CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-782

MEDICAL REVIEW(S)

Correspondence date:January 27, 2000
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MEDICAL OFFICER'S REVIEW OF NDA 50-782
ORIGINAL SUBMISSION

NOV 19 2000

SPONSOR: Clindagel LLC
Santa Rosa, CA

DRUG: Clindagel (Clindamycin [redacted] Gel) 1%

CLINICAL INDICATION: Acne vulgaris

Proposed labeling indication statement: 'For topical application in the treatment of acne vulgaris.'

FORMULATION:

Clindamycin phosphate	[redacted]
Methylparaben	
Carbomer 941	
Propylene glycol	
Polyethylene glycol	
Sodium hydroxide ([redacted]) qs pH	
Purified water [redacted]	

DOSAGE AND ADMINISTRATION: Applications once daily.

DATE OF SUBMISSION: January 27, 2000

REGULATORY STATUS: This is a 505(b)(2) application for a new dosing regimen of topical 1% clindamycin phosphate. Clindagel is indicated for QD treatment of acne, whereas the listed product, Cleocin T gel, is indicated for BID treatment of acne.

RELATED SUBMISSIONS: IND 56,487

PHARMACOLOGY AND CONTROLS REVIEWS: These are currently pending.

STATISTICAL REVIEW: This is currently pending.

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Medical Officer's review

Pre-IND meeting

A pre-IND meeting was held on February 23, 1998. The Agency clinical and biostatistical comments were as follows.

Clinical

1. The proposed dermal irritation study (CGEL-001) ia adequate in sample size (25-30 subjects), and in the methodology (the five point scale). It was requested that the study report include individual patient data.

2. The proposed dermal sensitization study, CGEL-002, is adequate in the sample size of 200 subjects. It was suggested [redacted] Also, more information on the grading scale should be provided, such as the definition of what constitutes a response, and the meaning of a half-grade change.

3. It was suggested that the control for both Studies CGEL-001 and CGEL-002 be the pioneer product; no other positive or negative control group would be required.

4. Based on the submitted spectrophotometry data which shows limited UV absorption, the FDA will waive photoxicity and photoallergy studies. It was noted that the methylparaben absorption was expected and is not clinically significant.

5. The following comments were made on the phase 3 study, CGEL-003.

- The sponsor was informed that in order to meet the 505 (b)(2) requirements, they would have to show that Clindagel QD is not inferior to the pioneer product at the labeled dosing frequency, that is, Cleocin T BID.

- There is no reasonable way to logistically mask the patients in such a study; however, there are ways in which the observer could be masked. The Agency asked that the sponsor develop means to mask the observer, such as having a dermatologist-observer who does not speak with the patient.

- The study design must be a three-arm, parallel group, single (investigator) blinded comparison of Clindagel QD, Cleocin T BID, and the Clindagel vehicle QD. An unequal randomization is permissible.

- the dichotomized investigator's global evaluation. Equivalency is defined as a confidence interval that passes through 0, and:

  - if the efficacy of the pioneer product is 90% or greater, then is not greater than 10%.
  - if the efficacy of the pioneer product is 80 to 89%, then is not greater than 15%.
  - if the efficacy of the pioneer product is < 80%, then is not greater than 20%.

- The power should be 80% or greater.

End of Phase 2 meeting

An End of Phase 2 meeting was held on January 19, 1999. The clinical and biostatistical comments were as follows.

Clinical

1. The Agency agrees with the general design of the Phase 3 studies.

2. As inclusion criteria, the Agency recommends a minimum of 25 inflammatory facial lesions (papules and pustules), instead of 10, in order to facilitate the demonstration of clinical effect. The Agency also recommends that no patients with active cyctic lesions be enrolled. The inclusion criterion of 20-100 non-inflammatory lesions appears reasonable.

3. Washout periods should be consistent with the expected duration of action of the applied product. The sponsor should present a rationale for washout periods at variance with those below.

   - Topical acne treatment - 4 weeks
   - Corticosteroids - 4 weeks
   - Topical or systemic anti-inflammatories - 4 weeks
   - Topical or systemic antibiotics - 4 weeks
   - Systemic retinoids - 3 months

4. The primary efficacy measurements should be 1) lesion counts, and 2) physician's global evaluation. Baseline and endpoint lesion counts should be presented for inflammatory, non-inflammatory, and total lesion counts. The levels of the investigator's global evaluation should be clearly defined, and should use static morphologic descriptors, i.e., the

state of the condition at the time of assessment. For the efficacy analysis the global assessment should be dichotomized to success/failure.

5. The Agency agrees with the protocol safety assessments being measured in the study.

6. The two Phase 1 studies (CGEL-001 and CGEL-002) and the two proposed Phase 3 studies appear to be sufficient to support the filing of the Clindagel NDA, provided that the sponsor documents in the NDA that the studies were performed with the final to-be-marketed formulation and that the drug product does not absorb in the 280 to 700 nm range (i.e., if the product does not absorb in the ultraviolet range, the requirement for phototoxicity and photosensitization studies may be waived.)

7. The FDA invites the sponsor to review the guidelines in ICH E7A document.

8. Clindamycin phosphate is a candidate for submission as a 505(b)(2).

9. Evidence to support approval should be a four arm study consisting of Clindagel QD, Clindagel BID, Cleocin T BID, and Clindagel vehicle, 1/2 QD and 1/2 BID.

10. Once daily dosing would need to be supported by dose ranging. Clindagel QD would need to be superior to Clindagel vehicle.

11. The labeling would reflect the results of Cleocin T BID vs Clindagel QD vs vehicle. The labeling would not discuss alternative dosing regimens of Clindagel (e.g., BID).

12. The sponsor did not discuss dose ranging in the briefing packet. The Agency would appreciate a rationale for the absence of dose ranging information.

13. The sponsor should be aware that particular patient exclusions from the study might warrant similar restrictions in the labeling. This might include exclusion of patients with beards or other facial hair, or a restriction to use of the same soap, makeup, and hair products during treatment.

Biostatistics

1. The Agency agrees that the ITT population is the primary efficacy population in superiority trials.

2. The randomization ratio of 3:1 is acceptable.

3. The proposed sample size is acceptable, assuming that the expected difference between the Clindagel and vehicle groups is 20% relative to the percent change from baseline to week 12 in total lesion count.

Other comments concerned statistical methodology.

Pre-NDA meeting

A pre-NDA meeting on IND 56,487 for Clindagel was held on November 15, 1999. The clinical and statistical portion of the Agency comments are as follows.

Clinical:

These studies are acceptable to allow the NDA to be filed, provided that it is shown that the drug product does not absorb light in the 280 to 700 nm range, so that a requirement for phototoxicity and photosensitization studies can be waived. It should also be documented that the studies were performed with the final formulation which is to be marketed.

Additional clinical comments:

1. A rationale should be provided for the selection of once daily dosing.
2. An assessment by the sponsor of why the results were better with QD dosing than with BID dosing should be included in the application.
3. A tabulation of the results of the comparison of QD applications of Clindagel with BID applications of Cleocin T should be included in the draft labeling.

Biostatistics:

1. The definition of the ITT population on page 104 is not clear. The term 'patients who used the study-drug' should be explained. At the pre-meeting on February 23, 1998, the sponsor was recommended to define the ITT population as every patient who was dispensed the study drug (active or vehicle).

2. The sponsor is requested to provide listings for the following four data sets:

   - all patients who were dispensed the study drug (active or vehicle)
   - the ITT endpoint population
   - the ITT 12 week population
   - the Per Protocol population

   Each of the data sets should have the following variables: Patient ID, center, last visit, endpoint, lesion counts and Investigator Global at baseline and at the last visit. In the first data set, for each patient excluded from other populations, the reason for the exclusion should be provided.

3. The sponsor is requested to provide the primary efficacy analysis comparing the Per Protocol populations of Clindagel vehicle once daily vs Clindagel vehicle twice daily.

4. In the Non-Inferiority Testing Section 4.3.5, Tables 12 and 13 have no regulatory value because they use the ITT population. For non-inferiority comparisons, the Per Protocol population should be used.

5. In the NDA submission, the following items are requested:

   - subgroup efficacy analysis (by baseline severity, age, gender, and race)
   - SAS data sets and programs (SAS version 6.12)

Overview of clinical studies

The clinical studies provided in this submission are as follows.

Study No.	Description
CGEL-001	Cumulative irritation
CGEL-002	Sensitization
CGEL-003	Safety and efficacy

These studies were done with the to-be-marketed formulation.

A report on Study CGEL-005, a dermal absorption study, was submitted as an amendment to the NDA on April 26, 2000.

Financial disclosure statement

The sponsor makes the following statement in regard to a certification of financial interests of clinical investigators.

'As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).'

Listed are all the investigators for Studies CGEL-001, CGEL-002, and CGEL-003.

Phase 1 studies

1) Study CGEL-001: Cumulative dermal irritation.

The investigator for this study was [redacted] of [redacted]

Thirty-five subjects were enrolled in the study, of which 25 completed the study. The subjects were male and female, 18-65 years of age, conforming to the Fitzpatrick skin classifications I, II, III, or IV on the following scale of six skin types.

I = always burns easily; never tans.
II = always burns easily; tans minimally.
III = burns moderately; tans gradually.
IV = burns minimally; always tans well.
V = rarely burns; tans profusely.
VI = never burns; deeply pigmented.

The test materials were Clindagel, the Clindagel vehicle, Cleocin T, and 0.5% SLS. Applications of the test materials were made under occlusive patches to the same skin sites of the back daily except for Sundays and holidays, for 21 applications. The test sites were randomized, and the evaluator was blinded to the test site assignments. Reactions were graded at 15 minutes after each patch removal, using the

following scale.

Score	Description
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

The effects on the superficial layers were given letter grades, with numerical equivalents for additive purposes, as follows.

Score	Description
A (0)	Slight glazed appearance
B (1)	Marked glazing
C (2)	Glazing with peeling and cracking
D (3)	Glazing with fissures
E (3)	Film of dried serous exudate covering all or portion of the patch site
F (3)	Small petechial erosions and/or scabs

When an additive score on both scales of 3 or higher for a test material was reached, no additional applications of the test material were made to that site. For cumulative scoring purposes, any score of 3 or higher was considered to be a 3 for the remainder of the test, even though applications at that site were discontinued.

Based on the total cumulative scores, the following classification system was used to categorize the irritation potential.

Score	Indications from test	Description of observed responses
0 to 127	Mild material - no experimental irritation	Essentially no evidence of cumulative irritation under the conditions of the test (i.e., continuous at concentration specified)
123 to 502	Probably mild in normal use	Evidence of slight potential for very mild cumulative irritation under conditions of test
503 to 1124	Possibly mild in normal use	Evidence of moderate potential for mild cumulative irritation under conditions of test
1125 to 1454	Experimental cumulative irritant	Evidence of strong potential for mild-to-moderate cumulative irritation under conditions of test
1455 to 1575	Experimental primary irritant	Evidence of potential for primary irritation under conditions of test

Results for the cumulative irritation scores for each test product, and their classifications, were as follows.

Test material	Cumulative score	Classification
0.5% SLS	1453	Experimental cumulative irritant
Clindagel vehicle	474	Probably mild in normal use
Clindagel	432	Probably mild in normal use
Cleocin T	426	Probably mild in normal use

There were no significant differences in the scores between Clindagel, the ~~Clin~~dagel vehicle, and Cleocin T.

The frequency distribution of scores over the 21 day period was as follows.

Frequency distribution of irritation scores				
Scores	SLS	Clindagel	Vehicle	Cleocin
0	24	256	218	248
1	17	178	191	183
2	21	62	67	64
3	463	29	49	30

2) Study CGEL-002: Sensitization.

The investigator for this study was [redacted] of [redacted]

This was a repeat insult patch test study on normal subjects, using the test materials 1% clindamycin phosphate gel, clindamycin phosphate gel vehicle, Cleocin T gel 1%, purified water, and propylene glycol.

Two hundred fifty-six subjects were enrolled in the study, of which 200 subjects completed the study. Of the subjects that did not complete the study, 54 discontinued for reasons unrelated to the test materials, and 2 subjects discontinued due to adverse events. The subjects were male and female, 18-65 years of age, conforming to the Fitzpatrick skin classifications I, II, III, or IV on the following scale of six skin types.

I = always burns easily; never tans.
II = always burns easily; tans minimally.
III = burns moderately; tans gradually.
IV = burns minimally; always tans well.
V = rarely burns; tans profusely.
VI = never burns; deeply pigmented.

During the induction phase, occlusive patches with the test materials were applied three times weekly for three weeks to the same skin sites on the back of each subject. Reactions were graded at 30 minutes after patch removal by a grader blinded to product assignments, using the following scales.

