Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Treclin 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 the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel
Translucent yellow gel

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treclin is indicated for the topical treatment of acne vulgaris when comedones, papules and pustules are present in patients 12 years 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.

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 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 Treclin, 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 is not recommended for use in children below 12 years of age, since safety and efficacyof Treclin in children have not been established.

Use in the Elderly (>65 years of age)
Safety and efficacy of Treclin 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, 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 is indicated for external (dermatological) use only. The application of Treclin should avoid eyes, eyelids, lips and nostrils. After the application the patient should wash hands.

4.3 Contraindications

- Pregnancy (see section 4.6)
- Women planning a pregnancy

Treclin is also 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)

4.4 Special warnings and precautions for use

Treclin is not for oral, ophthalmic, intranasal or intravaginal use.

Treclin 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 some other topical clindamycin products. This is unlikely to occur with Treclin, 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 Treclin 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 should be prescribed with caution in atopic subjects.

Treclin 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 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.

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 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 Treclin 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 (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 medicinal products and other forms of interactions

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 Fertility, pregnancy and lactation

Women of childbearing potential
Treclin should be given to women of childbearing potential only if effective contraception is used during treatment and for 1 month after discontinuation of treatment.

Pregnancy
Acnatac is contraindicated (see section 4.3) in pregnancy, or in women planning a pregnancy.
If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

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 fetus/new-born child. Clindamycin was not teratogenic in reproduction studies in rats and mice, using subcutaneous and oral doses of clindamycin (see section 5.3).

Tretinoin

Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

Breast-feeding
It is not known whether tretinoin and clindamycin are secreted in breast milk following the use of Treclin. 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, Treclin should not be used in women who are breast feeding.**

Fertility
There are no available data on fertility on Treclin.

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.

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 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, pruritis, 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 pruritis, 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

In the case of overdosage, topically applied clindamycin phosphate from Treclin 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. 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 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 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 *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

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 Treclin 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.

Clinical efficacy of Treclin

Three randomised double-blind clinical studies, including a total of 4550 patients with acne vulgaris with both inflammatory and non-inflammatory lesions were performed. Of these 1853 patients were treated with Treclin Gel, 846 with tretinoin, 1428 with clindamycin phosphate and 423 with Treclin Gel vehicle.

Patients with 20-50 facial acne inflammatory lesions (papules and pustules), 20- 100 facial acne non-inflammatory lesions (open and closed comedones), two or fewer nodules (defined as an inflammatory lesion greater than or equal to 5 mm in diameter) and without cysts were included. Lesions were counted at baseline and at weeks 2, 4, 8 and 12.

Primary measurements of efficacy for studies 7001.G2HP-06-02 and 7001.G2HP-07-02 were (1) mean percent change from baseline at Week 12 in inflammatory lesion counts, (2) mean percent change from baseline at Week 12 in non-inflammatory lesion counts, (3) mean percent change from baseline at Week 12 in total lesion counts, and (4) the percent of subjects who were clear or almost clear, at Week 12 as judged by an Evaluator's Global Severity Score (EGSS). Superiority vs. monotherapies was concluded if two of three lesion count variables and dichotomized EGSS were significant.

Treatment was applied once daily for 12 weeks and patients were evaluated and lesions counted at week 12.

Studies 7001.G2HP-06-02 and 7001.G2HP-07-02 compared Treclin to both mono treatments (clindamycin phosphate 1.2% gel and tretinoin 0.025% gel) and vehicle using a double-blind treatment regimen. The third clinical study (MP 1501-02) was conducted to compare Treclin to clindamycin alone.

The distribution of percent change in lesion counts was skewed, therefore the median percent change is shown in the following tables.

Median percent change (decrease) in the number of lesions at week 12

Lesion type	Treatment	Study			Meta-analysis
		G2HP_06_02 (n=1252)	G2HP_07_02 (n=1288)	MP1501_02 (n=2010)	All studies[1] (n=4550)
Inflammatory	**Acnatac**	52.6	61.3	70.0	65.2
	Clindamycin	46.4*	52.1*	64.5*	60.0*
	Tretinoin	42.9*	50.0*	n.a.	46.4*
	Vehicle	25.0*	38.9*	n.a	32.3*
Non-inflammatory	**Acnatac**	43.8	42.3	57.6	51.6
	Clindamycin	27.5*	32.2	48.2*	43.5*
	Tretinoin	36.2*	40.0	n.a.	37.3*
	Vehicle	23.0*	24.2*	n.a.	23.9*
Total	**Acnatac**	46.3	48.4	62.0	54.5
	Clindamycin	33.9*	40.9*	53.1*	48.1*
	Tretinoin	39.6*	39.7*	n.a.	39.6*
	Vehicle	22.2*	25.0*	n.a.	22.8*

p-values from ranked ANOVA

[1] for pairwise comparison vs. Tretinoin and Vehicle data from studies 7001-G2HP-06-02 and 7001-G2HP-07-02 were considered.

