PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

TRECLIN GEL 10 mg/g + 0,25 mg/g gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains 10 mg (1 %) clindamycin (as clindamycin phosphate) and 0,25 mg (0,025 %) tretinoin.

Excipients with known effect:

Methyl parahydroxybenzoate (E 218): 1,5 mg/g (0,15 %)

Propyl parahydroxybenzoate (E216): 0,3 mg/g (0,03 %)

Butylhydroxytoluene (E321): 0,2 mg/g (0,02 %)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gel

Translucent yellow gel

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TRECLIN GEL is indicated for the topical treatment of acne vulgaris of moderate severity when comedones, papules and pustules are present in patients 12 years of age or older (see section

4.4 and 5.1).

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

Prescribers should adhere to the principles of antibiotic stewardship.

4.2 Posology and method of administration

Posology

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 **TRECLIN 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.

The safety and efficacy of repeated treatment courses with **TRECLIN GEL** have not been established.

In case of a missed dose of **TRECLIN 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

TRECLIN GEL should not be used in children below 12 years of age, since safety and efficacy of **TRECLIN GEL** in children have not been established.

Use in the Elderly (> 65 years of age)

Safety and efficacy of **TRECLIN 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 **TRECLIN 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

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

4.3 Contraindications

TRECLIN 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 (see also Section 6.1).
- 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).

- in pregnancy or in women planning a pregnancy (see section 4.6).
- in women of childbearing potential not on effective contraception.
- in women breastfeeding their babies.

4.4 Special warnings and precautions for use

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

TRECLIN GEL is not recommended in treatment of mild acne vulgaris.

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 topical clindamycin as contained in **TRECLIN GEL**.

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

TRECLIN GEL should be prescribed with caution in atopic subjects.

TRECLIN 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 **TRECLIN 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 **TRECLIN 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 **TRECLIN GEL** until the severe erythema and peeling subside.

Gram-negative folliculitis has been reported during treatment with topical clindamycin 1 % as contained in **TRECLIN GEL**. If this should occur, therapy with **TRECLIN 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.

Cross resistance may occur with other antibiotics such as lincomycin or erythromycin (see section 4.5).

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 medicines 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

Increases in the Prothrombin time (PT) and International Normalised Ratio (INR) and/or bleeding, have been reported in patients treated with clindamycin as contained in **TRECLIN GEL** in

combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests (PT and INR), should therefore, be frequently monitored in patients treated with vitamin K antagonists.

Tretinoin causes enhanced permeability for other topically applied medicines.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

TRECLIN GEL should be prescribed to women of childbearing potential only if effective contraception was started at least one month before treatment and a laboratory pregnancy test performed 24 hours before initiation of treatment, was reported as negative. Effective contraception should be continued during treatment and for 1 month after discontinuation of treatment.

Male partners of women of childbearing potential on treatment with **TRECLIN GEL**, should use barrier contraception (e.g. condom) with sexual intercourse and continue to do so, until one month after the treatment was completed. Their female partners should be on effective contraception until one month after completion of treatment.

Pregnancy

TRECLIN GEL is contraindicated (see section 4.3) in pregnancy, or in women planning a pregnancy.

If **TRECLIN GEL** is used during pregnancy, or if the patient becomes pregnant while using **TRECLIN GEL**, treatment should be discontinued, and counseling of the patient and partner should be done.

Clindamycin

Safety of clindamycin in pregnancy has not been established.

Clindamycin was not teratogenic in reproduction studies in rats and mice, using subcutaneous and oral doses of clindamycin (see section 5.3).

Tretinoin

Tretinoin is teratogenic and orally administered retinoids have been associated with congenital abnormalities. Topically administered retinoids, such as tretinoin are assumed to result into low systemic exposure to tretinoin and its metabolites. However, because the level of systemic exposure to tretinoin and/or its metabolites that is teratogenic is unknown, teratogenicity due to topical application of tretinoin cannot be excluded. Factors such as a damaged skin, and/or excessive use may result in increased systemic exposure to tretinoin.

