LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Acnatac
(clindamycin phosphate and tretinoin)

SE/H/1134/01/DC

This module reflects the scientific discussion for the approval of Acnatac. The procedure was finalised on 28 February 2013. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Meda AB has applied for a marketing authorisation for Acnatac 10 mg/g + 0.25 mg/g gel. The active substances are clindamycin phosphate and tretinoin . For approved indications, see the Summary of Product Characteristics.

The procedure was referred to the CMDh due to PSRPH on the grounds that pregnancy should be listed as a contraindication in section 4.3 of the SmPC due to teratogenic concerns regarding tretinoin. During the CMDh referral the applicant submitted a comprehensive review of the available data on cutaneous absorption of tretinoin as well as pre-clinical and human safety data during pregnancy. At the CMDh meeting, the RMS and CMS presented their views on the outstanding issues and this was followed by an oral presentation by the applicant. Following the meeting, it was agreed that pregnancy will be listed in section 4.4. of the SmPC and the procedure was concluded positively.

II. QUALITY ASPECTS

II.1 Introduction

Acnatac is presented in the form of a gel containing 10 mg/g + 0.25 mg/g gel of clindamycin (as clindamycin phosphate) and tretinoin. The excipients are purified water, glycerol, carbomers, methyl parahydroxybenzoate, propyl parahydroxybenzoate, polysorbate 80, disodium edetate, citric acid (anhydrous), butylhydroxytoluene, and trometamol. The gel is filled in aluminium tubes with an epoxyphenolic internal lacquer, fitted with a polyethylene cap.

II.2 Drug Substance

Clindamycin phosphate and tretinoin have monographs in the Ph Eur.

Clincamycin phosphate is a white to off-white crystalline powder which is freely soluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone; practically insoluble in chloroform, in benzene, and in ether. The structure of clindamycin phosphate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Tretinoin is a yellow to light orange crystalline powder which is soluble in ethanol and isopropanol, and practically insoluble in water. The structure of tretinoin has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specifications include relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Acnatac gel is formulated using excipients described in the current Ph Eur. No raw materials used in the product are of human or animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with the storage restriction “Do not store above 25 °C. Do not freeze.”.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Acnatac gel contains two active ingredients, clindamycin and tretinoin, with different mechanisms of action which are thought to act complementary to each other in the treatment of acne vulgaris.
Clindamycin is a lincosamide antibiotic that acts by binding the 50S subunit of prokaryotic ribosomes and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis. Clindamycin has been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris. Tretinoin is a non-aromatic retinoid. Although the exact mode of action of tretinoin in the treatment of acne vulgaris is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedon formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedomes.

The pharmacodynamic properties of clindamycin and tretinoin are considered well established. No new primary pharmacodynamic studies have been performed, which is acceptable. Since the systemic uptake of Acnatac gel is very low and because it is only intended to be used locally, no secondary pharmacology or safety pharmacology studies are warranted.

III.2 Pharmacokinetics

Only published data is submitted. The pharmacokinetics of the individual components is considered well known. The absorption via the skin is shown (non-clinical and clinical) to be very low at the concentration of Acnatac gel intended to be used clinically. Regarding these circumstances it is acceptable that no new pharmacokinetic studies have been submitted in this application.

III.3 Toxicology

Both clindamycin and tretinoin have been used for a long time, both separately and in non-fixed combination, in the treatment of acne vulgaris and the toxicology of the substances is considered well known.

A 13-week dermal repeat-dose toxicology study was performed in Hanford minipigs with the formulation proposed for marketing. Based on skin morphology, the minipig is considered the most relevant animal species for the human situation. Three dose groups were used; 25 mg/kg/day, 75 mg/kg/day and 125 mg/kg/day. A dose-related increase in frequency of erythema was noted. The frequency of slight erythema was higher in the 125 mg/kg/day Acnatac group than in the control group. The frequency of erythema in the group treated with clindamycin only was low while the frequency in the tretinoin group was comparable to that of the 125 mg/kg/day Acnatac group. Thus, it appears that tretinoin in the 125 mg/kg/day Acnatac group is responsible for the higher frequency of erythema in this treatment group. This is an expected effect since erythema is a well known local tolerance effect seen after dermal treatment with tretinoin. Except for the erythema, no substance-related effects were seen up to the highest dose tested (125 mg/kg/day Acnatac) on the parameters studied. No signs of systemic induced toxicity were noted. The concentrations of clindamycin phosphate, tretinoin and its metabolites were generally below the lower limit of quantification of 1.0 ng/ml for tretionin and 0.5 ng/ml for clindamycin. The occasional measurable levels of clindamycin phosphate and tretinoin did not reflect a reasonable time course of absorption, elimination or the occurrence of t_{max}.

