid irritation, eyelid erythema, eyelid pruritus, eyelid swelling

*Post marketing surveillance data

OVERDOSE

Clindamycin

Topically applied clindamycin can be absorbed in sufficient amounts to produce systemic effects.

In the event of overdosage, general symptomatic and supportive measures are indicated as required.

Adapalene

Adapalene gel is not to be taken orally and is for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur.

The acute oral dose of adapalene gel required to produce toxic effects in mice is greater that 10 mg/kg. Nevertheless, unless the amount accidentally ingested is small, an appropriate method of gastric emptying should be considered.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamic properties

Clindamycin

Pharmacotherapeutic group: Anti-infectives for treatment of acne.

Microbiology

Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis. It binds to the 50S ribosomal subunit and affects both ribosome assembly and the translation process. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms: Anaerobic gram positive non spore forming bacilli, including:

- *Propionibacterium acnes*.

EUCAST has established and reported susceptibility interpretive criteria for gram-negative and gram-positive anaerobes (with theexception of *C. difficile*): susceptible, ≤4 mg/L; resistant, >4 mg/L.

In a U.S. surveillance study, clindamycin MICs were ≤4 mg/L for 97% of *P. acnes* isolates tested.

In some bacterial species, cross resistance has been demonstrated *in vitro* among lincosamides, macrolides, andstreptogramins B.

Clinical efficacy and safety
P. acnes produces an extracellular lipase that hydrolyses sebum triglycerides to glycerol, used by the organism as a growth substrate, and free fatty acids, which have pro-inflammatory and comedogenic properties. A double-blind study had been reported to examine the effect of topical 1% clindamycin hydrochloride hydrate in a hydroalcoholic vehicle as compared to the effect of the vehicle alone. Fourteen patients applied clindamycin or vehicle alone twice daily for eight weeks. Free fatty acid surface lipid percentages, quantitative bacterial counts, and clinical response were assessed every two weeks. A significant reduction (88%) in the percentage of free fatty acids in the surface lipids was seen in the clindamycin-treated group and not in the vehicle-treated group. Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin solution in a hydroalcoholic base to 9 patients (average age 22.3 years) with acne vulgaris. There was no significant change in the surface microflora. Despite the short duration of treatment, objective clinical improvement was seen in three of nine treated patients, while none was observed in the placebo-treated patients.

Adapalene
Pharmacotherapeutic Group: Anti-Acne Preparations for Topical Use

Adapalene is a retinoid-like compound which in, in vivo and in vitro models of inflammation, has been demonstrated to possess anti-inflammatory properties. Adapalene is essentially stable to oxygen and light and is chemically non reactive. Mechanically, adapalene binds like tretinoin to specific retinoic acid nuclear receptors but, unlike tretinoin notto cytosolic receptor binding proteins.

Adapalene applied cutaneously is comedolytic in the rhino mouse model and also has effects on the abnormal processes of epidermal keratinization and differentiation, both of which are present in the pathogenesis of acne vulgaris. The mode of action of adapalene is suggested to be a normalisation of differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Adapalene is superior to reference retinoids in standard anti-inflammatory assays, both in vivo and in vitro. Mechanistically, it inhibits chemotactic and chemokinetic responses of human polymorphonuclear leucocytes and also the metabolism by lipoxidation of arachidonic acid to pro-inflammatory mediators. This profile suggests that the cell mediated inflammatory component of acne may be modified by adapalene.

Pharmacokinetic properties
Clindamycin
Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution, very low levels of

clindamycin are present in the serum (0–3 ng/mL) and less than 0.2% of the dose is recovered in urine as clindamycin.

Clindamycin concentrations have been demonstrated in comedones from acne patients. The mean (±SD) concentration of clindamycin in extracted comedones after application of clindamycin topical solution for 4 weeks was 0.60 ± 0.11 mcg/mg.

Older people
Clinical studies for topical clindamycin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Adapalene
Absorption of adapalene through human skin is low, in clinical trial measurable plasma adapalene levels where not found following chronic cutaneous application to large areas of acneic skin with an analytical sensitivity of 0.15 ng/ml.

After administration of [^{14}C] adapalene in rats (IV, IP, oral and cutaneous), rabbits (IV, oral and cutaneous) and dogs(IV and oral), radioactivity was distributed in several tissues, the highest levels being found in liver, spleen, adrenals and ovaries. Metabolism in animals has been tentatively identified as being mainly by O-demethylation, hydroxylation and conjugation, and excretion is primarily by the biliary route.

Preclinical safety data
Clindamycin
Embryo fetal development studies using oral doses in rats and subcutaneous doses in rats and rabbits, revealed no evidence of developmental toxicity except at doses that produced maternal toxicity. In reproductive studies in rats there was no evidence of impaired fertility.

Clindamycin was not genotoxic when evaluated in the *in vivo* rat micronucleus test and the Ames test.

Long-term studies in animals to evaluate carcinogenic potential have not been reported with clindamycin.

Adapalene
In animal studies, adapalene was well tolerated on cutaneous application for periods of up to six months in rabbits and for up to two years in mice. The major symptom of toxicity found in all animal species by the oral route were related to a hypervitaminosis A syndrome, and included bone dissolution, elevated alkaline phosphatase and a slight anaemia. Large oral doses of adapalene produced no adverse neurological, caridovascular or respiratory effects in animals. Adapalene is not mutagenic. Lifetime studies with adapalene have been reported in mice at cutaneous doses of 0.6, 2 and 6 mg/kg/day and in rats at oral doses of 0.15, 0.5 and 1.5 mg/kg/day. The only significant finding was a statistically significant increase of benign phaeochromocytomas of the adrenal medulla among male rats receiving adapalene at 1.5 mg/kg/day. These changes are unlikely to be of relevance to the cutaneous use of adapalene.

Adapalene produces teratogenic effects by the oral route in rats and rabbits. At cutaneous doses up to 200-fold the therapeutic dose, producing circulating plasma levels of adapalene at least 35 to 120 times higher than plasma levels demonstrated in therapeutic use, adapalene increased the incidence of additional ribs in rats and rabbits, without increasing the incidence of major malformations.

It is not known whether adapalene is secreted in animal or human milk. In animal studies, infant rats suckled by mother with circulating levels of adapalene at least 300 times those demonstrated in clinical use developed normally.

EXPIRY DATE
Do not use later than the date of expiry.

PACKAGING INFORMATION
ACNETOR AD is available as 15gm tube.

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not exceeding 25°C. Do not Freeze. Keep out of reach of children. Replace the cap tightly after use.

MARKETED BY

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