Score	Description
Erythema scale	
0	No visible erythema
1	Mild erythema (faint pink to definite pink)
2	Moderate erythema (definite redness)
3	Severe erythema (very intense redness)
Elevated responses	
E	Edema - definite swelling
P	Papules - small, red, solid elevations; surface of reaction has granular feeling.
V	Vesicles - small, circumscribed elevations having translucent surfaces so that fluid is visible (blister-like). Vesicles are no larger than 0.5 cm in diameter.
B	Bullae - vesicles with a diameter > 0.5 cm; vesicles may coalesce to form one or a few large blisters that fill the patch site.
Other response characteristics	
S	Spreading - evidence of the reaction beyond the pad area (does not include obvious signs of leakage of test material away from pad.)
W	Weeping - evidence of release of fluid from a vesicular or bullous reaction.

Any erythema grade of 2 or greater, or any erythema grade of 1 with a letter grade of V or B necessitated relocation of the patch.

At 14 days after the last induction phase patch application, challenge patches were applied in duplicate to an original and alternate site, remaining in place for 48 hours. For the original site the patch was applied in approximately the same area as the induction phase patches. For the alternate site the patch was applied to a naive skin site on the upper arm or the back. The challenge sites were graded at 48 and 96 hours after application.

The scores during the induction phase for clindamycin gel were as follows.

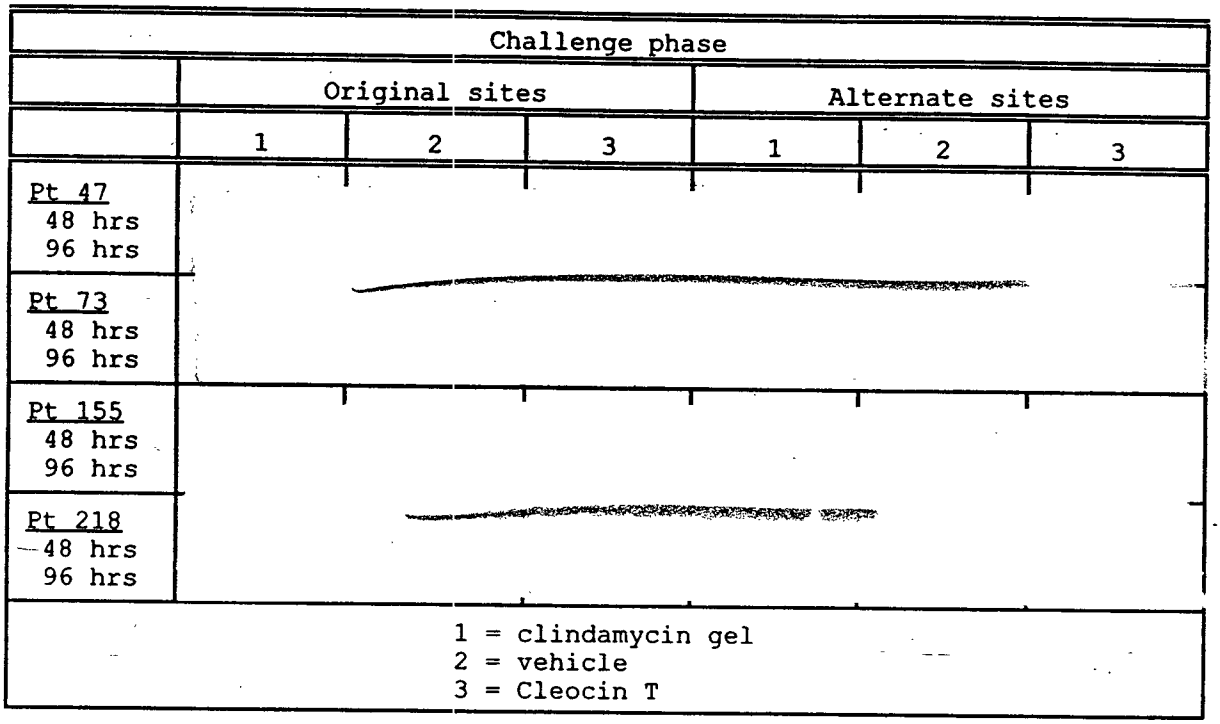
Induction phase - clindamycin gel (G=time of grading)									
Score	G1	G2	G3	G4	G5	G6	G7	G8	G9
0	160	146	154	150	150	144	128	136	113
1	35	51	43	49	48	54	70	64	81
2	4	2	2	1	1	1	2	0	0
3	1	0	0	0	0	0	0	0	0
1E	0	0	1	0	0	0	0	0	1
3E	0	0	0	0	0	0	0	0	1
2P	0	1	0	0	1	0	0	0	0

The scores in the challenge phase for clindamycin gel were as follows.

Challenge phase - clindamycin gel				
	Original sites		Alternate sites	
Score	48 hrs	96 hours	48 hours	96 hours
0	138	182	130	183
1	49	14	59	13
2	3	0	4	0
3	1	0	1	0
1E	4	2	1	1
2E	0	2	1	3
2EP	1	0	0	0

1 = mild erythema
2 = moderate erythema
3 = severe erythema
E = edema
P = papules

It was felt that the results of the challenge phase showed suggestive evidence of allergic contact dermatitis with clindamycin gel in four subjects. The results of the 96 hour evaluation in these subjects were as follows.



During induction subject 47 had possible blisters with clindamycin gel and the vehicle, and the patches were moved several times to new sites. At challenge the subject reported itching, and scabbing was noted after 96 hours at the clindamycin gel and vehicle sites.

Subject 155 reported itching of the test sites at challenge.

During induction subject 218 had the patches with clindamycin gel and the vehicle moved to new sites several times. Itching of the test sites was reported at challenge.

Subjects 47, 155, and 218 were rechallenged; results were as follows.

Rechallenge						
	Subject 47		Subject 155		Subject 218	
	48 hr	96 hr	48 hr	96 hr	48 hr	96 hr
Occlusive patches - original sites						
Clindamycin gel	[redacted]					
Vehicle						
Cleocin T						
Occlusive patches - naive sites						
Clindamycin gel	[redacted]					
Vehicle						
Cleocin T						
Semi-occlusive patches - naive sites						
Clindamycin gel	[redacted]					
Vehicle						
Cleocin T						

It was felt that the results of the rechallenge tests indicated that subjects 47 and 155 showed further suggestive evidence of allergic contact dermatitis. After a 24 day rest period these subjects underwent a provocative use test. Applications of clindamycin gel and the vehicle were made to the inner elbow fold of each arm to sites about the size of a quarter, twice daily for 14 days. No cleansing of the test sites was allowed until six hours after application.

The results of the provocative use test were that no reactions were found in either subject. The conclusion of the sponsor was that this is a good indicator that patch test positive subjects such as subjects 47 and 155 can tolerate repetitive exposures to clindamycin gel without developing any symptoms or signs of allergic contact dermatitis.

Adverse events were reported in three subjects, who were dropped from the study due to these events.

Subject # 127 reported intense itching at the vehicle patch site following the second application of induction patches.

Subject # 57 had severe irritation with the patch tape at the clindamycin phosphate gel patch site, with moderate erythema, severe edema, vesicles, papules, and early scab formation.

Subject # 88 developed a pruritic rash on the wrists and had evidence of a tape reaction. This was judged by the investigator to be allergic contact dermatitis, probably related to the test material.

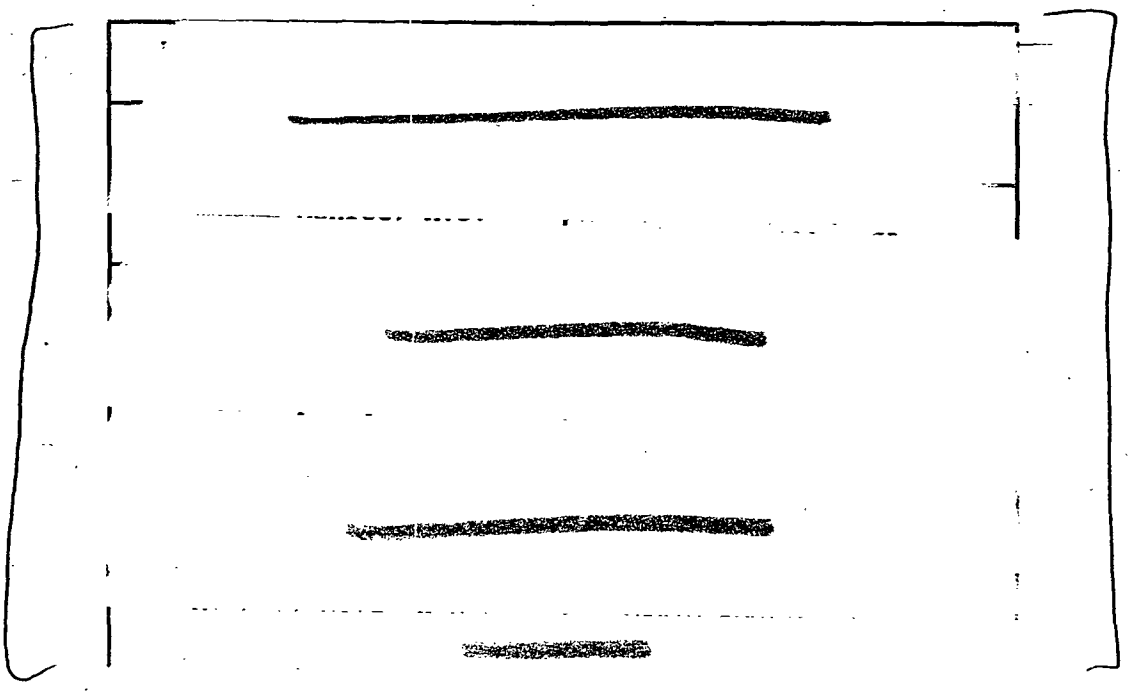
Reviewer's comments on Phase 1 studies: It is felt that these two studies on cumulative irritation and sensitization are adequate in design and conduct. Results of the cumulative irritation study show that the product is comparable to Cleocin T in the potential for irritation. In the sensitization study two of the 200 subjects apparently developed allergic contact sensitization to clindamycin gel. A provocative use test using applications of clindamycin gel BID for 14 days on the inner elbow fold did not elicit reactions in these two subjects.

Phototoxicity and photosensitivity studies have not been performed. As an amendment to the NDA, the sponsor has provided an absorption spectrum which shows absorption at about [redacted] nm, although the precise absorption is not clear. The sponsor has been requested to specify the wavelength(s) of absorption. Unless there is no UV absorption with the product in the 280 - 700 nm range, phototoxicity and photosensitization studies should be performed.

APPEARS THIS WAY
ON ORIGINAL

Study CGEL-003

The investigators for this study were as follows.



1) Study objective: The objectives were to determine the safety and efficacy of Clindagel, its vehicle, and Cleocin T gel in the treatment of acne.

2) Study design: This was a multicenter, randomized, evaluator-blind, vehicle controlled, parallel group comparison. Patients were randomized to the following treatment groups in a 2:1:2:1:2 ratio: Clindagel QD, Vehicle QD, Clindagel BID, Vehicle BID, and Cleocin T BID.

3) Inclusion criteria: Patients who met the following criteria were enrolled into the study.

a. Male or female patients, at least 12 years of age, with acne vulgaris.
b. A minimum of 25, but no more than 100, inflammatory facial lesions (papules, pustules) and a minimum of 20, but no more than 100, noninflammatory lesions (open and/or closed comedones).
c. Female patients who had negative in-office urine pregnancy test results.

d. Patients who used the same brand of soap, make-up, and/or hair products for a period of at least two weeks prior to visit 1/baseline and agreed not to change soap, make-up, or hair product brand/types during the study.

4) Exclusion criteria: Patients with the following conditions were excluded from enrollment in the study.

a. Clinically significant abnormal physical findings at the screening/baseline visit that would have interfered with the objectives of the study.
b. Acne conglobata, acne fulminans, secondary acne (chlorine, drug-induced acne, etc.), or any active facial cysts.
c. Underlying diseases or other dermatological conditions, such as atopic dermatitis, perioral dermatitis, or rosacea, that required the use of interfering topical or systemic therapy.
d. Male patients who had a beard or other facial hair that might have interfered with the study assessments.
e. A history or presence of regional enteritis or inflammatory bowel disease (eg ulcerative colitis, pseudomembranous colitis, chronic or recurrent diarrhea, or a history of antibiotic-associated colitis), or similar symptoms.
f. Use of concomitant treatments that may have influenced the therapeutic response or the evaluation of safety (eg, acne surgery, intralesional steroids, chronic use of non-steroidal anti-inflammatory agents, spironolactone, debridement, cryotherapy, dermabrasion, x-ray or ultraviolet therapy, etc).
g. Use of estrogens (eg, [redacted] birth control pills) for less than 12 weeks prior to visit 1/baseline. Patients who used estrogens 12 or more consecutive weeks prior to visit 1/baseline were not excluded unless the patient expected to change the dose or the drug or to discontinue estrogen use during the study.
h. Use of oral retinoids or therapeutic vitamin A supplements within the last 6 months.
i. Known sensitivities to the study preparations or to any of the ingredients in the study preparations.
j. Patients who did not undergo the specified washout periods for the following topical preparations applied to the face, or patients who required the concomitant use of any of the following topical preparations applied to the face:

Products	Washout period
Nonmedicated abradants, astringents, toners, facials, masks, or washes	1 week
Medicated abradants, astringents, toners, facials, masks, washes, or facial cleansers	4 weeks
Tanning booths/beds	4 weeks
Antibiotics (including antibacterials/antimicrobials)	4 weeks
Corticosteroids	4 weeks
Other non-inflammatories	4 weeks
Other acne treatments (eg, benzoyl peroxide, alphahydroxy acids, salicylic acid)	4 weeks
Retinoids	3 months

k. Patients who did not undergo the specified washout periods for the following systemic treatments, or patients who required the concomitant use of any of the following systemic treatments:

Products	Washout period
Antibiotics	4 weeks
Corticosteroids	4 weeks

l. Female patients who were pregnant, nursing, or planning a pregnancy within the study period.
m. Use of an investigational drug or participation in an investigational study within 30 days of visit 1/baseline. Use of an investigational drug and/or participation in an investigational study was prohibited during the study.
n. History of chronic alcohol or drug abuse.
o. Patients who were previously randomized into the study.

4) Treatment regimen: Patients were randomized into the treatment groups Clindagel QD, Vehicle QD, Clindagel BID, Vehicle BID, or Cleocin T BID on a ratio of 2:1:2:1:2, respectively. The duration of treatment was 12 weeks.

The patients were instructed to use a standardized cleanser, eg, a bland, nonmedicated facial cleanser, for routine cleansing. [redacted] soap was provided to the patients, but they were not required to use this soap.

5) Blinding techniques: Clindagel and the vehicle were masked so that neither the patient nor the investigator knew whether the patient was receiving Clindagel or the vehicle gel. However, a double-blind, double dummy technique was not used to mask the treatment groups from each other, and the patients knew whether they had been assigned to the QD or BID Clindagel/vehicle groups or the Cleocin T gel BID group. Therefore, an evaluator blind design was used to reduce the possibility of bias. An independent Drug Administrator was designated by each investigator, who had the following responsibilities:

   a. Randomization of all patients.
   b. Providing oral and written instructions in study gel use to the patients.
   c. Instructing patients not to discuss or show their study gel to anyone else at the treatment site.
   d. Instructing patients to direct all questions and requests concerning the study gel to the drug administrator and not to any other staff member.
   e. Checking patient's compliance with study gel use, dispensing additional units of study gel, and performing all drug accountability tasks.

6) Efficacy parameters: After the screening/baseline visit the patients returned for evaluation at weeks 2, 4, 8 and 12 for the following evaluations.

   a. Inflammatory and non-inflammatory lesion counts.

   b. An investigator's Global Severity Assessment. At baseline and at the final visit the evaluator assessed the severity of the acne on the Cook scale, taken from Cook et al, An Acne Grading Method Using Photographic Standards, Arch Derm. 1982, Vol 115, pp 571-575, May 1979. This is as follows.

Global Severity Assessment	
Grade	Description
0	Facial skin need not have been perfectly clear. A few scattered comedones or papules may have been present, but these should have been visible only on close examination.
1	Comedones and small papules were present and noticable from a distance of 1-3 feet away.
2	About one-fourth of the facial area was involved, with small papules (about 6 to 12) and comedones (a few pustules or large prominent papules may have been present).
3	Approximately 30% (26-49%) of facial area was involved with small papules (13 to 20) and small comedones (a few pustules or large prominent papules may have been present).
4	About half of the facial area was involved, with small papules and large or small comedones. A few pustules or large prominent papules were usually present. (If lesions are generally large, the patient may have had 'grade 4' severity, although less than half of the facial area was involved.)
5	More than half (51-74%) of the facial area was involved with large and small papules and comedones (lesser facial area of involvement was permissible if inflammatory lesions were large). A moderate number of pustules was usually present, some of which may have been large.
6	About three-fourths of the facial area was involved, with papules and/or large open comedones. (Lesser facial area of involvement was permissible if inflammatory lesions were large). Numerous pustules were usually present, some of which may have been large.
7	Greater than 75% but less than 85% of the facial area was involved with lesions with the majority being papules and large open comedones. Pustules may have been large and prominent.
8	Practically all of the facial area was involved with lesions. Large prominent pustules were usually visible. Lesions were usually highly inflammatory. Other types of acne (such as conglobata, including sinus and cystic types) may have been present.

7) Safety evaluation. Localized irritation was assessed at each return visit. The parameters evaluated were irritation as reported by the patient, and local erythema, peeling, and dryness, which were classified as absent, mild, moderate, or severe. The patient was queried at each visit in regard to adverse events.

Results were as follows.

1) Patient enrollment, disposition, and demographic characteristics: 667 patients were enrolled and randomized in a 2:1:2:1:2 ratio into the following treatment groups, respectively: Clindagel QD, Vehicle QD, Clindagel BID, Vehicle BID, and Cleocin T gel BID. The number of patients enrolled in each treatment group was as follows.

Patients randomized n=667				
Clindagel QD	Vehicle QD	Clindagel BID	Vehicle BID	Cleocin T BID
168	84	166	84	165

The demographic characteristics of all patients enrolled were as follows.

Demographic characteristics					
	Clindagel QD (n=168)	Vehicle QD (n=84)	Clindagel BID (n=166)	Vehicle BID (n=84)	Cleocin T BID (n=165)
Sex					
Male	80 (48%)	43 (51%)	79 (48%)	35 (42%)	86 (52%)
Female	88 (52%)	41 (49%)	87 (52%)	49 (58%)	79 (48%)
Race					
White	141 (84%)	74 (88%)	143 (86%)	77 (92%)	149 (90%)
Black	19 (11%)	6 (7%)	22 (13%)	7 (8%)	13 (8%)
Asian	5 (3%)	2 (2%)	1 (0.6%)	0	2 (1%)
AL-AN*	1 (0.6%)	0	0	0	0
Other	2 (1%)	2 (2%)	0	0	1 (0.6%)
Age					
Mean	19.6	20.0	18.8	19.2	18.9
Range	12-42	13-51	12-48	12-47	12-48
* American Indian - Alaska native					

The patient populations for analysis were as follows.

Analysis populations					
	Clindagel QD	Vehicle QD	Clindagel BID	Vehicle BID	Cleocin T BID
Randomized	168	84	166	84	165
ITT (endpoint)	162 (96%)	82 (98%)	161 (97%)	84 (100%)	162 (98%)
ITT (week 12)	147 (88%)	71 (85%)	145 (87%)	72 (86%)	145 (88%)
Per protocol (week 12)	139 (83%)	69 (82%)	140 (84%)	65 (77%)	140 (85%)
Safety	168 (100%)	84 (100%)	166 (100%)	84 (100%)	165 (100%)
Endpoint for the ITT patients was the last post-baseline visit carried forward. Week 12 for the ITT patients was defined as a last visit >/= 71 days post-baseline. Week 12 for the Per Protocol patients was defined as the last visit >/= 71 days post-baseline, but </= 97 days post-baseline.					

The number and percent of patients in each group that completed the study were as follows.

Number (%) of patients that completed the study					
	Clindagel QD	Vehicle QD	Clindagel BID	Vehicle BID	Cleocin T BID
Completed study	147 (88%)	71 (85%)	145 (87%)	72 (86%)	145 (88%)
Did not complete study	21 (13%)	13 (16%)	21 (13%)	12 (14%)	20 (12%)

The reasons for withdrawal from the study were as follows.

Reasons for withdrawal No. of patients					
	Clindagel QD	Vehicle QD	Clindagel BID	Vehicle BID	Cleocin T BID
Lack of efficacy	1	0	0	1	1
Adverse event	1	0	1	1	1
Patient request	3	5	1	4	3
Lost to followup	11	4	6	2	5
Protocol violations	5	4	12	4	10
Other	0	0	1	0	0

The number of patients that completed each visit was as follows.

Number of patients that completed each visit					
	Clindagel QD	Vehicle QD	Clindagel BID	Vehicle BID	Cleocin T BID
Baseline	168	84	166	84	165
Week 2	162	79	161	83	159
Week 4	156	79	158	80	155
Week 8	150	74	151	78	149
Week 12	147	71	145	72	145

2) Efficacy variables.

a. Lesion counts.

The mean lesion counts in each group at each return visit, the mean percent changes in lesion counts in the Clindagel QD and vehicle QD groups at each return visit, and the p values for the comparison of the latter, were as follows in the ITT population.

Inflammatory lesions Mean counts - ITT population					
	Clindagel QD	Clindagel[1] BID	Vehicle QD	Vehicle BID	Cleocin T BID
Baseline	37.6	39.0	38.2	36.3	37.7
Week 2	25.4	27.9	31.8	28.1	26.5
Week 4	21.9	23.5	26.4	23.2	23.2
Week 8	20.3	21.2	22.5	23.3	20.0
Week 12	16.9	16.8	22.0	19.2	17.6
Endpoint	18.4	18.5	23.8	21.1	18.8

Inflammatory lesions Mean percent change from baseline - ITT population			
	Clindagel QD	Vehicle QD	p value
Week 2	33.1	19.1	< 0.001
Week 4	41.4	32.3	0.016
Week 8	46.0	42.2	0.509
Week 12	55.4	42.9	0.008
Endpoint	51.5	39.8	0.015

Non-inflammatory lesions Mean counts - ITT population					
	Clindagel QD	Clindagel BID	Vehicle QD	Vehicle BID	Cleocin T BID
Baseline	44.8	49.5	42.6	46.2	45.8
Week 2	39.6	43.6	42.0	43.9	42.6
Week 4	37.3	40.4	38.9	40.3	40.2
Week 8	34.1	37.7	35.3	39.4	35.0
Week 12	31.8	33.7	33.7	32.1	29.1
Endpoint	32.3	35.1	34.7	33.3	30.8

Non-inflammatory lesions Mean percent change from baseline - ITT population			
	Clindagel QD	Vehicle QD	p value
Week 2	13.0	+ 0.6	0.002
Week 4	16.7	5.8	0.038
Week 8	21.1	14.6	0.305
Week 12	26.9	17.5	0.120
Endpoint	25.3	12.4	0.043

Total lesions Mean counts - ITT population					
	Clindagel QD	Clindagel BID	Vehicle QD	Vehicle BID	Cleocin T BID
Baseline	82.3	88.5	80.8	82.4	83.5
Week 2	65.0	71.5	73.8	72.0	69.0
Week 4	59.1	63.8	65.3	63.5	63.5
Week 8	54.4	58.9	57.7	62.7	54.9
Week 12	48.7	50.6	55.7	51.2	46.7
Endpoint	50.7	53.6	58.5	54.4	49.6

Total lesions Mean percent change from baseline - ITT population			
	Clindagel QD	Vehicle QD	p value
Week 2	22.8	8.9	< 0.001
Week 4	28.7	18.9	0.006
Week 8	33.6	28.0	0.231
Week 12	41.0	31.0	0.021
Endpoint	38.4	26.8	0.010

b. Investigator's Global Severity Assessment.

In response to a request by the Division, the sponsor has submitted the following analyses in the amendment of May 26, 2000.

In a comparison of Clindagel QD and Vehicle QD in the ITT population, the percentages of patients at endpoint that were in the categories showing the most improvement in the Global Severity Assessment, and the p values for pairwise comparison, were as follows.

Global Severity Assessment ITT population			
Severity scores	Clindagel QD n=156	Vehicle QD n=78	p value
0	12 (7.7%)	3 (3.8%)	0.24
0 or 1	32 (20.5%)	9 (11.5%)	0.076

In the original NDA submission the sponsor considered the primary efficacy variables to be the percent change in lesion counts at week 12, and the dichotomized Global Severity Assessment at week 12, in the ITT population, for the comparison between Clindagel QD and Vehicle QD. The Global Severity Assessment was collapsed into 1) good to excellent improvement, defined as a two point or better improvement from baseline, and 2) no change, fair, or worse, defined as less than a two point improvement.

The analyses of the proportion of patients showing at least a two point improvement in scores in the Global Severity Assessment at endpoint, and the p values for pairwise comparisons are as follows.

Global Severity Assessment Patients with a two point or better improvement from baseline ITT population					
	Clindagel QD	Clindagel BID	Vehicle QD	Vehicle BID	Cleocin T BID
Total # pts	156	158	78	81	157
2 point and better improvement	84 (53.8%)	80 (50.6%)	31 (39.7%)	36 (44.4%)	84 (53.5%)

p values - Global Severity Assessment Two point or better improvement from baseline ITT population	
Comparison	p value
Clindagel QD vs Vehicle QD	0.033
Clindagel BID vs Vehicle BID	0.290
Clindagel QD vs Cleocin T BID	0.874
Clindagel BID vs Cleocin T BID	0.662

The amount of improvement from baseline to endpoint in the Global Severity Assessment in the ITT population was as follows.