In a study in humans (n=12, men and women) 4 g Acnatac were applied once per day in 14 days. The gel was applied to the face, neck, back and chest. There were no indication of systemic absorption of tretinoin and over 50 % of the subjects had undetectable plasma levels (levels $\leq$ 1 ng/ml). Maximum clindamycin plasma concentrations generally did not exceed 3.5 ng/ml, except for in one subject whose plasma concentration levels reached a maximum of 13.1 ng/ml.

For tretinoin the applicant has performed a reverse bacterial mutation test (Study No. 1249-B1.R-01-09 [R4]), an *in vitro* chromsomal aberration test (Study No 1249-B1.R-02-09 [R5]) and an *in vivo* micronucleus test (Study No 1249-B1.R-03-09 [R6]). For clindamycin an *in vitro* chromsomal aberration test (Study No7001-U5HP-01-07 [R3]) has been performed. No mutagenic or clastrogenic effects were found in any of these studies. For clindamycin the applicant has referred to literature references including information about negative results in Ames test and in rat micronucleus test, but no original references describing the studies are included. However, since clindamycin is a well known substance that has been used for a long time for the applied indication and in similar formulation, the references provided are considered sufficient. No genotoxicity studies with the combination clindamycin and tretinoin have been performed and this is acceptable according to “Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005” when it can be shown that the separate substances are non-genotoxic. The genotoxicity profiles of clindamycin and tretinoin are not considered to be altered when the active substances are administered together.

The applicant has performed two long-term carcinogenicity studies with clindamycin in mice, one dermal study with doses up to 150 mg/kg/day and one oral study with doses up to 30 mg/kg/day. In the dermal carcinogenesis study (Study ID 1249-B1.R-04-09 [R7]) there was an increased incidence of epitelial hyperplasia in the highest dose group (150 mg/kg/day). Further, abcesses in the ovaries were observed in both treated groups (27, 150 mg/kg/day), but the increase was only statistically significant in the 150 mg/kg/day group. However, since the

incidence of abcesses was low and since these findings were not observed in the long-term oral carcinogenicity study (Study ID 1249-B1.R-05-09 [R8]) it is most likely a sporadic finding with no relevance for human safety. No carcinogenic potential was seen in any of the carcinogenicity studies. Regarding tretinoin, the applicant refers to two long-term dermal studies where mice were treated (0,025 and 0,1 %) three times per week for two years. No tretinoin-related carcinogenicity was observed (Tsubura, Y. 1979, Kligman, L. H. 1992). In general, carcinogenesis studies in two different species are required. Further, the literature references on carcinogenesis studies on tretinoin are not state of the art of today and are very briefly described and difficult to assess. The treatment duration of Acnatac is not supposed to be longer than 12 weeks, but intermittent use can be expected, and carcinogenicity studies would thus be warranted. However, since both clindamycin and tretinoin have been used for a long time for the applied indication and in similar formulations, further carcinogenesis studies on the respective substances are not considered to add relevant data to aid in clinical safety assessment. Also, since the toxicity profiles of the drug substances are not considered to be altered when administered together, new carcinogenesis studies on the combination are not required.

In the study 1249-B1.R-06-09 [R9], 1 year dermal photocarcinogenicity study on clindamycin phosphate, a dermal single-dose 1 week dose-range study and a dermal 8 weeks tolerance study, with or without exposure to simulated sunlight (albino hairless mice) were included. In the single dose study clindamycin phosphate in the highest dose (100 mg/kg) did not elicit responses to UVR indicative of either phototoxicity or photoprotection. In the 8-week photo-tolerance study (3 animals/group/sex administered dermally on the back and sides of the mice once a day 5 days/week), no clinical signs related to the treatment with clindamycin, other than slightly higher flaking and some incidence of skin thickening, were observed. In the 1 year dermal photocarcinogenicity study there was a small, but statistically significant acceleration of skin tumours ≥1 mm in the clindamycin group compared to the control group without administration but with the same UVR exposure. However, compared to the placebo+UVR control group no significant difference was seen. A slightly earlier tumour onset (sexes combined, 36 weeks compared to 34 weeks in control group without administration, but identically UVR exposed) was seen for animals treated with clindamycin (UVR exposure 120 RBU 5 times/week). Considering that this difference was small and the fact that the study included only one dose group of 10 animals (5 animals/sex) treated with clindamycin, it is difficult to make any conclusions from these results (clindamycin was only one of several treatments in this study). Furthermore, according to ICH Topic M3 “Non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals” (CPMP/ICH/286/95), note 6, testing for photocarcinogenicity in rodents using current available models (e.g. hairless rodent) is not considered useful in support of pharmaceutical development and generally is not recommended.

In a number of literature articles regarding photocarcinogenesis supplied by the applicant (for references see “Toxicology written summary”) on tretinoin ambiguous findings have been found. According to these studies tretinoin either increases, decreases or has no effect on photocarcinogenesis. A strict wording regarding protection from sunlight during treatment of Acnatac is, however, already included in the SmPC section 4.4, since it is known that sunlight can increase the irritant properties of tretinoin. Since tretinoin has phototoxic properties and a warning regarding exposure to sunlight is included in the SmPC for Acnatac, no phototoxic study on the combination of tretinoin and clindamycin is warranted. Clinical phase 1 studies on the combination (Acnatac) are, however, available regarding phototoxicity and photoallergy (please refer to clinical assessment).

Tretinoin is a well-known human teratogen whereas clindamycin has not been shown to have teratogenic or reprotoxic effects. When the reproductive/developmental toxicity profiles of the single components in a fixed combination is sufficiently characterized, additional studies on the combination may not be warranted ("Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005"). The applicant has performed one dermal developmental toxicity study (Segment II) on Acnatac in rabbits (Study No: 7001-G2HP-06-02 [R11]) together with a dose-range finding study (Study No: 7001-G2HP-04-02 [R10]). These studies did not show any reprotoxic or teratogenic effects, only expected local tolerance effects (mostly erythema) were seen. No further reproductive and developmental toxicity studies are considered warranted. Even though the systemic exposure is low, a strict wording regarding fertility, pregnancy and lactation should be applied, in the SmPC section 4.6, since tretinoin is a well-established human teratogen.

The local tolerance on Acnatac was evaluated in three studies. A primary Skin Irritation study (7001-G2HP-01-02 [R12]) did not show any primary irritant properties of the proposed formulation and no irritation was seen in a Primary Eye Irritation study (7001-G2HP-03-02 [R13]). Acnatac was not shown to be a contact sensitizer and did not induce any allergic response in a Skin Sensitization study performed by the applicant (7001-G2HP-02-02[R14]).

The formulation applied for is intended to be used in a population ≥ 12 years of age. Normally this requires a special risk/benefit assessment where the applicant takes into consideration any possible effects of the product on the ongoing developmental process in the age(s) group to be treated. Sometimes additional studies on juvenile animals will be required to allow such an assessment. However, since there are no special safety concerns for the topical formulation for the intended clinical use, and since the systemic exposure is very low, no additional studies on juvenile animals will be required. From a non-clinical point of view the use of the product applied for in the intended age group is acceptable.

III.4 Ecotoxicity/environmental risk assessment

The applicant has been asked to submit an environmental risk assessment (ERA) in accordance with guideline EMEA/CHMP/SWP/4447/00. In answer to this issue, the applicant has argued that tretinoin is a metabolite of vitamin A, and since vitamins are exempted from the guideline EMEA/CHMP/SWP/4447/00, no ERA would be needed for tretinoin. This is considered acceptable.

An ERA has been submitted for clindamycin which not completely could be endorsed. In order to conclude on the environmental risk assessment, the Applicant, endorsed by the RMS, will commit to:

- Submit an updated ERA considering the raised issues from RMS and CMS based on published data within 3 months after the end of the procedure
- Await assessment of the updated ERA by RMS / CMS
- In case that there are still missing data: The Applicant commits to do further ecotoxicological studies and submit the new data within 12 months after the assessment report is issued.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Acnatac gel is a locally applied, locally acting fixed combination product of two previously well-known active substances. Hence, the pharmacokinetic assessment is mainly aimed at an

assessment of clinical safety, related to the extent of systemic absorption of the active substances. From an efficacy perspective, pharmacokinetic data are of limited use.

One pharmacokinetic study has been submitted in this dossier. Study R1 was a phase II dermal absorption study aimed to assess the absorption and safety of Acnatac under maximal exposure by daily topical application in acne patients. It was a single centre, open-label, multiple dose study in subjects with moderate to severe acne vulgaris. A total of 13 patients were enrolled and received daily applications of Acnatac for 14 days, applied as a 4 gram dose to the face, neck, back and chest. Blood samples were drawn at screening, pre-dose on days -1, 1, 5, 10 and 14 and a complete PK profile was obtained on day 14.

The percutaneous absorption of tretinoin was low. Tretinoin plasma concentrations were below the lower limit of quantitation (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 main tretinoin metabolites, 13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid, were also low and very similar to baseline concentrations. Thus, the concentrations of tretinoin and its metabolites after topical administration of Acnatac were in the same range or only modestly elevated compared with endogenous levels.

Mean C_{max} of clindamycin was 2.6 ng/ml, with one individual having a C_{max} of 13.1 ng/ml, possibly due to local dermal irritation, which may have contributed to higher absorption. These levels of clindamycin are still considered very low in comparison with plasma concentrations achieved after oral or IV administration of clindamycin, which can be used in doses up to 600 mg 3 times daily administered intravenously.

The study was adequately designed and conducted in the target population, patients with acne vulgaris. The daily dose was 4 gram of gel applied to the face, neck, back and chest. Thus, this can be considered to represent a worst-case scenario, since the recommended posology for Acnatac is only facial application of a “pea-sized amount” of gel (no exact dose in gram is given in the SmPC, though). It was estimated that the dose in study R1 represents a four-fold higher dose than the anticipated typical upper clinical dose.

There was no comparison between the Acnatac combination gel vs. the mono-products. Hence, it is not possible to say whether the systemic absorption is similar or not, when used in combination. The available data, however, suggest that the systemic absorption of tretinoin and clindamycin is low, but some individuals may have a higher absorption. Clinical data do not suggest any problems due to systemic absorption.

No data on distribution, elimination, special populations or interactions were provided in the dossier. The lack of such data is acceptable for this product, being a new topical fixed combination of previously well-known active substances. In conclusion, the pharmacokinetic data presented in the dossier is sufficient and there are no outstanding issues.

IV.2 Pharmacodynamics

The mechanisms of action of clindamycin and tretinoin are considered well known. Clindamycin has an antibacterial activity but its main action is an anti-inflammatory effect on the acne vulgaris lesions. Tretinoin works by both comedolysis and by normalizing the maturation of follicular epithelium so that comedone formation ceases. From a mechanistic point of view, a combination treatment with the two active components may be of advantage.

IV.3 Clinical efficacy

The efficacy and safety of Acnatac is supported by Studies 7001-G2HP-06-02 and 7001-G2HP-07-02, two Phase 3 studies with identical design; double-blind, randomized, placebo-controlled, 4-arm clinical trials in males and females with acne vulgaris. A total of 1247 males and 1293 females were randomized to receive either Acnatac, or the monads clindamycin in vehicle gel, tretinoin in vehicle gel or the vehicle gel for 12 weeks. Furthermore, a double-blind, randomized, active-controlled study (MP-1501-02) was performed in which subjects (970 males and 1040 females) received either Acnatac or clindamycin in the vehicle gel. The inclusion and exclusion criteria were appropriate for the aims of the studies. The clinical studies were performed at different centres in the US, which is accepted although the product is proposed to be marketed in EU. The nature of the condition proposed to be marketed, acne vulgaris, is similar and also the treatment options in the EU and US.

Subjects were instructed to dispense the test product on the entire face, and not only on the lesion area once daily before bedtime. The posology of the monads is for tretinoin once daily application, while clindamycin should be applied twice daily both in the morning and in the evening.

The primary objective of the studies 7001-G2HP-06-02 and 7001-G2HP-07-02 was to evaluate efficacy and the aim was to demonstrate superiority for the combination versus its monads. The primary efficacy endpoints were:

- Two out of three of the following lesion counts: mean percent change from baseline at Week 12 in inflammatory lesion counts, mean percent change from baseline at Week 12 in non-inflammatory lesion counts, mean percent change from baseline at Week 12 in total lesion counts; and
- The percent of subjects who were clear or almost clear at Week 12, as judged by an Evaluator's Global Severity Score (EGSS).

In study MP-1501-02 superiority was considered to have been achieved if statistical significance (Acnatac gel versus clindamycin phosphate 1.2% gel) was achieved in the treatment comparison of the dichotomized EGSS at Week 12 and in at least two of the three comparisons of percent change from Baseline to Week 12 in lesion count (inflammatory, non-inflammatory and total lesion count).

The requirement of showing significance in two out of three lesion count variables is a potential multiplicity issue since two out of three can be chosen in three different ways. However, since the dependence of the outcomes (one being the sum of the other two) is quite strong the issue is considered minor and not influencing the conclusion of the trials.

The primary and secondary objectives are assessed as adequate for evaluating the efficacy and safety of the product proposed for marketing. The primary analysis population was the intent-to-treat (ITT) population, which included all randomized subjects who received study drug. All efficacy and safety analyses were based on the ITT population. Tests for superiority were also conducted for the PP subjects as a secondary and supportive set of analyses. Subjects were eligible for the PP analysis if they completed the 12-week evaluation without noteworthy study protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). Subjects who were discontinued due to treatment-related adverse events were included in the PP analysis.

A total of 4550 subjects were enrolled in the Phase 3 studies altogether. 711 subjects discontinued from the studies, the number of subjects that discontinued treatment was fairly equal among the treatment groups. The treatment groups seem generally well balanced with respect to sex and age, adolescents as young as 11 years old have been participating in the studies, which is of importance since this age group is supposed to be included in the indication for Acnatac. The treatment groups were also generally well balanced for clinical characteristics of acne vulgaris. In the two studies combined (7001-G2HP-06-02 and 7001-G2HP-07-02), the majority of subjects had acne vulgaris of moderate severity across all treatment groups (71-75%) while the rest of the subjects were equally divided between mild and severe acne vulgaris. In study MP-1501-02, on the other hand, approximately 75% of the subjects had acne vulgaris of moderate severity while the rest had severe acne vulgaris.

In study 7001-G2HP-06-02, the efficacy of Acnatac was highly significant and superior to vehicle both for inflammatory, non-inflammatory and total lesion counts in the overall population, including all ages. Statistical significance was also achieved for Acnatac versus clindamycin for non-inflammatory lesion and total lesions, but not for inflammatory lesions. Acnatac has significant efficacy versus tretinoin for inflammatory, non-inflammatory and total lesions in the overall age population. In the adolescent patient population, the clinical efficacy of Acnatac is fairly similar to the overall population with superiority of Acnatac shown versus all comparisons except for clindamycin and inflammatory lesion counts (see tables below).

In the global severity score, statistical significance of Acnatac was demonstrated versus vehicle and tretinoin both in the overall patient and the adolescent population. Statistical significance was however not achieved versus clindamycin. When using dichotomised values, a similar trend was observed. The Applicants objective to reach statistical significance in two out of three parameters (inflammatory, non-inflammatory and total) and in the dichotomised global severity score has not been fulfilled for the clindamycin comparison.

Percent change from baseline in lesion counts (Study 7001-G2HP-06-02)

		Age: overall			**Age:11-17 years**		
Lesion type	**Treatment**		**Comparison vs. Acnatac**			**Comparison vs. Acnatac**	
		LS mean[1]	**LS mean difference[1]**	**p-value[3]**	**LS mean[1]**	**LS mean difference[1]**	**p-value[3]**
Inflammatory	**Acnatac**	46.1	n.a.	n.a.	43.2	n.a.	n.a.
	Clindamycin	39.7	6.4	0.0586	36.5	6.7	0.1231
	Tretinoin	37.1	9.0	0.0013	31.8	11.4	0.0025
	Vehicle	19.7	26.4	<0.0001	10.0	33.2	<0.0001
Non-inflammatory	**Acnatac**	37.4	n.a.	n.a.	36.4	n.a	n.a.
	Clindamycin	24.4	13.1	0.0003	20.9	15.5	0.0011
	Tretinoin	31.9	5.6	0.0344	25.0	11.4	0.0007
	Vehicle	13.4	24.0	<0.0001	7.4	29.0	<0.0001
Total	**Acnatac**	41.7	n.a.	n.a.	39.9	n.a.	n.a
	Clindamycin	31.2	10.4	0.0002	27.7	12.2	0.0010
	Tretinoin	34.6	7.0	0.0020	28.4	11.5	<0.0001
	Vehicle	16.5	25.1	<0.0001	9.4	30.5	<0.0001

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-LOCF– Clear or almost clear				
Success	88 (21%)	34 (16%)	64 (15%)	18 (9%)
Failure	332 (79%)	174 (84%)	353 (85%)	189 (91%)
Total	420	208	417	207
P-value		0.172	0.032	<0.001
PP– Clear or almost clear				
Success	79 (25%)	25 (16%)	55 (18%)	18 (11%)
Failure	238 (75%)	130 (84%)	258 (82%)	145 (89%)
Total	317	155	313	163
P-value		0.037	0.015	<0.001
ITT – Clear or almost clear or show a two grade improvement				
Success	98 (23%)	36 (17%)	68 (16%)	19 (9%)
Failure	322 (77%)	172 (83%)	349 (84%)	188 (91%)
Total	420	208	417	207
P-value		0.085	0.009	<0.001
PP – Clear or almost clear or show a two grade improvement				
Success	90 (28%)	28 (18%)	60 (19%)	19 (12%)
Failure	227 (72%)	127 (82%)	253 (81%)	144 (88%)
Total	317	155	313	163
P-value		0.020	0.003	<0.001

In study 7001-G2HP-07-02, the efficacy of Acnatac is highly significant and superior to vehicle both for inflammatory, non-inflammatory and total lesion counts in the overall age population. In this age population, statistical significance is not achieved for Acnatac versus clindamycin for either inflammatory, non-inflammatory or total lesion counts. When comparing Acnatac with tretinoin, a significant effect is reached for inflammatory and total lesions, while that for non-inflammatory lesions reaches borderline significance. In adolescents, the clinical efficacy picture of the combination is fairly similar to the overall age population with superiority of Acnatac shown versus vehicle. For Acnatac versus clindamycin, statistical significance is reached for inflammatory and total lesions, but not for non-inflammatory lesions. When comparing Acnatac versus tretinoin, an identical picture was achieved that is statistical significance is reached for inflammatory and total lesions, but not for non-inflammatory lesions.

In the global severity score, statistical significance of Acnatac was demonstrated versus vehicle, clindamycin and tretionoin both in the overall patient and the adolescent population. When using dichotomised values, statistical significance was reached versus vehicle and tretinoin in the ITT, ITT-LOCF and PP populations studies, but not for clindamycin.

Percent change from baseline in lesion counts (Study 7001-G2HP-07-02)

Lesion type	Treatment	Age: overall			Age:11-17 years		
			Comparison vs. Acnatac			Comparison vs. Acnatac	
		LS mean[1]	LS mean difference[1]	p-value[3]	LS mean[1]	LS mean difference[1]	p-value[3]
Inflammatory	**Acnatac**	50.6	n.a.	n.a.	46.8	n.a.	n.a.
	Clindamycin	43.7	6.9	0.0712	36.3	10.4	0.0460
	Tretinoin	40.1	10.5	0.0006	37.7	9.1	0.0212
	Vehicle	31.9	18.7	<0.0001	22.0	24.7	<0.0001
Non-inflammatory	**Acnatac**	35.0	n.a.	n.a.	32.6	n.a	n.a.
	Clindamycin	29.9	5.1	0.1508	24.5	8.1	0.0801
	Tretinoin	29.5	5.5	0.0646	25.7	6.9	0.1007
	Vehicle	17.8	17.2	<0.0001	7.9	24.7	<0.0001
Total	**Acnatac**	41.1	n.a.	n.a.	38.0	n.a.	n.a
	Clindamycin	36.0	5.1	0.0774	30.2	7.8	0.0401
	Tretinoin	33.9	7.2	0.0041	30.7	7.3	0.0357
	Vehicle	23.0	18.2	<0.0001	12.8	25.2	<0.0001

Global Severity Score at Week 12 – presented as dichotomised values

	Acnatac	Clindamycin	Tretinoin	Vehicle
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-LOCF– Clear or almost clear				
Success	97 (23%)	38 (17%)	63 (15%)	17 (8%)
Failure	328 (77%)	180 (83%)	366 (85%)	199 (92%)
Total	425	218	429	216
P-value		0.094	0.002	<0.001
PP– Clear or almost clear				
Success	80 (27%)	34 (21%)	55 (18%)	14 (10%)
Failure	213 (73%)	127 (79%)	251 (82%)	130 (90%)
Total	293	161	306	144
P-value		0.130	0.005	<0.001
ITT – Clear or almost clear or show a two grade improvement				
Success	116 (27%)	44 (20%)	79 (18%)	23 (11%)
Failure	309 (73%)	174 (80%)	350 (82%)	193 (89%)
Total	425	218	429	216
P-value		0.041	0.002	<0.001
PP – Clear or almost clear or show a two grade improvement				
Success	99 (34%)	40 (25%)	73 (24%)	20 (14%)

Failure	194 (66%)	121 (75%)	233 (76%)	124 (86%)
Total	293	161	306	144
P-value		0.037	0.007	<0.001

Onset of efficacy was analysed in studies 7001-G2HP-06-02 and 7001-G2HP-07-02 (data not shown, please refer to the clinical AR). Superiority of Acnatac to vehicle was shown after the first assessment, after two weeks of treatment. Onset of action of clindamycin for percent change in inflammatory and total lesion counts was noted at Week 2, which also was the onset of action of Tretinoin against non-inflammatory and total lesions. Results from the onset of action analysis are in agreement with the mechanism of action of its individual components.

Overall, the results from the two studies 7001-G2HP-06-02 and 7001-G2HP-07-02 are concordant with each other. However, the Applicants objective to reach statistical significance in two out of three parameters (inflammatory, non-inflammatory and total) and in the dichotomised global severity score was not fulfilled. The Applicant therefore decided to perform another study that compared Acnatac with clindamycin alone (study MP-1501-02). When analysing data from this study it is evident that Acnatac is superior to clindamycin gel for inflammatory, non-inflammatory and total lesion type both in the overall age group and in patients aged 12-17.

In the global severity score, statistical significance of Acnatac (code name Clin-RA gel) was demonstrated versus vehicle, clindamycin gel both in the overall patient and the adolescent population. These results were further supported using dichotomised values.

Percent change from baseline in lesion (studyMP-1501-01)

Lesion type	Model as indicated in section 2.2	Age: overall			Age: 12-17		
		LS means		Treat-ment dif-ference (p-value)	LS means		Treatment difference (p-value)
		Clin-RA Gel	Clin-da-mycin		Clin-RA Gel	Clin-damy-cin	
Inflamma-tory	Model 1[1]	60.5	54.5	6.1 (0.0011)	59.4	53.6	5.8 (0.0204)
	Model 2[2]	59.2	53.0	6.2 (<.0001)	58.0	51.8	6.1 (0.0019)
Non-inflamma-tory	Model 1[1]	51.6	43.1	8.5 (<.0001)	50.0	42.2	7.8 (0.0002)
	Model 2[2]	49.2	40.7	8.5 (<.0001)	48.1	40.1	8.0 (<.0001)
Total	Model 1[1]	55.4	47.8	7.6 (<.0001)	53.8	46.6	7.2 (0.0002)
	Model 2[2]	53.8	46.1	7.6 (<.0001)	52.3	44.9	7.4 (<.0001)

[1] Estimated LS-means and LS means difference from Model 1, P-value from Model 3
[2] Estimated LS-means, LS means difference and p-value from Model 2
Source: Additional analyses for study MP-1501-02 TAB-2 [R7]

Dichotomised EGSS, ITT-population

	Clin RA N = 1008	**Clindamycin N = 1002**	***P* value***
Dichotomized EGSS			
Success[†]	381 (37.8)	318 (31.7)	0.002
Failure	627 (62.2)	684 (68.3)	

* *P* values are based on a 2-sided 5% test of the Cochran-Mantel-Haenszel Row Mean Score Statistic, adjusting for investigational center.

† Success was defined as clear or almost clear at Week 12, or at least a 2-grade improvement in EGSS from Baseline to Week 12. If no value was presented at Week 12, then the subject was considered a failure.

Clinical efficacy of clindamycin and tretionoin in combination has been demonstrated. As a response to issues raised in the Day 70 AR, a meta-analysis was performed across all studies (3 against clindamycin, 2 against tretinoin). The obtained mean overall add-on effect of Acnatac vs. clindamycin was 7.7 lesions which is comparable to the overall add-on effect vs. tretinoin (7.1 lesions). Therefore, according to the figures provided by the Applicant, the contribution of tretinoin to the overall effect is as high as the contribution of clindamycin, a view which is shared by the RMS. Thus, the efficacy of Acnatac is better than for the respective monads.

Similar results were obtained in the overall age group and in adolescents. A subgroup analysis with respect to severity of the disease (moderate or severe acne) has been performed as requested in the Day 70 AR demonstrating very similar results obtained in the overall population.

Concerning the issue on potential for development of antibiotic resistance, when combining the two actives, the risk of development of resistance decreased substantially when compared to clindamycin monotherapy. Thus the addition of tretinoin in the Acnatac formulation even when applied once daily effectively prevents the development of resistance which may be explained by the potential of tretinoin to facilitate the penetration of clindamycin into deeper layers of the skin and deeper into the comedones. Moreover, the efficacy of Acnatac is maintained after 8 weeks of treatment and beyond while it is known for clindamycin mono therapies that they may lose efficacy after about 8 weeks when resistance occurs.

The originally proposed indication for the product is: “Acnatac Gel is indicated for the topical treatment of mild to severe acne vulgaris in patients 12 years or older”. The population studied in the two pivotal studies (7001-G2HP-06-02 and 7001-G2HP-07-02) included very few subjects with mild acne (14% for the two studies combined). Furthermore, it was in the Day 70 AR questioned to treat mild acne vulgaris with a local antibiotic in a combination product. As a response, the Applicant has agreed to change the indication to *“Acnatac is indicated for topical treatment of Acne vulgaris when comedones, papules and pustules are present in patients 12 years or older”*, a wording which is accepted by the RMS.

For those patients that use clindamycin twice daily and tretinoin once daily, increased treatment compliance can be foreseen with a combination product that only needs to be used once daily. This is of particular importance in the largest target population for Acnatac, the adolescents.

IV.4 Clinical safety

Acnatac is a fixed combination product comprising clindamycin phosphate 1.2% (w/w) and tretinoin 0.025% (w/w) in a topical gel. The concentrations of the actives have been approved and used as monads for several years for treatment of acne vulgaris. Therefore, the clinical safety profiles are considered well known with the majority of adverse events being local.

A pharmacokinetic study with Acnatac conducted in patients with acne vulgaris with a daily dose of 4 gram of gel applied to the face, neck, back and chest showed low percutaneous absorption of tretinoin and clindamycin.

In support of the present application, safety of clindamycin phosphate and tretinoin was assessed in four Phase I safety studies (cumulative irritation, irritation and contact sensitization, phototoxicity and photoallergy). The main focus of the safety assessment of the product is the clinical efficacy and safety trials (Study 7001-G2HP-06-02, Study 7001-G2HP-07-02 and study MP-1501-02) and the long-term safety study (MP-1501-01). Furthermore, an additional safety assessment in patients aged 11 to <18 years have been performed in support of the proposed therapeutic indication including patients in the adolescent age group.

The four Phase I safety studies showed that Acnatac has a moderate irritation potential, exceeding the positive control sodium lauryl sulphate but with lower scores vs. the tretinoin product Retin A gel. Topically applied tretinoin is known to be irritating and since repeated application under occlusion was used the results are not unexpected. The gel vehicle had a low irritation potential. Acnatac and its vehicle seemed to have a low potential to induce phototoxicity and photoallergy. Tretinoin is, however, known to cause an increased sensitivity to UV radiation and a warning is included in section 4.4 of the SmPC for Acnatac, in accordance with other topical tretinoin products. This is considered acceptable.

The number of patients exposed in the pivotal efficacy and safety studies is 1853, and of these 213 patients were exposed for one year. Considering that Acnatac gel is a new combination formulation with identical strengths of well-known active substances, the extent of exposure is considered sufficient. The number of subjects that discontinued drug treatment was approximately equal among the treatment groups with the majority in the Acnatac group and in the tretinoin groups.
The incidence of drug-related AEs is overall considered low. The number of subjects reporting one or more adverse event is similar among the treated groups, clindamycin phosphate plus tretinoin, clindamycin phosphate, tretinoin and the vehicle group. The severity of the events was in majority assessed as mild to moderate. Nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, dry skin, cough, and sinusitis (descending order) were adverse events reported in the Acnatac group in at least 1% of treated subjects. Local adverse events are fairly common with the monads and the majority of local adverse events are caused by the retinoid tretinoin. The most relevant AE’s have been included in the SMPC section 4.8 for Acnatac.

The long term safety study showed that the proportion of AE severity was stable during the first 9 months of treatment and declined thereafter. However, Acnatac is only intended for use during 12 week courses, which can be prolonged after evaluation of the physician.

There were no deaths during the studies. A total of 23 subjects reported SAEs (11 in Phase 3 studies 7001-G2HP-06-02 and 7001-G2HP-07-02 combined; 6 in Phase 3 study MP-1501-02, and 6 in the long-term safety study MP-1501-01) a total of 29 SAEs. All of the reported SAEs were evaluated by the investigator as being unrelated to study medication. Clear tables of these SAE’s could not be found in the extensive documentation and should be submitted. Six subjects in the long-term safety study (MP-1501-01) had SAEs during the study. All the SAEs were by the Applicant considered unlikely to be related to study treatment, a view which is shared by the assessor.

The safety of Acnatac was reassessed in adolescents since this is a proposed target population of the product. Approximately 60% of patients in the three Phase 3 studies (7001-G2HP-06-02, 7001-G2HP-07-02 and MP-1501-02) were patients aged 12-17 years. Among male patients 74.3% were 12-17 years old, while among female patients only 41.4% were in the adolescent group which is in agreement with the clinical picture of acne. Overall, the Applicant’s opinion

that the severity profile of AEs was similar in adolescents and overall population is endorsed by the assessor. Thus from a safety perspective, there are no reasons not to grant approval of Acnatac in the adolescent population.

Considering that the systemic absorption of clindamycin phosphate and tretinoin is low and systemic adverse events with the monads are rare, absence of clinical laboratory evaluations can be accepted.

To conclude, no new safety concerns have been identified in the present dossier for the combination of clindamycin and tretinoin in the treatment of acne vulgaris.

Risk Management Plan
The Applicant has well justified that it is not necessary to set up and submit a Risk Management Plan for Acnatac, a combination product of two well known active substances registered and marketed for more than 30 years, an opinion which is shared by the MPA.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a quality point of view this application can be recommended for approval.

Concerning the environmental risk assessment, the applicant has to a satisfactory degree, approached the questions raised during the procedure. Therefore, in order to conclude on the environmental risk assessment, the applicant has committed to submit an updated ERA within 3 months after the end of the procedure.

From a clinical point of view, pharmacokinetic studies support a low systemic absorption of clindamycin and tretinoin from the gel formulation. Efficacy of the combination of Acnatac gel is supported by altogether three clinical phase 3 studies. Study 7001-G2HP-06-02 and 7001-G2HP-07-02 used identical design; double-blind, randomized, placebo-controlled, 4-arm clinical trials where males and females with acne vulgaris received either Acnatac gel, or the monads clindamycin in vehicle gel, tretinoin in vehicle gel or the vehicle gel for 12 weeks. Furthermore, a double-blind, randomized, active-controlled study (MP-1501-02) was performed in which subjects received either Acnatac gel or clindamycin in the vehicle gel.

Acnatac showed superiority versus vehicle and one of the monads, tretinoin in the two large Phase 3 clinical trials with identical design. Statistical significance was not achieved versus clindamycin which however was borderline. In the third phase 3 study, aimed at demonstrating superiority of the test product versus clindamycin, statistical significance was achieved. However, the magnitude of the add-on effect of Acnatac compared to clindamycin monotherapy is assessed as small. Similar efficacy results were obtained in the overall age group and in adolescents.

For those patients that need both clindamycin and tretinoin for management of acne vulgaris, Acnatac is considered a valuable contribution to the group of medicial products available in the proposed indication: *Acnatac 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.

The Applicant has made several changes to the SmPC during the procedure, which is considered acceptable to the RMS.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Acnatac 10 mg/g + 0.25 mg/g gel is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Acnatac 10 mg/g + 0.25 mg/g gel was successfully finalised on 28 February 2013.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se