* $p \leq 0.05$

Median percent change (decrease) in the number of lesions at week 12

Global Severity Score at Week 12 – presented as dichotomised values

	Acnatac	Clindamycin	Tretinoin	Vehicle
ITT-clear or almost clear *				
Success	85 (20%)	32 (15%)	62 (15%)	18 (9%)
Failure	335 (80%)	176 (85%)	355 (85%)	189 (91%)
Total	420	208	417	207
P-value		0.147	0.037	<0.001

ITT-clear or almost clear **							
Success	95 (22%)		38 (17%)		60 (14%)		16 (7%)
Failure	330 (78%)		180 (83%)		369 (86%)		200 (93%)
Total	425		218		429		216
P-value			0.122		0.001		<0.001
ITT- clear, almost clear or at least 2-grade improvement***							
Success		381 (38%)		318 (32%)			
Failure		627 (62%)		684 (68%)			
Total		1008		1002			
P-value				0.002			

[1] missingvaluesimputedasfailures
[*]Study7001-G2HP-06-02
[**]Study7001-G2HP-07-02
[***]StudyMP-1501-02

Paediatric Population
The percentage change in the number of lesions at week 12 for adolescents, between 12 and 17 years, in the individual trials and the metanalysis of these trials are provided below.

Median percent change (decrease) in the number of lesions at Week 12: Adolescents					
Lesion type	**Treatment**	**Study**			**Meta-analysis**
		G2HP_06_02 (n = 800)	**G2HP_07_02 (n = 795)**	**MP1501_02 (n = 1320)**	**All studies[1] (n = 2915)**
Inflammatory	**Acnatac**	50.0	56.2	66.7	62.5
	Clindamycin	40.4	46.7	64.0*	58.3*
	Tretinoin	38.5*	47.3*	n.a.	40.7*
	Vehicle	16.7*	25.4*	n.a.	21.4*
Non-inflammatory	**Acnatac**	43.4	40.2	55.6	50.0
	Clindamycin	23.4*	26.5*	48.7*	42.2*
	Tretinoin	30.2*	36.9	n.a.	32.8*
	Vehicle	13.5*	13.7*	n.a.	13.5*
Total	**Acnatac**	42.0	44.8	59.4	52.5
	Clindamycin	31.3*	34.2*	53.0*	46.4*
	Tretinoin	31.9*	38.1*	n.a.	35.6*
	Vehicle	14.6*	14.6*	n.a.	14.6*

p-values from ranked ANOVA
[1] for pairwise comparison vs. Tretinoin and Vehicle data from studies 7001-G2HP-06-02 and 7001-G2HP-07-02 were considered.
* $p \leq 0.05$

Although the studies were not powered for the subgroups and the results are not as consistent as for the changes in lesion counts, they also provide evidence for superiority of the combination product.

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 was minimal. Tretinoin plasma concentrations were below the lower limit of quantitation (LLOQ; I 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 1.4ng/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.l 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 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 longterm 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

Following preclinical studies of Treclin, clindamycin, and tretinoin support the safety of Treclin.

Treclin
A 13 week repeat-dose dermal toxicity study in minipigs revealed no toxic effects, apart from minor local irritation (erythema). Treclin Gel was shown not to be a primary skin irritant or ocular irritant in two local tolerance studies in rabbits, and it was shown not to be a contact sensitizer in guinea pigs.

In a dermal developmental toxicity study in rabbits no reproductive toxicity was seen.

Clindamycin
Systemically administered clindamycin does not affect fertility, mating ability, embryonic development, or post-natal development. In-vitro and in-vivo studies did not reveal any mutagenic potential of clindamycin. Clindamycin was not carcinogenic in mice in a 2-year dermal study with 1.2% clindamycin phosphate and a 2-year oral study in rats.

Tretinoin
In-vitro and in-vivo studies did not reveal any mutagenic potential of tretinoin. Tretinoin was not carcinogenic in mice in a 2-year dermal study with 0.1% tretinoin (a higher strength than Treclin). The systemic carcinogenic potential has not been studied. Oral tretinoin has been shown to be teratogenic in rats, mice, hamsters, rabbits, monkeys and humans. It severely affects fertility and peri-postnatal development. In animals, dermally applied tretinoin was not teratogenic at daily doses that were several times higher than the human recommended daily dose adjusted to body surface.

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

Do not store above 25°C. Do not freeze.

Keep the tube tightly closed.

6.5 Nature and contents of container

The pack sizes are 30g and 60g.
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 and other handling

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

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2010/044/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of Last Renewal: 28th February 2018

10 DATE OF REVISION OF THE TEXT

May 2019

11 DOSIMETRY

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS