Acnatac 10 mg/g + 0.25 mg/g Gel

2. Qualitative and quantitative composition
One gram of gel contains 10 mg (1%) clindamycin (as clindamycin-2-dihydrogen phosphate) and 0.25 mg (0.025%) tretinoin.
Other component(s) with known effect:
Methyl-4-hydroxybenzoate (E218): 1.5 mg/g (0.15%).
Propyl-4-hydroxybenzoate (E216): 0.3 mg/g (0.03%).
Butylated hydroxytoluene (E321): 0.2 mg/g (0.02%).
For a complete list of excipients, see section 6.1.

3. Pharmaceutical form
Gel.
Clear yellow gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Acnatac is used for the topical treatment of acne vulgaris when comedones, papules, and pustules are present in patients aged 12 years and older (see sections 4.4 and 5.1).
Official guidelines on the proper use of antibacterial agents and acne treatment should be considered.

4.2 Posology and method of administration
Dosage
Adults and adolescents (≥12 years)
Once daily before bedtime, the entire face should be washed with a mild soap and dried. A pea-sized amount of the medication is placed on a fingertip, dabbed on the chin, cheeks, nose, and forehead, and then gently rubbed over the entire face.

Treatment with Acnatac should not exceed 12 weeks without careful assessment. It should be noted that therapeutic improvement may not be observed until several weeks after starting treatment.
If a dose of Acnatac is missed, the patient should wait until the next dose at the usual time. Patients should not apply a double dose if the previous application was forgotten.

Use in children under 12 years
Acnatac is not recommended for use in children under 12 years as the safety and efficacy of Acnatac in children have not been established.
Use in elderly patients (over 65 years) with renal or

hepatic impairment
The safety and efficacy of Acnatac in patients over 65 years have not been established.
Given the low systemic exposure to clindamycin and tretinoin after topical administration of Acnatac, moderate renal or hepatic impairment is not expected to lead to clinically significant systemic exposure. However, serum concentrations of clindamycin and tretinoin have not been studied in patients with renal or hepatic disease after topical administration. In severe cases, individual decisions should be made.

Method of administration

Acnatac is intended for external (dermatological) use only. Application of Acnatac to the eyes, eyelids, lips, and nostrils should be avoided. After application, the patient should wash their hands.

4.3 Contraindications

Acnatac must not be used:

In patients with known hypersensitivity to the active substances clindamycin and/or tretinoin or any of the other ingredients listed in section 6, or lincomycin.
In patients with regional enteritis, ulcerative colitis, or known antibiotic-associated colitis.
In patients with a personal or family history of skin cancer.
In patients with a history of acute eczema, rosacea, and perioral dermatitis
In patients with pustular and deep cystic nodular acne forms (acne conglobata and acne fulminans)

4.4 Special warnings and precautions for use

Acnatac is not intended for oral, ophthalmic, intranasal, or intravaginal use.
Acnatac is not recommended for the treatment of mild acne vulgaris.
Acnatac should not be used during pregnancy, especially during the first trimester, nor in women of childbearing potential unless contraceptive measures are taken (see section 4.6).

Avoid contact with the mouth, eyes, mucous membranes, and open or eczematous skin. Application to sensitive skin areas should be done with caution. In case of accidental contact with the eyes, rinse with plenty of water.

Antibiotic-associated colitis (also known as Clostridium difficile-associated colitis or CDAD) has been reported in connection with the use of some other topical clindamycin preparations. It is unlikely to occur with Acnatac as plasma levels have been determined and the percutaneous absorption of clindamycin is clinically negligible.
In the case of prolonged or severe diarrhea or abdominal cramps, treatment with Acnatac should be discontinued immediately, as these symptoms could indicate antibiotic-associated colitis. Appropriate diagnostic procedures such as the determination of Clostridium difficile and toxin and, if necessary, a colonoscopy should be performed, and treatment options for colitis should be considered.

The use of more than the recommended amount or too frequent application can cause redness, burning, and other discomforts. In case of severe irritation, especially in the early stages of treatment, the treatment should be temporarily interrupted or the frequency of application reduced.
Acnatac should be prescribed with caution to patients with atopy.
Acnatac should not be used concurrently with other topical preparations (including cosmetics) as it may lead to intolerance and interactions with tretinoin. Special caution is required when using keratolytic substances such as sulfur, salicylic acid, benzoyl peroxide, or resorcinol and chemical abrasives. If the patient has been treated with such preparations, the peeling effect of these agents must subside before starting treatment with Acnatac.

Some medical cleansers and washing solutions have a strong drying effect. They should not be used in patients receiving topical treatment with tretinoin. Caution is advised when using soaps with peeling effects, soaps and cosmetics, as well as fragrances or citrus extracts.
Due to increased sensitivity to UV radiation, photosensitivity may occur during treatment with Acnatac Gel. Exposure to sunlight should therefore be minimized, and appropriate sunscreens with an SPF (sun protection factor) of at least 30 should be used, along with suitable protective clothing (e.g., a hat). Sunlamps (UV lamps) or tanning beds should be avoided during treatment, and in case of sunburn, this preparation should only be used after it has subsided. Patients with occupational exposure to strong sunlight and patients with congenital sensitivity to sunlight should be particularly cautious. If sunburn occurs, treatment with Acnatac should be interrupted until severe erythema and skin peeling have subsided.
Occasional gram-negative folliculitis has been reported during treatment with topical clindamycin 1% preparations. If this occurs, treatment with Acnatac should be discontinued and an alternative treatment initiated.

Long-term use of clindamycin can lead to resistance and/or overgrowth of non-sensitive skin bacteria or fungi; however, this is rare. Cross-resistance with other antibiotics such as lincomycin or erythromycin may occur (see section 4.5).
The concurrent use of oral and topical antibiotics should be avoided, especially if they have different chemical structures.
The other ingredients methyl-4-hydroxybenzoate (E218) and propyl-4-hydroxybenzoate (E216) may cause allergic reactions (possibly delayed reactions). The other ingredient butylated hydroxytoluene (E321) may cause localized skin irritation (e.g., contact dermatitis) or irritation of the eyes and mucous membranes.

4.5 Interactions with other medicinal products and other forms of interaction

Topical medications, medical soaps, and skin cleansers with a strong drying effect, as well as preparations with high alcohol concentration and astringents, should be used with caution. Concurrent treatment with corticosteroids should be avoided.
In vitro, an antagonism between erythromycin and clindamycin and a synergism with metronidazole has been demonstrated; antagonistic as well as synergistic effects have been described with aminoglycosides, and agonistic effects have been described with neuromuscular blockers.
Tretinoin causes increased permeability for other topically applied medications.

Vitamin K antagonists
In patients receiving clindamycin together with vitamin K antagonists (e.g., warfarin, acenocoumarol, fluindione), increased coagulation values (PT/INR) and/or bleeding have been reported. Therefore, coagulation values should be closely monitored in patients treated with vitamin K antagonists.

4.6 Fertility, pregnancy, and lactation

Acnatac should only be used by women of childbearing age if an effective method of contraception is used during treatment and for 1 month after its end.
Pregnancy

There are no adequate data on the use of Acnatac in pregnant women. Acnatac did not cause any reproductive toxic effects in a topical developmental toxicity study in rabbits (see section 5.3).

Clindamycin
In a limited number of pregnancies with first trimester clindamycin exposure, no adverse effects of clindamycin on pregnancy or the health of the fetus/newborn were observed. Clindamycin was not teratogenic in reproductive studies in rats and mice when administered subcutaneously and orally (see section 5.3).

Tretinoin
Tretinoin is a well-known human teratogen after systemic administration; however, the available data after topical administration in pregnant women are limited. Oral tretinoin doses are teratogenic in animals, and there is evidence of embryotoxicity from studies in which tretinoin was applied dermally (see section 5.3). Acnatac should not be used during pregnancy, especially during the first trimester, and in women who may become pregnant.

Lactation
It is not known whether tretinoin and clindamycin are excreted in breast milk after the use of Acnatac. It has been reported that oral and parenteral administration of clindamycin leads to the transfer of clindamycin into breast milk. It is known that orally administered retinoids and their metabolites are excreted in breast milk. Therefore, Acnatac should not be used in breastfeeding women.

Fertility Clindamycin
There are no data on fertility under Acnatac.
Reproductive studies in rats and mice using subcutaneous and oral doses of clindamycin showed no evidence of impaired fertility.

Tretinoin
Systemically administered tretinoin significantly impairs fertility. There are only limited data available on fertility after topical application in humans.

4.7 Effects on the ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been conducted. It is unlikely that treatment with Acnatac will have any effects on the ability to drive or use machines.

4.8 Side effects

Within the organ classes, side effects are listed according to their frequency (number of patients expected to experience the side effects). The following categories are used:
Very common (≥1/10),
Common (≥1/100 to <1/10),
Occasional (≥1/1,000 to <1/100),
Rare (≥1/10,000 to <1/1,000),
Very rare (<1/10,000),
Not known (frequency cannot be estimated from the available data).
The frequency indications in clinical studies are:

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:
Occasionally: Acne, dry skin, erythema, seborrhea, photosensitivity reactions, pruritus, rash, exfoliative rash,
Exfoliation of the skin, sunburn
Rare: Dermatitis, herpes simplex, macular rash, skin bleeding, burning sensation on the skin, skin depigmentation, skin irritation.

General disorders and administration site conditions:
Occasionally: Local reactions at the application site such as: burning, dermatitis, dryness, and erythema
Rare: Local reactions at the application site such as: irritation, swelling, erosion, discoloration, pruritus, scaling, sensation of heat, pain

Children and adolescents
The proportion of children and adolescents (12 – 17 years) with drug-specific side effects was consistent with the corresponding proportion in the overall population. The incidence of dry skin in adolescents (12 – 17 years) was slightly higher than in the overall population.

Reporting of suspected adverse reactions
The reporting of suspected adverse reactions after approval is of great importance. It enables continuous monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are encouraged to report any suspected adverse reactions via the national reporting system.

Austria
Federal Office for Safety in Health Care
Traisengasse 5
1200 Vienna
Austria
Fax. +43 (0) 50 555 36207
Website: http://www.basg.gv.at/

4.9 Overdose

Acnatac Gel is intended exclusively for topical use. Excessive use of Acnatac Gel may lead to pronounced redness, peeling, or other discomforts. If excessive application occurs due to

accidental or overzealous use, the face should be gently washed with mild soap and lukewarm water. Acnatac should be discontinued for several days before resuming treatment.
In the case of an overdose, topically applied clindamycin phosphate from Acnatac can be absorbed in an amount sufficient to cause systemic effects. Gastrointestinal side effects such as abdominal pain, nausea, vomiting, and diarrhea may occur (see section 4.4).

In the event of accidental ingestion, treatment should be symptomatic. The same side effects are expected as with clindamycin (such as abdominal pain, nausea, vomiting, and diarrhea) and tretinoin (such as teratogenesis in women of childbearing age). In such cases, Acnatac Gel should be discontinued and a pregnancy test should be conducted in women of childbearing age.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Acne treatment for topical use; Clindamycin, combinations ATC code: D10AF51
Acnatac combines two active ingredients with different mechanisms of action (see below).

Clindamycin:
Clindamycin is a semi-synthetic derivative of the parent substance lincomycin, produced by Streptomyces lincolnensis, and acts predominantly bacteriostatically. Clindamycin binds to the 50S ribosomal subunits of sensitive bacteria and prevents the elongation of peptide chains by disrupting peptidyl transfer, thereby suppressing bacterial protein synthesis. Clindamycin phosphate is inactive in vitro, but through rapid in vivo hydrolysis, the substance is converted into the antibacterial active clindamycin.
It has been shown that clindamycin has in vitro activity against Propionibacterium acnes, a pathophysiological factor influencing the development of acne vulgaris. Clindamycin also has an anti-inflammatory effect on acne lesions.
The breakpoint for testing clindamycin susceptibility for P. acnes as a representative of gram-positive anaerobes is 4 mg/ml (breakpoints recommended by the European Committee on Antimicrobial Susceptibility Testing - EUCAST).

Tretinoin:
Topical tretinoin has both comedolytic and anti-inflammatory properties. Tretinoin reduces the cohesiveness of follicular epithelial cells, thereby reducing the formation of microcomedones. Additionally, tretinoin stimulates mitotic activity and increased cell turnover of the follicular epithelium, leading to the expulsion of comedones. The comedolytic activity is associated with a normalization of the desquamation of the follicular epithelium. Tretinoin exerts an anti-inflammatory effect via toll-like receptors (TLRs).
A combination therapy with clindamycin and tretinoin contained in Acnatac Gel not only combines the individual effects of the two active ingredients but also complements them. There is also evidence in the literature showing that tretinoin increases the penetration of clindamycin when used together. Thus, this combination therapy targets multiple pathogenic factors: disturbed follicular keratinization, proliferation of P. acnes, inflammation, and increased sebum production.

Clinical efficacy of Acnatac

Three randomized, double-blind clinical studies were conducted, including a total of 4,550 patients with acne vulgaris with both inflammatory and non-inflammatory lesions. Of these, 1,853 patients were treated with Acnatac Gel, 846 with tretinoin, 1,428 with clindamycin phosphate, and 423 with Acnatac Gel vehicle.
Patients with 20 – 50 inflammatory acne lesions (papules and pustules) on the face, 20 – 100 non-inflammatory acne lesions (open and closed comedones) on the face, two or fewer nodules (defined as inflammatory lesions greater than or equal to 5 mm in diameter), and no cysts were included. The lesions were counted as baseline and in weeks 2, 4, 8, and 12.
The primary efficacy measures of studies 7001.G2HP-06-02 and 7001.G2HP-07-02 were: (1) the mean percentage change from baseline in the number of inflammatory lesions at week 12, (2) the mean percentage change from baseline in the number of non-inflammatory lesions at week 12, (3) the mean percentage change from baseline in the total number of lesions at week 12, and (4) the percentage of patients who were free or almost free of lesions at week 12, as assessed by an Evaluator's Global Severity Score (EGSS). Superiority over the monotherapies was concluded if two out of three lesion count variables and the dichotomized EGSS were significant.
The treatment was administered once daily for 12 weeks, with patients assessed and lesions counted at week 12.
Studies 7001.G2HP-06-02 and 7001.G2HP-07-02 compared Acnatac with both monotherapies (Clindamycin phosphate 1.2% gel and Tretinoin 0.025% gel) and vehicle using a double-blind treatment design. The third clinical study (MP1501-02) was used to compare Acnatac with Clindamycin alone.
Due to the skewed distribution, the percentage change in lesion count is presented as the median percentage change in the following tables.

Median percentage change (reduction) in the number of lesions at week 12					
Lesion type	Treatment	Study			Meta-analysis
		G2HP-06-02 (n=1,252)	G2HP-07-02 (n=1,288)	MP1501-02 (n=2,010)	All studies[1] (n=4,550)
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 ANOVA with ranked variables [1]for a pairwise comparison vs. tretinoin and vehicle, data from studies 7001-G2HP06-02 and 7001-G2HP-07-02 were considered. *p ≤0.05					

Global severity in week 12 - presented as dichotomized 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 - pure or almost pure**				
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 - pure, almost pure or improvement by at least 2 grades***				
Success	381 (38%)	318 (32%)		
Failure	627 (62%)	684 (68%)		
Total	1008	1002		
p-value		0.002		

1 missing value was counted as treatment failure
* Study 7001-G2HP-06-02
** Study 7001-G2HP-07-02
*** Study MP-1501-02
Children and adolescents
The percentage change in the number of lesions at week 12 in adolescents aged 12 to 17 years in the individual studies and in the meta-analysis of these studies is listed below.