Breast feeding

Women should not breastfeed their babies if they are on treatment with **TRECLIN GEL**. Both retinoids, such as tretinoin, their metabolites and clindamycin cross into breastmilk.

Fertility

There are no available data on fertility on **TRECLIN GEL**.

Clindamycin

Reproduction studies in rats and mice, using subcutaneous and oral doses of clindamycin, revealed no evidence of impaired fertility.

Tretinoin

Systemically administered tretinoin severely affects fertility. Available data regarding fertility after topical administration in humans are limited and a negative effect on fertility cannot be excluded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. It is unlikely that treatment with **TRECLIN GEL** will have any effect on the ability to drive and use machines.

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, pruritus, rash, exfoliative rash, skin exfoliation, sunburn

Rare: Dermatitis, herpes simplex, rash macular, 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 **TRECLIN GEL** is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions**

Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

TRECLIN GEL Gel is for topical use only. If **TRECLIN GEL** 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. **TRECLIN GEL** should be discontinued for several days before resuming therapy.

In the case of overdosage, topically applied clindamycin phosphate from **TRECLIN GEL** can be absorbed in sufficient amounts to cause systemic effects. Gastrointestinal side effects including abdominal pain, nausea, vomiting and diarrhoea may occur (see section 4.4).

In the event of accidental ingestion, treatment should be symptomatic and supportive. 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, **TRECLIN GEL** Gel should be discontinued and pregnancy testing should be carried out in women of childbearing potential.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Acne Preparations for Topical Use; clindamycin, combinations

ATC code: D10AF51

TRECLIN GEL combines two active substances, which act through different mechanisms of action (see below).

Clindamycin:

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 Cutibacterium acnes (*Propionibacterium acnes)*, one pathophysiological factor that influence the development of acne vulgaris. Clindamycin also exerts an anti-inflammatory effect on the acne vulgaris lesions.

Tretinoin:

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).

Combination of clindamycin and tretinoin, as in **TRECLIN GEL** Gel, combines the individual actions of both active components and when applied together, tretinoin increases the penetration of clindamycin. Combination therapy with **TRECLIN GEL** targets multiple pathogenic factors:

abnormal follicular keratinization, *P. acnes* proliferation, inflammation and increased sebum production.

5.2 Pharmacokinetic properties

In an open-label, multiple-dose study treating 12 subjects with moderate to severe acne, the percutaneous absorption of tretinoin following 14 consecutive daily applications of approximately 4 g of **TRECLIN GEL** was minimal. Tretinoin plasma concentrations were below the lower limit of quantitation (LLOQ; 1 ng/mL) in 50 % to 92 % of subjects at any given time point following administration and were near the LLOQ in the remaining subjects, with values ranging from 1,0 to 1,6 ng/mL. The plasma concentrations of the key tretinoin metabolites, 13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid, ranged from 1.0 to 1,4 ng/mL and from 1,6 to 6,5 ng/mL, respectively. Plasma concentrations for clindamycin generally did not exceed 3,5 ng/mL, with the exception of one subject whose plasma concentration reached 13,1 ng/mL.

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 all trans 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 phosphate is converted within the skin by phosphatases, to clindamycin. Thus, conversion to clindamycin is a major determinant of antimicrobial activity in the skin layers following topical application of clindamycin phosphate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

purified water

glycerol

carbomers

methyl parahydroxybenzoate (E218)

propyl parahydroxybenzoate (E216)

polysorbate 80

disodium edetate

citric acid, anhydrous

butylhydroxytoluene (E321)

trometamol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

After first opening: 3 months

6.4 Special precautions for storage

Store at or 25 ºC. Do not freeze.

Keep the tube tightly closed.

6.5 Nature and contents of container

The pack sizes are 30 g and 60 g.

Both packs comprise of an aluminium tube with an epoxyphenolic internal lacquer, fitted with a polyethylene cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd.

4 Brewery Street,

Isando, Johannesburg,

1609

8 REGISTRATION NUMBER

49/13.12/0499

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 August 2020

10 DATE OF REVISION OF THE TEXT

28 February 2025