Global Severity Assessment Change in scores from baseline to endpoint ITT population			
Change from baseline	Clindagel QD n=156	Vehicle QD n=78	p value
-6	0	0	0.007
-5	4 (2.6%)	0	
-4	13 (8.3%)	2 (2.6%)	
-3	28 (17.9%)	12 (15.4%)	
-2	39 (25.0%)	17 (21.8%)	
-1	39 (25.0%)	22 (28.2%)	
0	25 (16.0%)	20 (25.6%)	
+1	6 (3.8%)	4 (5.1%)	
+2	2 (1.3%)	1 (1.3%)	
+3	0	0	

The sponsor evaluated the non-inferiority of Clindagel QD to Cleocin T BID and Clindagel BID to Cleocin T BID for lesion counts and the dichotomized Global Severity Assessment (DGSA) on the Per Protocol population at week 12. The mean percent change in lesion counts and the DGSA at week 12 in this population were as follows.

Lesion counts Mean percent change - Per Protocol population			
	Clindagel QD n=139	Clindagel BID n=140	Cleocin BID n=140
Inflammatory	- 54.5	- 55.8	- 53.2
Non-inflammatory	- 27.5	-32.1	-35.0
Total	- 40.8	-43.3	- 43.1

Global Severity Assessment Patients with a two point or better improvement from baseline Per Protocol population			
	Clindagel QD n=139	Clindagel BID n=140	Cleocin BID n=140
2 point and better improvement	80 (57.6%)	77 (55.0%)	78 (55.7%)

According to the sponsor's analysis, Clindagel QD and Clindagel BID were not inferior to Cleocin T BID in the percent reduction of inflammatory lesions, but it could not be concluded that Clindagel QD and Clindagel BID are not inferior to Cleocin T BID in the reduction of non-inflammatory or total lesion counts, nor in the Global Severity Assessment.

3) Safety evaluation.

The incidence and severity of signs of local irritation in a) the active treatment groups, and b) the Clindagel QD and vehicle QD groups, were as follows.

Irritation			
	Clindagel QD n=168	Clindagel BID n=166	Cleocin BID n=165
Baseline			
Absent	129 (77%)	130 (79%)	134 (81%)
Mild	27 (16%)	23 (14%)	20 (12%)
Moderate	11 (7%)	9 (6%)	9 (6%)
Severe	1 (0.6%)	3 (2%)	2 (1%)
Week 12			
Absent	141 (97%)	143 (99%)	138 (95%)
Mild	5 (3%)	2 (1%)	4 (3%)
Moderate	0	0	3 (2%)
Severe	0	0	0
Endpoint			
Absent	155 (96%)	157 (98%)	153 (94%)
Mild	6 (4%)	3 (2%)	6 (4%)
Moderate	1 (0.6%)	1 (0.6%)	3 (2%)
Severe	0	0	0

Irritation		
	Clindagel QD n=168	Vehicle QD n=84
Baseline		
Absent	129 (77%)	61 (73%)
Mild	27 (16%)	15 (18%)
Moderate	11 (7%)	51 (61%)
Severe	1 (0.6%)	3 (4%)
Week 12		
Absent	141 (97%)	69 (97%)
Mild	5 (3%)	1 (1%)
Moderate	0	1 (1%)
Endpoint		
Absent	155 (96%)	77 (94%)
Mild	6 (4%)	2 (2%)
Moderate	1 (0.6%)	3 (4%)
Severe	0	0

Erythema			
	Clindagel QD n=168	Clindagel BID n=166	Cleocin BID n=165
Baseline			
Absent	78 (46%)	77 (47%)	66 (40%)
Mild	68 (41%)	68 (41%)	75 (46%)
Moderate	20 (12%)	18 (11%)	21 (13%)
Severe	2 (1%)	2 (1%)	3 (2%)
Week 12			
Absent	101 (69%)	105 (72%)	97 (67%)
Mild	41 (28%)	38 (26%)	40 (28%)
Moderate	4 (3%)	2 (1%)	8 (6%)
Severe	0	0	0
Endpoint			
Absent	112 (69%)	113 (70%)	106 (65%)
Mild	44 (27%)	42 (26%)	48 (30%)
Moderate	6 (4%)	6 (4%)	8 (5%)
Severe	0	0	0

Erythema		
	Clindagel QD n=168	Vehicle QD n=84
Baseline		
Absent	78 (46%)	36 (43%)
Mild	68 (41%)	41 (49%)
Moderate	20 (12%)	4 (5%)
Severe	2 (1%)	3 (4%)
Week 12		
Absent	101 (69%)	50 (70%)
Mild	41 (28%)	19 (27%)
Moderate	4 (3%)	2 (3%)
Endpoint		
Absent	112 (69%)	55 (67%)
Mild	44 (27%)	22 (27%)
Moderate	6 (4%)	5 (6%)
Severe	0	0

Peeling			
	Clindagel QD n=168	Clindagel BID n=166	Cleocin BID n=165
Baseline			
Absent	145 (86%)	150 (91%)	144 (87%)
Mild	21 (13%)	15 (9%)	16 (10%)
Moderate	2 (1%)	0	5 (3%)
Severe	0	0	0
Week 12			
Absent	142 (97%)	141 (97%)	140 (97%)
Mild	4 (3%)	4 (3%)	5 (3%)
Moderate	0	0	0
Severe	0	0	0
Endpoint			
Absent	156 (96%)	155 (96%)	155 (96%)
Mild	6 (4%)	6 (4%)	7 (4%)
Moderate	0	0	0
Severe	0	0	0

Peeling		
	Clindagel QD n=168	Vehicle QD n=84
Baseline		
Absent	145 (86%)	73 (87%)
Mild	21 (13%)	9 (11%)
Moderate	2 (1%)	1 (1%)
Severe	0	1 (1%)
Week 12		
Absent	142 (97%)	67 (94%)
Mild	4 (3%)	3 (4%)
Moderate	0	1 (1%)
Endpoint		
Absent	156 (96%)	76 (93%)
Mild	6 (4%)	5 (6%)
Moderate	0	1 (1%)

Dryness			
	Clindagel QD n=168	Clindagel BID n=166	Cleocin BID n=165
Baseline			
Absent	134 (80%)	137 (83%)	140 (85%)
Mild	30 (18%)	25 (15%)	21 (13%)
Moderate	4 (2%)	3 (2%)	4 (2%)
Severe	0	0	0
Week 12			
Absent	141 (97%)	138 (95%)	136 (94%)
Mild	5 (3%)	74 (5%)	9 (6%)
Moderate	0	0	0
Severe	0	0	0
Endpoint			
Absent	154 (95%)	152 (94%)	152 (94%)
Mild	8 (5%)	9 (6%)	10 (6%)
Moderate	0	0	0
Severe	0	0	0

Dryness		
	Clindagel QD n=168	Vehicle QD n=84
Baseline		
Absent	134 (80%)	68 (81%)
Mild	30 (18%)	13 (16%)
Moderate	4 (2%)	2 (2%)
Severe	0	1 (1%)
Week 12		
Absent	141 (97%)	67 (94%)
Mild	5 (3%)	4 (6%)
Endpoint		
Absent	154 (95%)	75 (92%)
Mild	8 (5%)	7 (9%)
Moderate	0	0

The adverse events of the skin and appendages which were reported were as follows.

Reviewer's comments - Study CGEL 003: The requirement for a 505(b)(2) application for a topical product is that the effectiveness of the product should be demonstrated in a comparison with the product vehicle, which may be done in a single clinical study. Our current policy requirements for a demonstration of effectiveness for an acne product are that the product must demonstrate in the ITT population a superiority over the product vehicle in the mean percent reduction from baseline of two of the three categories of lesions (inflammatory, non-inflammatory, and total lesions), and in the proportion of patients that are clear or almost clear in the investigator's global evaluation, generally represented by the top two categories of the global assessment.

Clindagel was superior to the vehicle in the mean percent change in inflammatory and total lesion counts at week 12 and at endpoint, and was superior to the vehicle in the mean percent change in non-inflammatory lesion counts at endpoint but not at week 12.

Clindagel was not superior to the vehicle in the proportion of patients having a severity score of 0 or a severity score of 0 or 1 at endpoint in the investigator's Global Severity Assessment. Although a superiority was not shown in the proportion of patients with a score of 0 or 1 at the end of treatment, other analyses of the results of the Global Severity Assessment do show a superiority of Clindagel over the vehicle, and are supportive of the effectiveness. Clindagel QD was superior to vehicle QD in the distribution of the changes in Global Severity Assessment scores from baseline (p=0.007), and in the percentage of patients with a 2 point or greater improvement from baseline (p=0.033). On the basis of these results, together with the demonstrated superiority in lesion counts, this reviewer concludes that the effectiveness of Clindagel for its labeling indication has been adequately demonstrated.

The safety of Clindagel was comparable to that of the listed product, Cleocin T gel. The sponsor needs to explain why so many patients had signs of irritation at baseline.

Summary and evaluation: This is a 505(b)(2) application for Clindagel, which differs from the indication and usage of the listed product, Cleocin T gel, only in the frequency of applications. Clindagel is intended for QD applications, while Cleocin T is applied BID. The clinical part of this NDA submission consists of Phase 1 studies on cumulative irritation and sensitization, and a Phase 3 study on safety and effectiveness.

It is felt that the studies on cumulative irritation and sensitization are adequate in design and conduct. Results of the cumulative irritation study show that the product is comparable to Cleocin T in the potential for irritation. In the sensitization study two of the 200 subjects apparently developed allergic contact sensitization to clindamycin gel. A provocative use test using applications of clindamycin gel BID for 14 days on the inner elbow fold did not elicit reactions in these two subjects.

Phototoxicity and photosensitization studies have not been provided. The sponsor should either provide such studies or submit a UV absorption spectrum for the product which shows no absorption in the 280-700 nm range, in order to waive the requirements for these studies.

Study CGEL-003, the Phase 3 study on safety and effectiveness, was a controlled, evaluator-blind, multicenter comparison of Clindagel QD, Clindagel BID, vehicle QD, vehicle BID, and Cleocin T gel BID in patients with acne, with treatment for 12 weeks. The current policy requirements for an acne product are that the superiority of the product over its vehicle be shown in the mean percent reduction of two of the three categories of lesions (inflammatory, non-inflammatory, and total lesion counts), and in the dichotomized investigator's global evaluation. Superiority of Clindagel over the vehicle was shown in the mean percent reduction of inflammatory and total lesion counts, but was not shown in the dichotomized investigator's Global Severity Assessment, that is, the proportion of patients with a score of 0 or 1 at the end of treatment.

It is felt by this reviewer that although a superiority was not shown in the dichotomized Global Severity Assessment, other analyses of the results of the Global Severity Assessment do show a superiority of Clindagel over the vehicle, and are supportive of the effectiveness. Clindagel QD was superior to vehicle QD in the distribution of the changes in Global Severity Assessment scores from baseline, and in the percentage of patients with a 2 point or greater improvement from baseline. On the basis of these results, together with the demonstrated superiority in lesion counts, this reviewer concludes that the effectiveness of Clindagel for its labeling indication has been adequately demonstrated.

The safety of Clindagel was comparable to that of Cleocin T gel.

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 50-782

SPONSOR: Clindagel LLC
Santa Rosa, CA

DRUG: Clindagel (Clindamycin [redacted] Gel) 1%

CLINICAL INDICATION: Acne vulgaris

REASON FOR AMENDMENT: Safety update

DATE OF AMENDMENT: November 15, 2000

In this safety update on Clindagel, the sponsor states that all clinical studies are complete, and there is no new safety information to report.

Reviewer's comments: Clinical studies have been completed and there is no new safety information reported. Therefore, the safety profile of Clindagel remains as described in the review of the original submission of NDA 50-782.

[/S/]

Phyllis A. Huene, M.D.

11/15/00

Cc: Orig NDA 50-782
HFD-540 Division files
HFD-540\Wilkin
HFD-540\Walker
HFD-540\Huene
HFD-540/Freidlin
HFD-540\Kumar
HFD-540\Turujman
HFD-540\Jacobs

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ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA 50-782

SPONSOR: Clindagel LLC
Santa Rosa, CA

DRUG: Clindagel (Clindamycin [redacted] Gel) 1%

CLINICAL INDICATION: Acne vulgaris

REASON FOR ADDENDUM: Review of facsimiles of 11/6/00 and 11/8/00

In the facsimiles of 11/6/00 and 11/8/00 the sponsor has provided a response to our questions concerning the absorption spectrum for Clindagel, and the cutaneous findings of irritation, erythema, peeling, and dryness at baseline in clinical study CGEL-003.

An additional enlarged absorption spectrum is provided. This shows the peak absorption to be slightly [redacted] (stated by the sponsor to be [redacted] with a minimal amount of absorption at [redacted]

The cutaneous findings at baseline were primarily irritation and/or erythema, with only a few cases of peeling or dryness. The irritation at baseline was self reported by the patients and was not an objective assessment by the investigator; this may have been related to the acne itself. The erythema reported was primarily due to the inflammation associated with the acne lesions.

Reviewer's evaluation: The absorption spectrum provided is sufficient to allow a waiver of clinical phototoxicity and photosensitivity studies on Clindagel. The cutaneous effects described at baseline in the patients in Study CGEL-003 appeared to be associated with the acne, rather than being manifestations of cutaneous irritation. It is felt that these issues have been satisfactorily addressed.

[/S/]

Phyllis A. Huene, M.D.

11/13/00