Median percentage 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 = 1,320)	All studies[1] (n = 2,915)
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 ANOVA with ranked variables 1 For a pairwise comparison vs. tretinoin and vehicle, data from studies 7001-G2HP06-02 and 7001-G2HP-07-02 were considered. * $p \leq 0.05$					

Although the studies did not have sufficient power for the subgroups and the results are not as consistent as for the changes in lesion count, they also provide evidence for the superiority of the combination product.

5.2 Pharmacokinetic properties

In an open-label multiple-dose study, where 12 patients with moderate to severe acne were treated, the percutaneous absorption of tretinoin after 14 consecutive daily applications of approximately 4 g Acnatac was minimal. Plasma concentrations of tretinoin were below the lower limit of quantitation (LLOQ; 1 ng/ml) at any given time after administration in 50 to 92% of patients, and in the remaining patients, values ranged from 1.0 to 1.6 ng/ml near the LLOQ. Plasma concentrations of the main metabolites of tretinoin, 13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid, were 1.0 to 1.4 ng/ml and 1.6 to 6.5 ng/ml, respectively. Plasma concentrations of clindamycin generally did not exceed 3.5 ng/ml, except for one patient whose plasma concentration reached 13.1 ng/ml.

Tretinoin
Tretinoin occurs in the body as a metabolite of retinol and exhibits a certain degree of growth-promoting vitamin A activity. Representative, well-controlled clinical studies have shown that topically administered tretinoin does not increase plasma levels of all-trans-retinoic acid (tretinoin). After a single topical application of radiolabeled tretinoin, the blood concentration of retinoic acid remained unchanged over a period of 2 – 48 hours. Neither single nor long-term treatment with topical tretinoin formulations alters systemic retinoid levels, which remain within the range of the body's natural endogenous levels.

Clindamycin
Clindamycin phosphate is converted in the skin by phosphatases into the more active form of clindamycin. The conversion to clindamycin is therefore a crucial factor for the antimicrobial effect in the skin layers after topical application of clindamycin phosphate.

5.3 Preclinical safety data

The following preclinical studies with Acnatac, clindamycin, and tretinoin support the safety of Acnatac. Acnatac
A 13-week dermal toxicity study with repeated administration in minipigs showed no toxic effects apart from slight local irritation (erythema). In two local tolerance studies in rabbits, Acnatac gel was found to be non-primary skin or eye irritating, and no contact sensitizing effect was observed in guinea pigs.
In a dermal developmental toxicity study in rabbits, no reproductive toxicity was observed.

Clindamycin
Systemically administered clindamycin does not impair fertility, mating ability, embryonic development, or postnatal development. In vitro and in vivo studies showed no mutagenic potential of clindamycin. Clindamycin was not carcinogenic in a 2-year dermal study in mice with 1.2% clindamycin phosphate and in a 2-year oral study in rats.

Tretinoin
In vitro and in vivo studies showed no mutagenic potential of tretinoin. Tretinoin was not carcinogenic in a 2-year dermal study in mice with 0.1% tretinoin (at a higher strength than

Acnatac). The systemic carcinogenic potential was not investigated. Oral tretinoin was teratogenic in rats, mice, hamsters, rabbits, monkeys, and humans. It significantly impairs fertility and peri-/postnatal development. In animals, dermally applied tretinoin was not teratogenic at daily doses several times higher than the recommended human daily dose based on body surface area.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients purified water,

glycerol,
carbomer 981,
methyl-4-hydroxybenzoate (E218),
propyl-4-hydroxybenzoate (E216),
polysorbate 80,
disodium edetate,
citric acid,
butylated hydroxytoluene (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 the container

The pack sizes are 30 g and 60 g.
Both packs contain an aluminum tube with epoxy phenol internal lacquer and a polyethylene cap.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling instructions

No special requirements.

7. Marketing authorization holder Meda Pharma GmbH, Vienna.

8. Marketing authorization number 1–31861

9. Date of authorization/renewal of the authorization
March 26, 2013.

10. Date of revision of the text
October 2014
Prescription/Pharmacy-only

Prescription and pharmacy-only, repeated dispensing prohibited.