1.6 Product Information

1.6.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)

(SPC, CONTAINER LABELING & PATIENT INFORMATION LEAFLET, MOCK-UPS AND SPECIMENS)

SPC – Summary of the Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

CLEAR T GEL (Clindamycin & Tretinoin Gel)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clindamycin Phosphate USP equivalent to Clindamycin	1.0 % w/w
Tretinoin USP	0.025 % w/w
In an aqueous gel base	q.s

For full list of Excipients refer 6.1.

3. PHARMACEUTICAL FORM

Gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLEAR T GEL is indicated for the topical treatment of acne vulgaris when comedones, papules and pustules are present in patients 12 years or older. Consideration should be given to official guidance on the appropriate use of antibacterial agents and acne treatment.

4.2 Posology and method of administration

Adults and adolescents (≥ 12 years)

Once daily at bedtime the entire face should be washed with mild soap and dried. A pea-sized amount of medication should be squeezed onto one fingertip, dot onto the chin, cheeks, nose, and forehead; then gently rub over the entire face.

Treatment with CLEAR T GEL should not exceed 12 weeks of continuous use without careful evaluation. It should be noted that therapeutic improvement may not be observed for several weeks after starting treatment.

In case of a missed dose of CLEAR T GEL, the patient should wait for the next dose at the usual time. Patients should not double the dose to make up for the forgotten dose.

Use in Children below 12 years of age

CLEAR T GEL is not recommended for use in children below 12 years of age, since safety and efficacy of CLEAR T GEL in children have not been established.

Use in the Elderly (>65 years of age)

Safety and efficacy of CLEAR T GEL in patients above the age of 65 years have not been established.

Renal and hepatic impairment

In view of the low systemic exposure to clindamycin and tretinoin following topical administration of CLEAR T GEL, moderate renal or hepatic impairment is not expected to result in systemic exposure of clinical concern. However, clindamycin and tretinoin serum concentrations have not been studied in patients with renal or hepatic disease following topical administration. Individual decisions are advisable in severe cases.

Method of administration

CLEAR T GEL is indicated for external (dermatological) use only. The application of CLEAR T GEL should avoid eyes, eyelids, lips and nostrils. After the application the patient should wash hands.

4.3 Contraindications

CLEAR T GEL is contraindicated:

• In patients who have a history of hypersensitivity to the active substances clindamycin and/or tretinoin or to any of the excipients or lincomycin
• In patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis
• In patients who have a personal or familial history of skin cancer
• In patients who have a history of acute eczemas, rosacea and perioral dermatitis
• In patients with pustular and deep cystic nodular acne varieties (acne conglobata and acne fulminans).

4.4 Special warnings and precautions for use.

CLEAR T GEL is not for oral, ophthalmic, intranasal or intravaginal use.

CLEAR T GEL is not recommended in treatment of mild acne vulgaris.

CLEAR T GEL should not be used in pregnancy, especially during the first trimester, and in women of childbearing potential not using contraception.

Contact with the mouth, eyes and mucous membranes and with abraded or eczematous skin should be avoided. Application to sensitive areas of skin should be made with caution. In the event of accidental contact with the eyes, bathe with large amounts of water.

Antibiotic-associated colitis (also known as *Clostridium difficile-associated colitis* or *CDAD*) has been reported with the use of some other topical clindamycin products. This is unlikely to occur with CLEAR T GEL, as plasma levels have been determined and the percutaneous absorption of clindamycin is clinically negligible.

If prolonged or significant diarrhoea occurs or the patient suffers from abdominal cramps, treatment with CLEAR T 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.

Use of more than the recommended amount or too frequent application may cause redness, stinging and discomfort. If severe irritation occurs, especially in the early stage of therapy, patient should be advised to discontinue temporarily or reduce the frequency of application.

CLEAR T GEL should be prescribed with caution in atopic subjects.

CLEAR T GEL should not be applied at the same time as other topical preparations (including cosmetics) because of possible incompatibility and interaction with tretinoin. Particular caution should be exercised in the use of keratolytic agents such as sulphur, salicylic acid, benzoyl peroxide or resorcinol and chemical abrasives. If the patient has been treated with such preparations, the effect of the peeling agents must subside before any commencement of CLEAR T GEL therapy.

Some medicated cleansers and scrubbing solutions have a strong drying effect. They should not be used in patients receiving tretinoin topical therapy**.** Abrasive soaps, soaps and cosmetics as well as spices or lime should be used with caution.

Because of increased susceptibility to UV radiation, photosensitivity may occur during treatment with CLEAR T GEL Gel. Exposure to sunlight should therefore be minimised and appropriate sunscreen products with a SPF (Sun Protection Factor) of at least 30, together with suitable protective apparel (e.g. a hat), should be used. Use of sun lamps or sun beds should be avoided during treatment and patients with sunburn should not use this product until recovered

Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. If sunburn occurs, discontinue therapy with CLEAR T GEL until the severe erythema and peeling subside.

Occasional gram-negative folliculitis has been reported during treatment with clindamycin 1% topical products. If this should occur, therapy with CLEAR T GEL should be discontinued and alternative therapy should be initiated.

Long-term use of clindamycin may cause resistance and/or overgrowth of non-susceptible dermal bacteria or fungi although this is a rare occurrence.

Cross resistance may occur with other antibiotics such as lincomycin or erythromycin Simultaneous use of oral and topical antibiotics should be avoided, particularly if chemically different.

The excipients methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) may cause allergic reactions (possibly delayed). The excipient butylhydroxytoluene (E321) may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant topical medication as well as medicated soaps and cleansers that have a strong drying effect and products with high concentrations of alcohol as well as astringents should be used with caution. The concomitant treatment with corticosteroids should be avoided.

In vitro, antagonism has been demonstrated between erythromycin and clindamycin, synergy has been shown with metronidazole, both antagonistic and synergistic effects have been observed with aminoglycosides and agonistic action has been described with neuromuscular blocking 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.

Tretinoin causes enhanced permeability for other topically applied medicinal agents.

4.6 Pregnancy and lactation

There are no adequate data from the use of CLEAR T GEL in pregnant women. CLEAR T GEL did not cause any reprotoxic effects in a topical study on developmental toxicity in rabbits.

Clindamycin

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. Clindamycin was not teratogenic in reproduction studies in rats and mice, using subcutaneous and oral doses of clindamycin.

Tretinoin

Tretinoin is a well-known human teratogen following systemic administration but the available data after topical administration in pregnant women is limited. Oral doses of tretinoin are teratogenic in animals and there is evidence of embryotoxicity from studies

where tretinoin is applied dermally. CLEAR T GEL should not be used in pregnancy, especially during the first trimester, and in women who may become pregnant.

Breast-feeding

It is not known whether tretinoin and clindamycin are secreted in breast milk following the use of CLEAR T GEL. Oral and parenteral administration of clindamycin has been reported to result in the appearance of clindamycin in breast milk. It is known that orally administered retinoids and their metabolites are secreted in breast milk. Therefore, CLEAR T GEL should not be used in women who are breast feeding.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:
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)

Not known (cannot be estimated from the available data)

Reported frequencies in clinical trials are as following:

Immune system disorders:

Rare: Hypersensitivity

Endocrine disorders:

Rare: Hypothyroidism

Nervous system disorders:

Rare: Headache

Eye disorders:

Rare: Eye irritation

Gastrointestinal disorders:

Rare: Gastroenteritis, nausea

Skin and subcutaneous tissue disorders:

Uncommon: Acne, dry skin, erythema, seborrhoea, photosensitivity reaction, pruritis, rash, exfoliative rash, skin exfoliation, sunburn

Rare: Dermatitis, herpes simplex, macular rash, skin bleeding, skin burning sensation, skin depigmentation, skin irritation.

General disorders and administration site conditions:

Uncommon: Application site reaction, application site burning, application site dermatitis, application site dryness, application site erythema,

Rare: Application site irritation, application site swelling, application site erosion, application site discolouration, application site pruritus, application site desquamation, feeling hot, pain

Paediatric population

The proportion of paediatric patients (12-17 years) reporting a specific drug-related adverse reaction was consistent with that which was reported in the overall population. The incidence of dry skin in adolescent population (12-17 years) was slightly higher in clinical trials than in the overall population.

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.

4.9 Overdose

CLEAR T GEL is for topical use only. If CLEAR T GEL is applied excessively, marked redness, peeling or discomfort can occur. If excess application occurs accidentally or through over-enthusiastic use, the face should be gently washed with a mild soap and lukewarm water. CLEAR T GEL should be discontinued for several days before resuming therapy.

In the case of overdosage, topically applied clindamycin phosphate from CLEAR T GEL can be absorbed in sufficient amounts to cause systemic effects. Gastrointestinal side effects including abdominal pain, nausea, vomiting and diarrhoea may occur.

In the event of accidental ingestion, treatment should be symptomatic. The same adverse reactions effects as those expected with clindamycin (i.e. abdominal pain, nausea, vomiting and diarrhoea) and tretinoin (including teratogenesis in women of childbearing years) are expected. In such cases, CLEAR T GEL should be discontinued and pregnancy testing should be carried out in women of childbearing potential.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clindamycin:

ATC Code: J01FF01

Clindamycin is a semisynthetic derivative of the parent compound lincomycin that is produced by *Streptomyces lincolnensis* and is predominantly bacteriostatic. Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis. Although clindamycin phosphate is inactive *in-vitro*, rapid *in-vivo* hydrolysis converts this compound to the antibacterial active clindamycin.

Clindamycin has been shown to have *in vitro* activity against *Propionibacterium acnes,* one pathophysiological factor that influence the development of acne vulgaris. Clindamycin also exerts an anti-inflammatory effect on the acne vulgaris lesions.

The break-point for susceptibility testing of clindamycin is 4 mg/ml for *P. acnes* as a representative of Gram-positive anaerobes (breakpoints for susceptibility recommended by the European Committee on Antimicrobial Susceptibility Testing - EUCAST).

Tretinoin:

ATC Code: D10AD01

Topical tretinoin has both comedolytic and anti-inflammatory effects. Tretinoin decreases cohesiveness of follicular epithelial cells resulting in decreased microcomedone formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells, causing extrusion of the comedones. The comedolytic activity is related to a normalisation of the desquamation of the follicular epithelium. Tretinoin exerts anti-inflammatory effect via suppression of toll-like receptors (TLRs).

A combination therapy of clindamycin and tretinoin, as in CLEAR T GEL Gel, not only combines the individual actions of both active agents but also complements their certain actions. There is also evidence in the literature to show that when applied together, tretinoin increases the penetration of clindamycin. Thus, this combination therapy targets multiple pathogenic factors: abnormal follicular keratinization, *P.acnes* proliferation, inflammation and increased sebum production.

5.2 Pharmacokinetic properties

Tretinoin

Tretinoin occurs in the body as a metabolite of retinol, and it exhibits a certain degree of Vitamin A growth-promoting activity. Representative well-controlled clinical studies conclude that topically applied tretinoin does not increase plasma alltrans retinoic acid

(tretinoin). Following a single topical application of radiolabelled tretinoin, the blood concentration of retinoic acid was found to be unchanged from 2-48 hours. Neither single-dose nor long-term treatment with topical tretinoin formulations does alter systemic retinoid levels, which remain within the range of body's natural endogenous levels.

Clindamycin

Clindamycin is converted within the skin by phosphatases, leading to the more potent from of clindamycin. Thus, conversion to clindamycin is a major determinant of antimicrobial activity in the skin layers following topical application of clindamycin phosphate.

5.3 Preclinical safety data

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sr. No.	Ingredients	Specification
1.	Sodium Methyl Hydroxybenzoate	BP
2.	Sodium Propyl Hydroxybenzoate	BP
3.	Propylene Glycol	BP
4.	Carbomer 940	USP
5.	Disodium Edetate	BP
6.	Isopropyl Alcohol	BP
7.	Polyoxyl 40 Hydrogenated Castor Oil (Creshmer RH40)	USP
8.	Triethanolamine	BP
9.	Fragrance Lemon Cologne	IHS
10.	Butylated Hydroxytoluene	BP
11.	Purified Water	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 25°C in Dry & Dark place. Do not Freeze.

6.5 Nature and contents of container

20 g tube.

6.6 Special precautions for disposal

Do not use the medicine without the prescription of Registered Medical Practitioner.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT