CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

MEDICAL REVIEW(S)

AUG 15 2000

HFD-540 Trac No: 006197
Doc ID: BM

Correspondence date: July 14, 2000
CDER Stamp date: July 17, 2000

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 50-741
AMENDMENT TO RESUBMISSION

DATE: July 31, 2000

SPONSOR: Stiefel Laboratories
Oak Hill, NY

DRUG: Clindoxyl Gel

ACTIVE INGREDIENTS: Clindamycin phosphate equivalent to 1% clindamycin, and 5% benzoyl peroxide.

PROPOSED INDICATION: Acne

REASON FOR RESUBMISSION: Response to the non-approvable letters of May 14, 1997 and January 30, 1998.

DATE OF RESUBMISSION: March 3, 2000

DATE OF CURRENT AMENDMENT: July 14, 2000

The submission of July 14, 2000 provides a financial disclosure certification, and information on the safety and efficacy of Clindoxyl Gel in children, as requested in the Division's telecon of June 26, 2000. A pediatric waiver is also requested for ages below 12 years.

Financial disclosure

The sponsor provides the following statement:

> 'As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) 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 under Studies 156, 158, and 157.

Pediatric information and waiver request

The sponsor requests a waiver of the requirement for pediatric studies for ages up to 12 years. They state that the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in this age group, and is not likely to be used in a substantial number of patients.

A subset analysis of the results in patients aged 12-16 years in Studies 156 and 158 is provided. Approximately 50% of the patients were in the 12-16 year age group, with the remainder aged 17-31 years. The results in the 12-16 year age group were either comparable or were superior to the results in the whole study population. The local tolerance was also comparable to that in the larger population.

Reviewer's evaluation: The financial disclosure statement is adequate to meet the requirements for Studies 156, 158, and 157.

It is felt that a waiver of the requirements for pediatric studies for the age groups of up to 12 years should be granted.

/S/

Phyllis A. Huene, M.D.

7/31/00

Cc: Orig NDA 50-741
HFD-540 Division files
HFD-540\Wilkin
HFD-540\Walker SW 8/3/00
HFD-540\Huene
HFD-540/Freidlin
HFD-540\Cintron
HFD-540\Vidra
HFD-540\Jacobs 8/15/00
n50741.aml

✓Not in DFS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
HFD-520/Fran LeSane,SCSO/ Al Sheldon, TL	Olga Cintron, DDDDP, HFD-540

D.	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 16, 2000.		50-741	Major amendment (AZ)	March 3, 2000.

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Clindoxyl Gel		Anti-bacterial agent	August 1, 2000.

NAME OF FIRM: Stiefel Labs.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ✓☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:
  - ☐ **Tradename evaluation**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ A OR B NDA REVIEW ☐ OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

NDA 50-741 was submitted on May 3, 1996. FDA issued a not approvable letter on May 14, 1997. The Sponsor submitted a major amendment in response to the deficiencies delineated on the not approvable letter. This resubmission includes a microbiology section and proposed draft labeling. Please review for acceptability. HFD-540 has scheduled a labeling day for August 7, 2000.

SIGNATURE OF REQUESTER Olga Cintron /S/	METHOD OF DELIVERY (Check one) E-MAIL ✓☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

AUG 15 2000

HFD-540 Trac No: 005379
Doc ID: AZ

Correspondence date: March 3, 2000
CDER Stamp date: March 6, 2000

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 50-741
RESUBMISSION - MAJOR AMENDMENT

DATE: June 26, 2000

SPONSOR: Stiefel Laboratories
Oak Hill, NY

DRUG: Clindoxyl Gel

ACTIVE INGREDIENTS: Clindamycin phosphate equivalent to 1% clindamycin, and 5% benzoyl peroxide.

PROPOSED INDICATION: Acne

Labeling indication: 'Clindoxyl Gel is indicated for the topical treatment of acne vulgaris.'

REASON FOR AMENDMENT: Response to the non-approvable letters of May 14, 1997 and January 30, 1998.

DATE OF SUBMISSION: March 3, 2000

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Medical Officer's review

Sponsor's introductory statement

Prior communications with the Agency concerning NDA 50-741 included the non-approvable letters of May 14, 1997 and January 30, 1998, a teleconference of February 20, 1998, and an Agency draft letter of March 9, 1998, which restated the pertinent items in the first three communications. The sponsor states that their response is generally keyed to the March 9, 1998 communication, and includes, as appropriate, additional points referenced only in the May 14, 1997 communication.

The sponsor states that the FDA recommended that an additional clinical study be performed, which should be a multicentered, controlled study with three arms: Clindoxyl Gel, clindamycin, and benzoyl peroxide. The results of the study should demonstrate the superiority of Clindoxyl gel over both clindamycin and benzoyl peroxide. In response the sponsor has submitted two studies, each of which in their judgment meets these criteria. In addition, sensitization data are submitted.

Non-approvable letter of May 14, 1997

The clinical portion of the non-approvable letter of May 14, 1997 is as follows.

'The deficiencies are summarized as follows:

> Clinical: The efficacy of Clindoxyl Gel has not been demonstrated over benzoyl peroxide gel alone in the treatment of acne vulgaris. We recommend an additional clinical trial investigating the safety and efficacy of Clindoxyl Gel versus benzoyl peroxide gel in the treatment of acne vulgaris, in order to establish the clinical superiority of Clindoxyl Gel over benzoyl peroxide gel alone.
>
> Although not the basis for the Not Approvable action of this application, the following areas should be addressed in any resubmission: Failure to demonstrate that Clinoxyl Gel poses a minimal safety hazard to patients as a contact sensitizer.'

Previous medical officer's review

The medical officer's review of the original submission was done by Dr. Susan Walker on May 13, 1997.

Three clinical safety and efficacy studies were performed; these were Studies 150, 151, and 152. Each of these studies were

controlled clinical trials using four treatment arms: Clindoxyl Gel, 5% benzoyl peroxide gel, 1% clindamycin phosphate gel, and vehicle gel. Applications were made QD for 11 weeks.

The pivotal trials were Studies 151 and 152, as these were both multicenter trials, while Study 150 was a single center trial.

1) Study 151

A total of 273 patients were enrolled into this study, of which 231 completed the study. The efficacy parameters were lesion counts for inflammatory and non-inflammatory lesions, total lesion counts, and an investigator's assessment of global improvement. All analyses were done on the 'Preferred Data Set', which was the Per Protocol population.

The number of valid patients in the four treatment groups at week 11 was as follows.

Valid patients - Week 11			
Clindoxyl	Benzoyl peroxide	Clindamycin	Vehicle
67	68	60	31

The mean baseline lesion counts, the mean reduction in counts at week 11, and the mean percent reduction in counts at week 11, were as follows.

Non-inflammatory lesion counts - Study 151				
	Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
Baseline	48.5	46.0	48.6	52.6
Mean reduction	16.3	8.2	18.5	[0.8]
Mean % reduction	34.9	15.3	40.4	[9.6]

[ ] = increases

Inflammatory lesion counts - Study 151				
	Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
Baseline	29.9	25.5	25.8	28.0
Mean reduction	12.4	8.3	14.6	+ 0.5
Mean % reduction	39.4	35.9	58.4	+ 7.6

Total lesion counts - Study 151				
	Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
Baseline	78.4	71.4	74.4	80.6
Mean reduction	28.7	16.6	33.1	0.3
Mean % reduction	38.3	26.5	47.7	+ 6.0

The p values for the comparisons between treatments in the mean reduction in lesion counts at week 11 were as follows.

Inflammatory lesions Mean reduction	
Comparison	p value
Clindoxyl vs vehicle	0.000
Clindoxyl vs benzoyl peroxide	0.278
Clindoxyl vs clindamycin	0.005
Benzoyl peroxide vs vehicle	0.000
Clindamycin vs vehicle	0.001

Non-inflammatory lesions Mean reduction	
Comparison	p value
Clindoxyl vs vehicle	0.001
Clindoxyl vs benzoyl peroxide	0.549
Clindoxyl vs clindamycin	0.012
Benzoyl peroxide vs vehicle	0.003
Clindamycin vs vehicle	0.166

Total lesions Mean reduction	
Comparison	p value
Clindoxyl vs vehicle	0.000
Clindoxyl vs benzoyl peroxide	0.344
Clindoxyl vs clindamycin	0.001

The p values for the comparisons between treatments in the mean percent reduction in lesion counts at week 11 were as follows.

Inflammatory lesions Mean percent reduction	
Comparison	p value
Clindoxyl vs vehicle	0.000
Clindoxyl vs benzoyl peroxide	0.003
Clindoxyl vs clindamycin	0.000
Benzoyl peroxide vs vehicle	0.000
Clindamycin vs vehicle	0.000

Non-inflammatory lesions Mean percent reduction	
Comparison	p value
Clindoxyl vs vehicle	0.000
Clindoxyl vs benzoyl peroxide	0.456
Clindoxyl vs clindamycin	0.003
Benzoyl peroxide vs vehicle	0.000
Clindamycin vs vehicle	0.018

Total lesions Mean percent reduction	
Comparison	p value
Clindoxyl vs vehicle	0.000
Clindoxyl vs benzoyl peroxide	0.097
Clindoxyl vs clindamycin	0.001

The scale for the investigator's global evaluation was as follows.

Investigator's Global Evaluation		
0	Worsening	
1	Poor	0% to 25% improvement
2	Fair	26% to 50% improvement
3	Good	51% to 75% improvement
4	Excellent	76% to 100% improvement

The percentage of patients with a Good to Excellent rating at 11 weeks was as follows.

Good to Excellent rating			
Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
28 (41.1%)	21 (35%)	42 (62.7%)	2 (6.5%)

The p values for pairwise comparisons of the proportion of patients with a Good to Excellent rating were as follows.

Good to Excellent rating	
Comparison	p value
Clindoxyl vs vehicle	0.000
Clindoxyl vs clindamycin	0.002
Clindoxyl vs benzoyl peroxide	0.013
Benzoyl peroxide vs vehicle	0.000
Clindamycin vs vehicle	0.003

The reviewer's conclusion was that this study demonstrates that Clindoxyl Gel is clinically and statistically superior to both clindamycin phosphate gel and the vehicle gel in the treatment of acne vulgaris. However, the study has not demonstrated the superiority of Clindoxyl Gel when compared with benzoyl peroxide gel alone in the reduction of non-inflammatory lesion counts, inflammatory lesion counts, or total lesion counts. The study did demonstrate the superiority of Clindoxyl Gel compared to benzoyl peroxide gel in global assessment. (It is noted that for evaluation of the results of the lesion counts, Dr. Walker considered both the mean reduction in lesion counts and the mean percent reduction in lesion counts.)

2) Study 152

A total of 280 patients were enrolled into this study. The efficacy parameters were lesion counts for inflammatory and non-inflammatory lesions, total lesion counts, and an investigator's assessment of global improvement. All analyses were done on the 'Preferred Data Set', which was the Per Protocol population.

The number of valid patients in the four treatment groups at week 11 was as follows.

Valid patients - Week 11			
Clindoxyl	Benzoyl peroxide	Clindamycin	Vehicle
73	70	70	37

The mean baseline lesion counts, the mean reduction in counts at week 11, and the mean percent reduction in counts at week 11, were as follows.

Non-inflammatory lesion counts - Study 152				
	Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
Baseline	37.2	34.1	41.6	39.8
Mean reduction	8.7	4.5	12.5	5.5
Mean % reduction	18.8	11.2	25.7	15.4

Inflammatory lesion counts - Study 152				
	Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
Baseline	21.0	20.2	20.4	21.2
Mean reduction	7.0	8.1	8.8	5.8
Mean % reduction	33.5	39.8	43.4	28.6

Total lesion counts - Study 152				
	Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
Baseline	58.2	54.3	62.0	61.0
Mean reduction	15.7	12.6	21.2	11.3
Mean % reduction	25.5	23.5	32.5	20.6

The p values for the comparisons between treatments in the mean reduction in lesion counts at week 11 were as follows.

Inflammatory lesions Mean reduction	
Comparison	p value
Clindoxyl vs vehicle	0.046
Clindoxyl vs benzoyl peroxide	0.151
Clindoxyl vs clindamycin	0.538
Benzoyl peroxide vs vehicle	0.420
Clindamycin vs vehicle	0.139

Non-inflammatory lesions Mean reduction	
Comparison	p value
Clindoxyl vs vehicle	0.008
Clindoxyl vs benzoyl peroxide	0.079
Clindoxyl vs clindamycin	0.000
Benzoyl peroxide vs vehicle	0.234
Clindamycin vs vehicle	0.731

Total lesions Mean reduction	
Comparison	p value
Clindoxyl vs vehicle	0.003
Clindoxyl vs benzoyl peroxide	0.044
Clindoxyl vs clindamycin	0.002

The p values for the comparisons between treatments in the mean percent reduction in lesion counts at week 11 were as follows.

Inflammatory lesions Mean percent reduction	
Comparison	p value
Clindoxyl vs vehicle	0.051
Clindoxyl vs benzoyl peroxide	0.107
Clindoxyl vs clindamycin	0.517
Benzoyl peroxide vs vehicle	0.537
Clindamycin vs vehicle	0.158

Non-inflammatory lesions Mean percent reduction	
Comparison	p value
Clindoxyl vs vehicle	0.037
Clindoxyl vs benzoyl peroxide	0.091
Clindoxyl vs clindamycin	0.000
Benzoyl peroxide vs vehicle	0.490
Clindamycin vs vehicle	0.406

Total lesions Mean percent reduction	
Comparison	p value
Clindoxyl vs vehicle	0.015
Clindoxyl vs benzoyl peroxide	0.076
Clindoxyl vs clindamycin	0.021

The scale for the investigator's global evaluation was as follows.

Investigator's Global Evaluation		
0	Worsening	
1	Poor	0% to 25% improvement
2	Fair	26% to 50% improvement
3	Good	51% to 75% improvement
4	Excellent	76% to 100% improvement

The percentage of patients with a Good to Excellent rating at 11 weeks was as follows.

Good to Excellent			
Benzoyl peroxide n=68	Clindamycin n=60	Clindoxyl n=67	Vehicle n=31
23 (32.9%)	31 (44.3%)	23 (31.5%)	13 (35.1%)

The p values for pairwise comparisons of the proportion of patients with a Good to Excellent rating were as follows.

Good to Excellent rating	
Comparison	p value
Clindoxyl vs vehicle	0.577
Clindoxyl vs clindamycin	0.197
Clindoxyl vs benzoyl peroxide	0.745
Benzoyl peroxide vs vehicle	0.775
Clindamycin vs vehicle	0.558

The reviewer's conclusion was that for lesion counts Clindoxyl Gel was able to demonstrate clinical and statistical superiority to the vehicle gel and to clindamycin phosphate gel in both the reduction and percent reduction in lesion counts at week 11. This

again demonstrates the improved efficacy of the benzoyl peroxide/clindamycin phosphate gel combination compared to clindamycin phosphate gel alone. However, this study has failed to demonstrate the contribution of clindamycin phosphate to the combination - i.e. the combination has not demonstrated superiority to benzoyl peroxide gel alone. The results of the global assessment are not supportive of the efficacy of the combination product, as each active treatment arm was demonstrated to be superior to the combination.

Dr. Walker's overall conclusions were as follows.

1) Comparisons with clindamycin phosphate: In two controlled multicenter trials (151 and 152), Clindoxyl Gel has demonstrated superiority to clindamycin phosphate gel in the reduction of at least one subtype of acne lesions (inflammatory or non-inflammatory) and in the reduction of total lesion counts. In Study 151, Clindoxyl gel was superior to clindamycin phosphate gel in the reduction of non-inflammatory lesion counts, inflammatory lesion counts, total lesion counts, and the global assessment. In Study 152, Clindoxyl gel was superior to clindamycin phosphate gel in the reduction of non-inflammatory lesions counts and total lesion counts. In addition, the superior efficacy of Clindoxyl gel is supported by the results of a single investigator study (Site 150) in which Clindoxyl Gel demonstrated superiority in the reduction of total lesion counts and in the global assessment.

2) Comparisons with benzoyl peroxide: In two controlled multicenter trials (151 and 152) Clindoxyl gel has failed to demonstrate superiority to benzoyl peroxide gel in the treatment of acne vulgaris. It has failed to demonstrate superiority over benzoyl peroxide in the reduction of inflammatory lesions, non-inflammatory lesions, or total lesions. Clindoxyl Gel did demonstrate superiority over benzoyl peroxide gel in the global assessment in Study 151. The combination might not be expected to be superior to benzoyl peroxide gel in the treatment of non-inflammatory lesions, but it should then be superior in the treatment of inflammatory lesions in order to justify adding clindamycin phosphate in a combination product. There is not persuasive evidence that the addition of clindamycin phosphate is more effective than benzoyl peroxide alone in the treatment of acne, especially inflammatory lesions. This may be due to the fact that the lesion counts for inflammatory acne were generally low in this study, and the effectiveness of the combination product could not be demonstrated with such low

numbers.

In addition, the contact sensitization study was performed on only 27 subjects, whereas at least 200 subjects are needed for evaluation of sensitization potential.

The overall recommendations were that a Not Approvable letter be issued, based on the following:

1) Failure of the manufacturer to use components which were produced in accordance with Good Manufacturing Practices.
2) Failure to characterize the metabolic and oxidative products of clindamycin phosphate when combined with benzoyl peroxide.
3) Failure to demonstrate that Clindoxyl gel has no greater potential for absorption of clindamycin than clindamycin phosphate gel alone.
4) Failure to prove efficacy over benzoyl peroxide gel alone in the treatment of lesions of acne vulgaris.
5) Failure to demonstrate that Clindoxyl gel poses minimal safety hazard to the patient as a contact sensitizer.

Overview of clinical studies

The studies provided in this submission are as follows.

Study #	Description	# pts
157	Sensitization	210
156	Double blind, multicenter efficacy and safety	288
158	Double blind, multicenter efficacy and safety	358

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

Study 157: Sensitization

This study was performed by [redacted] Of 218 subjects enrolled in the study, 8 subjects did not complete the study. One of these had a related adverse event; the remainder discontinued for reasons unrelated to the test product administration. Of the 210 subjects that completed the study, two were considered invalid because they developed allergic contact dermatitis to one of the components of Clindoxyl Gel at the second induction reading and were considered to have had a pre-existent sensitization.

During the induction phase, 0.1 ml of Clindoxyl Gel was applied under a semi-occlusive patch to the back of each subject. The patch was removed after 48 hours and the site was graded for reaction. This procedure was repeated at the same skin site three times weekly for three weeks. At 14 days after the induction phase, challenge applications were made to new skin sites, using 0.1 ml of each Clindoxyl Gel, 5% benzoyl peroxide gel, clindamycin gel (clindamycin phosphate equivalent to 1% clindamycin), and vehicle gel, under semi-occlusive patches. The patches were removed after 48 hours, and the test sites were evaluated immediately and at 48 hours later.

The scales used for evaluation of reactions during the induction and challenge phases were as follows.

Grading scale - induction phase	
Score	Description
0	No reaction
1	Faint or just perceptible macular erythema in a speckled/follicular, patchy or confluent pattern.
2	Moderate erythema in a speckled/follicular, patchy or confluent pattern. Also, a moderate erythema in a speckled/follicular, patchy or confluent pattern that is minimally elevated (just palpable).
3	Moderate erythema on a definitely smooth plaque (confluent) or a papulo-vesicular plaque. The pattern can be patchy or speckled. At least 10% of the test site involved.
4	Brisk (striking) erythema and firm edema as an indurated plaque or prominent red papules/pustules with or without weeping or erosions of either. These lesions may be tender and no more than 5-10% of the test area need be involved. Test sites having a single or several small erosive lesions also qualify for this rating.

Grading scale - challenge phase	
Score	Description
0	No reaction
1	Faint or just perceptible macular erythema in a speckled/follicular, patchy or confluent pattern.
2	Moderate erythema in a confluent pattern that conforms to or extends beyond the test site. There may be edema of the area that is just palpable (barely elevated).
3	Moderate erythema on a definitely edematous plaque (confluent); the surface may be smooth or a papulo-vesicular plaque. The pattern conforms to or extends beyond the test site and is quite persistent.
4	Brisk (striking) erythema and firm edema as an indurated plaque or prominent red papules/pustules with or without weeping. These lesions may be both pruritic and tender.This intensity of an allergic reaction does spread beyond the test site if not a solid fixed object. This degree of allergy may be discernible for several weeks.

Results were that 18 of the 208 valid subjects developed allergic contact dermatitis to Clindoxyl Gel as a result of the three week induction phase. All 18 subjects also had allergic responses to the benzoyl peroxide gel. In additon, 5 subjects had an allergic reaction only to the benzoyl peroxide gel in the challenge phase. There were no allergic reactions to the vehicle gel or the clindamycin gel.

The individual scores during the induction and challenge phases with Clindoxyl Gel were as follows.

Individual scores - induction phase									
Score	Evaluations								
	1	2	3	4	5	6	7	8	9
0									
1									
2									
3									

Individual scores - challenge phase		
Score	Evaluations *	
	1	2
0		
1		
2		
3		
* 1 = at patch removal 2 = 48 hours later		

The sponsor's conclusion was that the incidence of sensitization to Clindoxyl Gel is 8.7%. The sponsor states that this incidence is similar to the incidence of approximately 10% that has been observed historically with products containing benzoyl peroxide.

Reviewer's comments: This reviewer is in agreement with the sponsor's conclusions. It is felt that this study is adequate to determine the sensitization potential of Clinoxyl Gel.

Study 156

The investigators for this study were as follows.

Leonard Swinyer, MD Salt Lake City, UT	Terry Jones, MD Bryan, TX
Michael Jarrett, MD Austin, TX	J. Michael Maloney, MD Denver, CO
Dan Chalker, MD Augusta, GA	Alan Shalita, MD Port Chester, NY
Eduardo Tschen, MD Albuquerque, NM	Bruce Miller, MD Portland, OR

1) Study Title: A Multicenter, Double-Blind Comparison of the Efficacy and Safety of Clindoxyl Gel, Benzoyl Peroxide Gel, and Clindamycin Gel in the Once Daily Treatment of Acne Vulgaris for 11 Weeks.

2) Study objective: This was to compare the efficacy of Clindoxyl Gel to Clindamycin gel and Benzoyl peroxide gel in the topical treatment of acne vulgaris. A secondary objective was to compare the relative safety of these gels.

3) Study design: This was a parallel group, double-blind controlled comparison of Clindoxyl Gel, Clindamycin gel, and Benzoyl peroxide gel, with equal and randomized assignment to the treatment groups.

4) Inclusion criteria: Patients with the following characteristics were enrolled in the study.

a. 13 to 30 years of age.
b. acne of the face, with a minimum of 25 and a maximum of 55 inflammatory lesions, a minimum of 12 non-inflammatory lesions, and no more than 3 nodulocystic lesions.

5) Exclusion criteria: Patients were excluded from enrollment in the study for the following reasons.

a. use of medicated shampoos or medicated cleansers of any type within one week of admission to the study.
b. treatment with topical antibiotics or topical acne treatments of any type within two weeks of admission to the study.
c. treatment for more than five days with systemic antibiotics known to have an effect on acne, systemic corticosteroids, topical corticosteroids anywhere on or near the face or over an extensive area (limited use of topical corticosteroids on small distal areas was permitted), or any medication which might have interfered with the study results, within one month of admission to the study.
d. treatment with oral retinoids within six months of admission to the study.
e. a known history of hypersensitivity or idiosyncratic reaction to benzoyl peroxide, clindamycin, lincomycin, or any of the components of the study medication.
f. requirement for any significant concomitant medication.
g. a severe systemic disease or any other disease that might affect the evaluation of the study medications.
h. history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.
i. pregnancy or lactation.
j. females not using an effective form of contraception, including abstinence, for three months (four months for oral contraception) before admission to the study. An effective form of contraception was also to be used throughout the study period. Systemic contraceptives, except anti-androgen

compounds, were allowed provided that the same contraceptive was used four months before and throughout the study period.

k. not reasonably agreeable to participate in the entire study program.

6) Treatment regimen: Application of the study medications were made to the face once daily, in the evening, for 11 weeks. If excessive irritation or dryness developed, the investigator might instruct the patient to temporarily decrease the frequency of applications, and this was noted on the case report.

7) Effectiveness parameters: Return visits were made at weeks 2, 5, 8, and 11, for the following evaluations.

a. Lesion counts: Inflammatory and non-inflammatory lesions were counted at baseline and at each return visit.

b. Investigator's global evaluation: This was done at each return visit, using the following scale.

Investigator's Global Evaluation		
0	Worsening	
1	Poor	0% to 25% improvement
2	Fair	26% to 50% improvement
3	Good	51% to 75% improvement
4	Excellent	76% to 100% improvement

8) Safety evaluation. At each return visit adverse events reported by the patient were recorded, with the severity, duration, relationship to the test medication, and outcome of the event. Also at each return visit the investigator scored the occurrence and severity of facial erythema, peeling, burning, dryness, or other effects on the following scale.

Local tolerance scale		
0	absent	
1	mild	slightly noticeable
2	moderate	definitely noticeable, seldom interferes with daily activities or sleep
3	severe	intensely noticeable, interferes with daily activities or sleep.

At the final visit for each patient the overall tolerance to the test medication was assessed by the investigator on the following scale.

Local tolerance scale		
0	poor	numerous moderate to severe treatment-related local tolerance observations throughout the treatment period
1	fair	numerous mild to moderate treatment-related local tolerance observations throughout the treatment period
2	good	a single mild or no treatment-related local tolerance observations at end of treatment period with few mild or moderate observations during early treatment
3	excellent	no treatment-related local tolerance observations at end of treatment period with no or only a few mild observations during early treatment

Results were as follows.

1) Baseline and demographic characteristics: 288 patients were enrolled into the study, of which 257 patients completed the study. The characteristics of all patients enrolled were as follows.

Baseline and demographic characteristics			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Gender			
Male	50 (52%)	57 (59%)	57 (59%)
Female	46 (48%)	39 (41%)	39 (41%)
Race			
Caucasian	70 (73%)	73 (76%)	65 (68%)
Black	8 (8%)	8 (8%)	12 (13%)
Hispanic	16 (17%)	11 (12%)	16 (17%)
Other	2 (2%)	4 (4%)	3 (3%)
lesion counts			
Inflammatory	34	35	33
Non-inflammatory	46	48	50
Total	79	83	83

The disposition of the patients and the reasons for premature withdrawal were as follows.

Reasons for premature withdrawal			
	Benzoyl peroxide	Clindamycin	Clindoxyl
# patients entered	96	96	96
# patients completed	87	85	85
Lost to followup	5	7	6
Entry criteria violation	0	0	1
Not able to participate	3	3	3
Uncooperative	1	1	1

2) Efficacy variables.

Results are presented for the ITT population, which was defined as comprising all patients. The last observation was carried forward.

a. Lesion counts.

The mean lesion counts, and the mean percent reduction in lesion counts from baseline were as follows.

Mean inflammatory lesion counts			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Baseline	33.6	34.5	32.9
Week 2	22.1	23.6	20.2
Week 5	17.4	20.4	15.7
Week 8	16.3	20.3	15.2
Week 11	15.0	18.2	14.2

Inflammatory lesion counts Mean percent reduction from baseline			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Week 2	34.3	33.2	38.4
Week 5	49.4	42.2	53.4
Week 8	52.3	42.5	54.9
Week 11	56.7	48.6	57.3

Mean non-inflammatory lesion counts			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Baseline	45.8	48.3	49.6
Week 2	41.2	44.0	43.5
Week 5	37.8	41.9	36.9
Week 8	34.9	41.3	34.8
Week 11	32.6	39.1	30.5

Non-inflammatory lesion counts Mean percent reduction from baseline			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Week 2	8.3	9.2	17.5
Week 5	17.8	13.1	30.8
Week 8	24.6	14.2	33.4
Week 11	28.7	18.0	39.0

Mean total lesion counts			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Baseline	79.4	82.8	82.5
Week 2	63.2	67.6	63.8
Week 5	55.2	62.4	52.6
Week 8	51.2	61.6	50.0
Week 11	47.6	57.3	44.7

Total lesion counts Mean percent reduction from baseline			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Week 2	22.1	21.1	27.4
Week 5	34.2	27.5	41.6
Week 8	39.2	28.5	44.1
Week 11	43.3	33.3	49.8

p values Mean percent reduction from baseline in lesion counts			
	Clindoxyl vs Benzoyl peroxide	Clindoxyl vs Clindamycin	Benzoyl peroxide vs clindamycin
Inflammatory lesions	0.845	0.030	0.048
Non-inflammatory lesions	0.048	0.000	0.037
Total lesions	0.080	0.000	0.008

b. Investigator's global assessment.

The global improvement scores at week 11 for the ITT population were as follows.

Global improvement scores - week 11			
Score	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
0	5 (5.2%)	10 (10.4%)	6 (6.3%)
1	18 (18.8%)	19 (19.8%)	13 (13.5%)
2	23 (24.0%)	20 (20.8%)	19 (19.8%)
3	26 (27.1%)	29 (30.2%)	26 (27.1%)
4	24 (25.0%)	18 (18.8%)	32 (33.3%)
0 = worse 1 = 0% to 25% improvement 2 = 26% to 50% improvement 3 = 51% to 75% improvement 4 = 76% to 100% improvement			

The p values for the success rates, defined as global improvement scores of 3 or 4, were as follows.

p values - Success rates (Global improvement scores of 3 or 4)		
Clindoxyl vs Benzoyl peroxide	Clindoxyl vs Clindamycin	Benzoyl peroxide vs clindamycin
0.213	0.088	0.640

3) Safety assessments.

The local tolerance is expressed as the percentages of patients with worsening of the scores for local symptomatology over those present at baseline. The local tolerance scale was: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

Erythema			
Maximum worsening of score	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
0	92%	96%	88%
1	8%	4%	10%
2	0	0	2%
3	0	0	0

Peeling			
Maximum worsening of score	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
0	88%	98%	91%
1	12%	2%	9%
2	0	0	0
3	0	0	0

Burning			
Maximum worsening of score	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
0	96%	98%	97%
1	4%	2%	3%
2	0	0	0
3	0	0	0

Dryness			
Maximum worsening of score	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
0	82%	94%	86%
1	18%	6%	13%
2	0	0	1%
3	0	0	0

The overall local tolerance rating was as follows.

Local tolerance			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Poor	0	0	1%
Fair	1%	0	0
Good	5%	4%	4%
Excellent	93%	96%	95%

The adverse events at the application site, and adverse events of the skin and appendages were as follows.

Adverse events			
	Benzoyl peroxide n=96	Clindamycin n=96	Clindoxyl n=96
Application site			
Application site reaction	0	0	1
Melanosis	0	1	0
Paresthesia	0	0	1
Photosensitivity reaction	1	1	1
Skin and appendages			
Rash	1	0	0
Urticaria	0	1	0
Wound	0	0	1

Of the adverse events reported, the sponsor felt that two events in the Clindoxyl Gel group and one event in the benzoyl peroxide gel group were treatment-related. In the Clindoxyl group one patient had mild facial burning for the first eight days of the study, and another had moderate erythema and dryness and mild peeling and burning of the face for the first five weeks of the study. One patient in the benzoyl peroxide group had a moderate neck rash for two days during the first week of the study. None of these patients were discontinued from the study.

One patient in the benzoyl peroxide group reported transient diarrhea; there were no reports of diarrhea in the other groups.

Reviewer's comments - Study 156: The current policy on the requirements for a demonstration of effectiveness for a combination product in acne is that the product must demonstrate superiority over each of its components in the percent reduction from baseline of two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and in the dichotomized investigator's global evaluation, in the ITT population.

Based on these requirements, the results of this study do not demonstrate the effectiveness of the combination product, because the superiority of the combination over benzoyl peroxide has not

been shown. Clindoxyl Gel was superior to clindamycin in the percent reduction of the three categories of lesion counts, and was superior to benzoyl peroxide in the percent reduction of non-inflammatory lesions, but was not superior to benzoyl peroxide in the percent reduction of inflammatory lesions or total lesion counts. Clindoxyl Gel was not superior to either benzoyl peroxide or clindamycin in the 'Success Rate', defined as 51% or greater improvement from baseline in the investigator's global evaluation.

The sponsor based their conclusions in regard to efficacy on the results of analyses in the valid (Per Protocol) population. They considered the primary efficacy variables to be the reduction and percent reduction from baseline in the inflammatory lesion counts, and on the global improvement scores. The results for the percent reduction in lesion counts and for the global evaluation (Success Rate) were similar to those in the ITT population, except that in the valid population Clindoxyl was superior to benzoyl peroxide in the percent reduction of both non-inflammatory and total lesion counts. The p values for the comparisons in the valid population were as follows.

p values - Study 156 - lesion counts % reduction at week 11 Valid population			
Comparison	Inflammatory	Noninflammatory	Total
Clindoxyl vs benzoyl peroxide	0.867	0.021	0.037
Clindoxyl vs clindamycin	0.031	0.000	0.000

p values - Study 156 Success rates Valid population	
Comparison	p value
Clindoxyl vs benzoyl peroxide	0.101
Clindoxyl vs clindamycin	0.051

The sponsor's conclusions in regard to effectiveness were as follows: 'Substantial evidence of efficacy was observed. A significantly greater proportion of patients had good to excellent global improvement after 11 weeks treatment with Clindoxyl Gel (68%) than with Clindamycin Gel (54%) and there was a trend for a greater proportion compared to Benzoyl Peroxide Gel (55%). In addition, Clindoxyl Gel treatment for 11 weeks resulted in significantly greater reductions and percent reductions in non-inflammatory lesions and total lesions than all other treatments and greater reductions and percent reductions in inflammatory lesions than Clindamycin Gel treatment.'

Study 158

The investigators for this study were as follows.

H. Irving Katz, M.D. Fridley, NM	Elyse Rafal, M.D. East Setauket, NY
Diane Thiboutot, M.D. Hershey, PA	David Pariser, M.D. Norfolk, VA
Debra Breneman, M.D. Cincinnati, OH	Stephen Kraus, M.D. Atlanta, GA
Ronald Savin, M.D. New Haven, CT	Peter Winters, M.D. Indianapolis, IN

1) Study Title: A Multicenter, Double-Blind Comparison of the Efficacy and Safety of Clindoxyl Gel, Benzoyl Peroxide Gel, Clindamycin Gel, and Vehicle Gel in the Once Daily Treatment of Acne Vulgaris for 11 Weeks.

2) Study objective: This was to compare the efficacy of Clindoxyl Gel to clindamycin gel and benzoyl peroxide gel in the topical treatment of acne vulgaris. A secondary objective was to compare the active gels to the vehicle gel, and to determine the relative safety of these gels.

3) Study design: This was a parallel group, double blind controlled comparison of Clindoxyl Gel, clindamycin gel, benzoyl peroxide gel, and vehicle gel, with randomized assignment to the treatment groups. The treatment assignments were computer generated so as to result in assigment of 14 to 16 patients to each of the Clindoxyl and benzoyl peroxide groups, and 6 to 9 patients to each of the clindamycin and vehicle groups.

4) Inclusion criteria: Patients with the following characteristics were enrolled in the study.

a. 13 to 30 years of age.
b. acne of the face, with a minimum of 25 and a maximum of 55 inflammatory lesions, a minimum of 12 and a maximum of 150 non-inflammatory lesions, and no more than 3 nodulocystic lesions.

5) Exclusion criteria: Patients were excluded from enrollment in the study for the following reasons.

a. use of medicated shampoos or medicated cleansers of any type within one week of admission to the study.
b. treatment with topical antibiotics or topical acne treatments of any type within two weeks of admission to the study.
c. treatment for more than five days with systemic antibiotics known to have an effect on acne, systemic corticosteroids, topical corticosteroids anywhere on or near the face or over an extensive area (limited use of topical corticosteroids on small distal areas, and inhalants and nasal sprays were permitted), any investigational drug product, or any medication which might have interfered with the study results, within one month of admission to the study.
d. treatment with oral retinoids within six months of admission to the study.
e. a known history of hypersensitivity or idiosyncratic reaction to benzoyl peroxide, clindamycin, lincomycin, or any of the components of the study medication.
f. requirement for any significant concomitant medication.
g. a severe systemic disease or any other disease that might affect the evaluation of the study medications.
h. pregnancy or lactation.
i. females not using an effective form of contraception, including abstinence, for three months (four months for oral contraception) before admission to the study.
j. not reasonably agreeable to participate in the entire study program.

6) Treatment regimen: Application of the study medications were made to the face once daily, in the evening, for 11 weeks. If excessive irritation or dryness developed, the investigator instructed the patient to temporarily decrease the frequency of applications, and this was noted on the case report.

7) Effectiveness parameters: Return visits were made at weeks 2, 5, 8, and 11, for the following evaluations.

a. Lesion counts: Inflammatory and non-inflammatory lesions were counted at baseline and at each return visit.

b. Investigator's global evaluation: This was done at each return visit, using the following scale.

Investigator's Global Evaluation		
0	Worsening	
1	Poor	0% to 25% improvement
2	Fair	26% to 50% improvement
3	Good	51% to 75% improvement
4	Excellent	76% to 100% improvement

8) Safety evaluation. At each return visit the patient was queried as to adverse events; these were recorded, with the severity, duration, relationship to the test medication, and outcome of the event. Also at each return visit the investigator scored the occurrence and severity of facial erythema, peeling, burning, dryness, or other effects on the following scale.

Local tolerance scale		
0	absent	
1	mild	slightly noticeable
2	moderate	definitely noticeable, seldom interferes with daily activities or sleep
3	severe	intensely noticeable, interferes with daily activities or sleep.

At the final visit for each patient the overall tolerance to the test medication was assessed by the investigator on the following scale.

Local tolerance scale		
0	poor	numerous moderate to severe treatment-related local tolerance observations throughout the treatment period
1	fair	numerous mild to moderate treatment-related local tolerance observations throughout the treatment period
2	good	a single mild or no treatment-related local tolerance observations at end of treatment period with few mild or moderate observations during early treatment
3	excellent	no treatment-related local tolerance observations at end of treatment period with no or only a few mild observations during early treatment

Results were as follows.

1) Baseline and demographic characteristics: 358 patients were enrolled into the study, of which 289 patients completed the study. The characteristics of all patients enrolled were as follows.

Baseline and demographic characteristics				
	Benzoyl peroxide n=112	Clindamycin n=65	Clindoxyl n=113	Vehicle n=68
Gender				
Male	64 (57%)	40 (62%)	51 (45%)	38 (56%)
Female	48 (43%)	25 (39%)	62 (55%)	30 (44%)
Race				
Caucasian	94 (84%)	54 (83%)	99 (88%)	57 (84%)
Black	12 (11%)	6 (9%)	13 (12%)	9 (13%)
Hispanic	2 (2%)	3 (5%)	0	2 (3%)
Other	4 (4%)	2 (3%)	1 (1%)	0
Lesion counts				
Inflammatory	31	33	33	31
Non-inflammatory	34	35	37	37
Total	65	69	69	68

The disposition of the patients and the reasons for premature withdrawal were as follows.

Reasons for premature withdrawal				
	Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
# patients entered # patients completed	112 91	65 52	113 92	68 54
Adverse event	1	0	0	1
Concomitant medication	2	0	1	0
Concurrent illness	0	1	0	0
Lost to followup	10	7	11	8
Entry criteria violation	1	0	3	0
Not able to participate	2	0	3	3
Pregnancy	1	0	0	0
Protocol violation	1	2	1	0
Refused treatment	3	0	0	0
Inadvertently dropped	0	0	1	0
Uncooperative	0	1	1	1
Acne worse	0	2	0	1

2) Efficacy variables.

Results are presented for the ITT population, which was defined as comprising all patients. The last observation was carried forward.

a. Lesion counts.

The mean lesion counts, and the mean percent reduction in lesion counts from baseline were as follows.

Mean inflammatory lesion counts				
	Benzoyl peroxide n=112	Clindamycin n=65	Clindoxyl n=113	Vehicle n=68
Baseline	31.3	33.1	32.5	30.6
Week 2	24.9	27.9	24.3	25.6
Week 5	20.4	25.7	18.4	23.7
Week 8	19.8	22.7	16.1	24.2
Week 11	18.5	22.9	15.3	22.5

Inflammatory lesion counts Mean percent reduction from baseline				
	Benzoyl peroxide n=112	Clindamycin n=65	Clindoxyl n=113	Vehicle n=68
Week 2	20.0	17.6	24.1	17.5
Week 5	35.4	24.6	42.7	24.2
Week 8	36.8	33.5	49.3	23.5
Week 11	41.0	32.6	52.1	28.5

Mean non-inflammatory lesion counts				
	Benzoyl peroxide n=112	Clindamycin n=65	Clindoxyl n=113	Vehicle n=68
Baseline	34.1	35.4	36.6	36.9
Week 2	30.0	33.3	31.6	33.1
Week 5	27.6	32.1	28.2	33.4
Week 8	26.0	30.6	26.1	33.8
Week 11	25.7	28.6	23.8	34.7

Non-inflammatory lesion counts Mean percent reduction from baseline				
	Benzoyl peroxide n=112	Clindamycin n=65	Clindoxyl n=113	Vehicle n=68
Week 2	8.3	2.5	11.1	3.1
Week 5	16.6	3.6	19.4	3.3
Week 8	22.6	9.6	21.1	2.9
Week 11	22.8	16.5	25.3	+ 7.4

Mean total lesion counts				
	Benzoyl peroxide n=112	Clindamycin n=65	Clindoxyl n=113	Vehicle n=68
Baseline	65.3	68.5	69.1	67.5
Week 2	54.8	61.2	56.0	58.7
Week 5	48.0	57.9	46.6	57.1
Week 8	45.8	53.2	42.2	58.0
Week 11	44.1	51.4	39.2	57.2

Total lesion counts Mean percent reduction from baseline				
	Benzoyl peroxide n=112	Clindamycin n=65	Clindoxyl n=113	Vehicle n=68
Week 2	15.8	11.0	18.3	12.7
Week 5	27.5	16.0	31.7	15.8
Week 8	31.2	23.3	36.9	16.7
Week 11	33.8	25.6	40.5	15.5

The p values for the comparisons between treatments in the mean percent reduction in lesion counts in the ITT population were as follows.

Inflammatory lesions	
Comparison	p value
Clindoxyl vs vehicle	0.000
Clindoxyl vs benzoyl peroxide	0.008
Clindoxyl vs clindamycin	0.000
Benzoyl peroxide vs vehicle	0.019
Clindamycin vs vehicle	0.487
Benzoyl peroxide vs clindamycin	0.127

Non-inflammatory lesions	
Comparison	p value
Clindoxyl vs vehicle	0.001
Clindoxyl vs benzoyl peroxide	0.633
Clindoxyl vs clindamycin	0.316
Benzoyl peroxide vs vehicle	0.004
Clindamycin vs vehicle	0.040
Benzoyl peroxide vs clindamycin	0.552

Total lesions	
Comparison	p value
Clindoxyl vs vehicle	0.000
Clindoxyl vs benzoyl peroxide	0.109
Clindoxyl vs clindamycin	0.005
Benzoyl peroxide vs vehicle	0.001
Clindamycin vs vehicle	0.108
Benzoyl peroxide vs clindamycin	0.150

b. Investigator's global assessment.

The global improvement scores at week 11 for the ITT population were as follows.

Global improvement scores - week 11				
Score	Benzoyl peroxide n=112	Clindamycin n=65	Clindoxyl n=113	Vehicle n=68
0	19 (17.0%)	10 (15.4%)	14 (12.4%)	18 (26.5%)
1	23 (20.5%)	23 (35.4%)	19 (16.8%)	22 (32.4%)
2	30 (26.8%)	16 (24.6%)	25 (22.1%)	12 (17.6%)
3	21 (18.8%)	14 (21.5%)	30 (26.5%)	13 (19.1%)
4	19 (17.0%)	2 (3.1%)	25 (22.1%)	3 (4.4%)
0 = worse 1 = 0% to 25% improvement 2 = 26% to 50% improvement 3 = 51% to 75% improvement 4 = 76% to 100% improvement				

The p values for pairwise comparisons of the Success rates, defined as a score of 3 or 4, were as follows.

Success rates	
Comparison	p value
Clindoxyl vs vehicle	0.001
Clindoxyl vs clindamycin	0.001
Clindoxyl vs benzoyl peroxide	0.042
Benzoyl peroxide vs vehicle	0.067
Clindamycin vs vehicle	0.876
Benzoyl peroxide vs clindamycin	0.101

3) Safety evaluation.

Local tolerance scores were compared to baseline scores, and the frequency of treatment emergent signs and symptoms was tabulated, as follows.

Erythema - Treatment emergent No. and % of subjects with worsening scores over baseline					
	Week 2	Week 5	Week 8	Week 11	Any
Benzoyl peroxide	11 (11%)	7 (7%)	5 (6%)	7 (8%)	20 (19%)
Clindamycin	4 (7%)	3 (6%)	3 (6%)	3 (6%)	4 (7%)
Clindoxyl	9 (9%)	10 (10%)	7 (8%)	9 (10%)	14 (14%)
Vehicle	7 (11%)	8 (14%)	8 (15%)	6 (11%)	13 (20%)

Peeling - Treatment emergent No. and % of subjects with worsening scores over baseline					
	Week 2	Week 5	Week 8	Week 11	Any
Benzoyl peroxide	12 (12%)	12 (12%)	5 (6%)	3 (3%)	23 (22%)
Clindamycin	1 (2%)	1 (2%)	5 (9%)	2 (4%)	6 (10%)
Clindoxyl	16(16%)	11 (12%)	8 (9%)	6 (7%)	26 (25%)
Vehicle	0	1 (2%)	3 (6%)	0	3 (5%)

Burning - Treatment emergent No. and % of subjects with worsening scores over baseline					
	Week 2	Week 5	Week 8	Week 11	Any
Benzoyl peroxide	3 (3%)	2 (2%)	2 (2%)	1 (1%)	7 (7%)
Clindamycin	1 (2%)	3 (6%)	2 (4%)	1 (2%)	5 (8%)
Clindoxyl	5(5%)	3 (3%)	3 (4%)	2 (2%)	9 (9%)
Vehicle	2 (3%)	0	0	1 (2%)	3 (5%)

Dryness - Treatment emergent No. and % of subjects with worsening scores over baseline					
	Week 2	Week 5	Week 8	Week 11	Any
Benzoyl peroxide	8 (8%)	11 (11%)	4 (4%)	7 (8%)	18 (17%)
Clindamycin	3 (5%)	4 (7%)	7 (13%)	7 (14%)	13 (21%)
Clindoxyl	17(17%)	12 (13%)	11 (13%)	6 (7%)	27 (26%)
Vehicle	3 (8%)	4 (7%)	6 (11%)	1 (2%)	12 (18%)

The distribution of patients by the overall tolerance score was as follows.

	Poor	Fair	Good	Excellent
Benzoyl peroxide	0	2 (2%)	18 (17%)	84 (81%)
Clindamycin	0	1 (2%)	12 (20%)	48 (79%)
Clindoxyl	0	1 (1%)	21 (20%)	82 (79%)
Vehicle	1 (2%)	1 (2%)	11 (17%)	53 (80%)

The adverse events at the application site, and adverse events of the skin and appendages were as follows.

Adverse events				
	Benzoyl peroxide	Clindamycin	Clindoxyl	Vehicle
Application site				
Abscess	1	0	0	0
Contact dermatitis	1	0	0	0
Paresthesia	1	0	0	0
Photosensitivity reaction	0	0	0	1
Rash	0	1	0	0
Dry skin	0	0	0	1
Skin and appendages				
Infection	1	0	0	0
Pain	0	0	0	1
Wound	0	0	2	1

Three patients developed diarrhea during the study. One patient in the clindamycin group developed severe diarrhea two days after study entry and was withdrawn from the study. One patient in the Clindoxyl group developed mild diarrhea which lasted two days during the first week of the study. One patient in the benzoyl peroxide group developed moderate diarrhea which lasted for four days during the seventh week of the study.

Reviewer's comments - Study 158: As was stated in the comments for Study 156, the current policy on the requirements for a demonstration of effectiveness for a combination product in acne is that the product must demonstrate superiority over each of its components in the percent reduction from baseline of two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and in the dichotomized investigator's global evaluation, in the ITT population.

Based on these requirements, the results of this study do not demonstrate the effectiveness of the combination product, because the superiority of the combination over benzoyl peroxide has not been shown. Clindoxyl Gel was superior to clindamycin in the percent reduction of inflammatory and total lesion counts, and was superior to benzoyl peroxide in the percent reduction of inflammatory lesions, but was not superior to benzoyl peroxide in the percent reduction of non-inflammatory lesions or total lesion counts. Clindoxyl Gel was superior to clindamycin and to benzoyl peroxide in the 'Success Rate', defined as 51% or greater improvement from baseline in the investigator's global evaluation.

The sponsor based their conclusions in regard to efficacy on the results of analyses in the valid (Per Protocol) population. They considered the primary efficacy variables to be the percent reduction from baseline in the inflammatory, non-inflammatory, and total lesion counts, and on the global improvement scores. The results for the percent reduction in lesion counts were similar to those in the ITT population; Clindoxyl Gel was superior to clindamycin in the percent reduction of inflammatory and total lesion counts, and was superior to benzoyl peroxide in the percent reduction of inflammatory lesions, but was not superior to benzoyl peroxide in the percent reduction of non-inflammatory lesions or total lesion counts. Clinoxyl Gel was superior to clindamycin but was not superior to benzoyl peroxide in the Success Rate, based on the global evaluation. The p values for the comparisons in the valid population were as follows.

p values - Study 158 - lesion counts % reduction at week 11 Valid population			
Comparison	Inflammatory	Noninflammatory	Total
Clindoxyl vs benzoyl peroxide	0.005	0.521	0.076
Clindoxyl vs clindamycin	0.000	0.204	0.002

p values - Study 158 Success rates Valid population	
Comparison	p value
Clindoxyl vs benzoyl peroxide	0.059
Clindoxyl vs clindamycin	0.000

The sponsor's conclusions in regard to effectiveness were as follows: 'Substantial evidence of efficacy was observed. A significantly greater proportion of patients had good to excellent global improvement after 11 weeks treatment with Clindoxyl Gel (58%) than with Clindamycin Gel (30%) and Vehicle Gel (26%) and there was a trend for a greater proportion compared to Benzoyl Peroxide Gel (44%). Also, the summary measure for global improvement was significantly greater for Clindoxyl Gel than all other treatments. In addition, Clindoxyl Gel treatment for 11 weeks resulted in significantly greater reductions and percent reductions in inflammatory lesions and significantly greater reductions in total lesions than all other treatments. Also, Clindoxyl Gel treatment resulted in significantly greater reductions in non-inflammatory lesions and percent reductions in total lesions than the Clindamycin Gel and Vehicle Gel groups.'

<u>Summary and evaluation</u>: This resubmission of NDA 50-751 for Clindoxyl Gel provides two clinical safety and efficacy studies, and a study on sensitization potential, in response to the non-approvable letter of 5/14/97.

It is felt that the sensitization study is adequate to determine the sensitization potential of Clindoxyl gel.

The non-approvable letter stated that an additional clinical trial is recommended to establish the clinical superiority of Clinoxyl Gel over benzoyl peroxide gel in the treatment of acne. The new studies in the resubmission, Studies 156 and 158, are intended to demonstrate the superiority of Clinoxyl Gel over its components, benzoyl peroxide and clindamycin. Both studies were double blind controlled, multicenter comparisons, with applications once daily for 11 weeks. Study 156 compared Clindoxyl Gel to clindamycin gel and benzoyl peroxide gel; Study 158 had the same treatment arms, with also a vehicle gel arm. The effectiveness parameters were the same in both studies, consisting of lesion counts and an investigator's global evaluation of the percentage of improvement from baseline.

This reviewer's evaluation of these studies was in accordance with current policy that the requirements for a demonstration of effectiveness for a combination product in acne are that the product must demonstrate superiority over each of its components in the percent reduction from baseline of two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and in the dichotomized investigator's global evaluation, in the ITT population.

Study 156: The results of this study do not demonstrate the effectiveness of the combination product, because the superiority of the combination over benzoyl peroxide has not been shown. Clindoxyl Gel was superior to clindamycin in the percent reduction of the three categories of lesion counts, and was superior to benzoyl peroxide in the percent reduction of non-inflammatory lesions, but was not superior to benzoyl peroxide in the percent reduction of inflammatory lesions or total lesion counts. Clindoxyl Gel was not superior to either benzoyl peroxide or clindamycin in the 'Success Rate', defined as 51% or greater improvement from baseline in the investigator's global evaluation.

Study 158: The results of this study do not demonstrate the effectiveness of the combination product, because the superiority of the combination over benzoyl-peroxide has not been shown. Clindoxyl Gel was superior to clindamycin in the percent reduction of inflammatory and total lesion counts, and was superior to benzoyl peroxide in the percent reduction of inflammatory lesions, but was not superior to benzoyl peroxide in the percent reduction of non-inflammatory lesions or total lesion counts. Clindoxyl Gel was superior to clindamycin and to benzoyl peroxide in the 'Success Rate', defined as 51% or greater improvement from baseline in the investigator's global evaluation.

Conclusions: *It is felt that the studies submitted do not demonstrate that Clindoxyl Gel is superior in effectiveness to its component benzoyl peroxide.*

Recommendations: *It is recommended that this NDA for Clindoxyl Gel in the treatment of acne not be approved.*

/S/

Phyllis A. Huene, M.D. 8/7/00

Cc: Orig NDA 50-741
HFD-540 Division files
HFD-540\Wilkin
HFD-540\Walker GW 8/9/00
HFD-540\Huene
HFD-540/Freidlin
HFD-540\Cintron
HFD-540\Vidra
HFD-540\Jacobs

✓Not in DFS

The objective enumeration in Studies 156 and 158 of lesion counts showed significant differences in one category only which were not consistent between the two studies, viz., Study 156 found the combination superior to benzoyl peroxide in noninflammatory lesions only while Study 158 found the combination to be superior to benzoyl peroxide in inflammatory lesions only. It is plausible that these studies were unsuccessful overall because of underpowering. GW 8/15/00

1. TITLE AND GENERAL INFORMATION

MEDICAL OFFICER'S REVIEW OF NDA 50-741

Submission Date	15 May 96
First Draft	01 May 97
Second Draft	13 May 97
PDUFA Date	14 May 97
Medical Reviewer	Susan J. Walker, M.D.

Drug Name:

Drug:	Clindamycin phosphate 1% and benzoyl peroxide 5%
Proposed trade name:	Clindoxyl™ Gel

Sponsor:	Stieffel Labs Coral Gables, FL 33134
Pharmacologic Category:	Anti-bacterial agent
Proposed Indication:	Topical treatment of acne vulgaris.
Dosage Form and Route of Administration:	Topical gel
NDA Drug Classification:	4S
Related INDs:	[redacted]
Related NDAs:	See Section 6.2
Related Reviews:	Biostatistics reviews dated 10 Feb 97 and addendum 12 May 97 Biopharmaceutics review dated 12 May 97 Pharmacology review dated 18 October 96 Chemistry review dated 17 April 97 Microbiology review dated 7 Nov 96

2. TABLE OF CONTENTS

3. MATERIAL REVIEWED

- NDA 50-741 VOLUMES: 1.1, 1.07-1.16, 1.27, 1.28
- NDA 50-741 AMENDMENT DATED 27 AUG 96
- [redacted]
- [redacted]
- [redacted]

4. CHEMISTRY/MANUFACTURING CONTROLS

Clindoxyl™ Gel is a viscous, opaque, white to slightly yellow, aqueous gel containing both clindamycin phosphate (equivalent to 1% clindamycin) and benzoyl peroxide (5%). The formulation contains the preservative methylparaben, the gelling agent carbomer 940, slip agents poloxamer and dimethicone, thickener/slip agent hydrated silica, the chelator edetate disodium, the wetting agent disodium lauryl sulfosuccinate, sodium hydroxide for pH adjustment, and glycerin for emolliency in a purified water carrier.

Formulation:

Benzoyl Peroxide	
Clindamycin Phosphate	
Carbomer 940	
Dimethicone	
Disodium Lauryl Sulfosuccinate	
Edetate Disodium	
Glycerin	
[redacted]	
Methylparaben	
Poloxamer	
Purified Water	
Sodium Hydroxide	
To Make Total:	

The drug product manufactured for use in the clinical trials which support this NDA was manufactured with a bulk clindamycin phosphate supplied by [redacted] This company was found to be in violation of Good Manufacturing Practices (GMP), and identified deficiencies

have resulted in a Not Approvable recommendation on the basis of Chemistry, Manufacturing and Controls violations. The clinical implication of this Not Approvable action is that the product used in the pivotal trials was not manufactured in accordance with Good Manufacturing Practice (GMP), and therefore is considered to be adulterated. A Health Hazard Analysis was completed by the Office of Generic Drugs. The bulk drug substance supplied by [redacted] to several generic companies was not found to contain impurities which are not present in the Reference Listed Drug, and it did conform to compendial specifications for clindamycin phosphate. However, the testing done did not provide full assurance that the potency of the drug was unaffected or that there were no chemical components which might lead to safety concerns. OGD recommended a Class II recall of the [redacted] drug product as the quality, purity, potency and consistency of this generic could not be assured. The focus of this review was bulk drug product for generic Ceclor™, clindamycin phosphate, and minocycline; it primarily addresses the efficacy and safety issues pursuant to drugs manufactured to treat diseases with systemic infectious indications.

5. ANIMAL PHARMACOLOGY/TOXICOLOGY

The sponsor has performed only one preclinical study with Clindoxyl™ Gel, a 28 day Repeated Dose Dermal Toxicity study in Sprague Dawley Rats (93G-2325; Nov-Dec 1993), which is reviewed by pharmacology for this NDA. This subchronic dermal toxicity study, conducted at a dose level 200 times the human dose, showed no signs of toxicity.

The sponsor presents referenced information from multiple preclinical studies (not done by the sponsor) involving clindamycin or benzoyl peroxide. These are both currently marketed products which are used extensively in the treatment of acne vulgaris.

There is an outstanding issue involving the potential tumor promoting status of benzoyl peroxide. Regulatory guidance concerning benzoyl peroxide was excluded from the Final Monograph on Topical Acne Drug Products for Over-the-counter Use (Effective date August 16, 1992) due to concerns related to potential carcinogenicity of this active ingredient. Benzoyl peroxide was reclassified from Class I (Generally regarded as safe and effective and not misbranded) to Class III (Available data insufficient to classify as safe and effective, and further testing is required) and is currently approved for OTC use up to 10% strength. The agency in its tentative final monograph (50 FR 2172 at 2181) proposed monograph status for the ingredient benzoyl peroxide for OTC topical use in the treatment of acne. However, following this proposal the agency became aware of a study by Slaga, *et al.* that raised a safety concern regarding benzoyl peroxide as a tumor promoter in mice and a study by Kurokawa, *et al.* that reported benzoyl peroxide to have tumor initiation potential. Neither of these studies was discussed by the Panel or by the Agency in the Federal Register publications identified above. Subsequently, a drug manufacturer's association submitted data and information in support of the safety of benzoyl peroxide. FDA has evaluated these data and information and determined that the studies show that benzoyl peroxide is a skin tumor promoter in more than one strain of mice as well as in other laboratory animals tested. To date, topical studies (which have shown only tumor promotion) have been of short duration (about 52 weeks), which the Agency considers insufficient to rule out the potential for carcinogenicity. Although extensive animal data and human epidemiology data are available, the agency was unable to state that benzoyl peroxide is generally recognized as safe and effective in the final monograph.

The relevance of the above finding for humans is unknown. Benzoyl peroxide is a widely used and effective ingredient in the topical treatment of acne. The Agency was concerned about continued OTC marketing during the several years it would take to resolve the safety issues raised by the studies discussed above. Because of this concern, the Agency discussed this matter with its Dermatologic Drugs Advisory Committee (the Committee) on April 10, 1992. The Committee was asked to assess the safety and efficacy data available for benzoyl peroxide, to consider the benefit to risk ratio, and to recommend whether the product should continue to be available for use while further safety data are developed. The Committee voted unanimously that benzoyl peroxide should remain available as an OTC drug product. The Committee also recommended that new carcinogenicity studies be conducted. These studies are proceeding under the sponsorship of the ——— , and final Agency action on benzoyl peroxide is anticipated following the completion and evaluation of these studies.

Reviewer Comment: *The pharmacology review should discuss the need for any additional studies with Clindoxyl™ Gel, such as a subchronic dermal toxicity study and a photocarcinogenicity study.*

6. CLINICAL BACKGROUND

6.1 RELEVANT HUMAN EXPERIENCE

Topical antibacterial agents have been used effectively to treat acne vulgaris for more than a decade. Individually, benzoyl peroxide and clindamycin phosphate have been incorporated into various topical formulations which have been shown to be effective in reducing the lesions of acne vulgaris.

6.2 IMPORTANT INFORMATION FROM RELATED INDS AND NDAS

Systemic and topical clindamycin phosphate has previously been approved for use under the 14 NDAs which are listed below. There are three currently marketed clindamycin phosphate formulations which are extensively used in dermatologic practice, and these are highlighted below.

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NDA	DRUG NAME	APPROVED	SPONSOR	FORMULATION	INDICATION
50-162	Cleocin HCL Caps	22Feb70(520)	Pharmacia Upjohn	Cleocin Phosphate USP	
50-163	Cleocin Solution	29Jul70 (520)	Pharmacia Upjohn		
50-428	Cleocin Palmitate Flavored granules	16Sep71(520)	Pharmacia Upjohn	Clindamycin Palmitate HCL	
50-441	Cleocin Phosphate Solution	02Oct72(520)	Pharmacia Upjohn	Clindamycin Phosphate	
50-537	Cleocin Topical Soln	09Jul80 (540)	Pharmacia Upjohn	Clindamycin Phosphate	Acne
50-600	Cleocin T Topical Lotion	31May89 (540)	Pharmacia Upjohn	Clindamycin Phosphate	Acne
50-615	Cleocin T Topical Gel	07Jan87 (540)	Pharmacia Upjohn	Clindamycin Phosphate	Acne
50-635	Clindamycin Phosphate in 5%dextrose for injection	22Dec89 (520)	Fujisawa		
50-636	Clindamycin Phosphate in 5%dextrose for injection	22Dec89 (520)	Fujisawa		
50-639	Cleocin Phosphate IV	30Aug89 (520)	Pharmacia Upjohn	Clindamycin Phosphate	
50-648	Clindamycin Phosphate injection	29Dec89 (520)	Baxter		
50-669	Clindamycin Phosphate Powder	NA (520) 28Mar91	Paddock		
50-680	Cleocin Vaginal Cream	11Aug92	Pharmacia Upjohn	Clindamycin Phosphate	

Topical benzoyl peroxide, 2.5% to 10%, is available for use as an over the counter treatment for acne vulgaris. It has been available OTC for approximately 60 years, and is also used extensively in clinical practice. Benzoyl peroxide is available in combination with erythromycin (Benzamycin® Gel-Dermik) for acne treatment. The Benzamycin® NDA was approved in 1984, and is the only benzoyl peroxide combination product for acne which is currently approved in the USA.

6.3 FOREIGN EXPERIENCE

Neither Clindoxyl™ Gel nor any other product containing both benzoyl peroxide and clindamycin phosphate has been marketed anywhere in the world.

6.4 HUMAN PHARMACOLOGY, PHARMACOKINETICS, PHARMACODYNAMICS

Pharmacology

Clindamycin phosphate and benzoyl peroxide are antibacterial agents with different mechanisms of action which have been shown to be effective in topical treatment of acne vulgaris when used as single entity drugs.

6.4.1 CLINDAMYCIN

Description

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic derived from the parent compound lincomycin. The chemical name for clindamycin phosphate is 7(s)-chloro-7-deoxylincomycin-2-phosphate.

Mechanism of Action

Clindamycin inhibits bacterial protein synthesis by its action at the bacterial ribosome. Clindamycin binds preferentially to the 50 S ribosomal subunit and affects the process of peptide chain initiation. Clindamycin phosphate is inactive *in vitro* - rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin. Clindamycin phosphate has not been shown to be keratolytic, does not change the sebum excretion rate, but has been shown to inhibit the chemotactic activity of human leukocytes in vitro, which may be an important mechanism by which certain antimicrobial agents suppress inflammatory skin disease.

Absorption and distribution

In man, clindamycin is nearly completely absorbed following oral administration, and peak plasma concentrations of 2 to 3 µg/ml are attained within 1 hour after ingestion of 150 mg. After intramuscular injection of clindamycin phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in children.

Systemic absorption of clindamycin after topical administration is possible. This was confirmed in a clinical study of systemic absorption of clindamycin after topical administration of clindamycin phosphate in a 1% solution (Cleocin-T) (Eller, 1989). Twelve subjects without acne applied 1ml of the solution to the face every 12 hours for 4 days. Absolute bioavailability averaged 1.7%. No appreciable systemic accumulation from the repeated topical applications was noted. Peak serum concentrations ranged from less than 0.5 ng/ml to 6 ng/ml when measured 4 to 96 hr after the first dose (Eller, 1989). A similar study with 1% clindamycin hydrochloride gave a bioavailability of 7.5% with peak serum concentrations of 4 to 20 ng/ml (Eller, 1989). Systemic absorption of clindamycin in acne patients after application of a 1% solution of clindamycin hydrochloride was also higher, 4-5%, when measured on the 3rd and 27th days of treatment (Barza, 1982). Absorption varied greatly from person to person but did not correlate with skin pigmentation or severity of acne. Serum concentrations were less than 0.4 µg/ml for all patients, although clindamycin was found in the urine of patients.

Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg/ml in an isopropyl alcohol and water solution, very low levels of clindamycin were present in serum (0-3 ng/ml) and less than 0.2% of the dose was recovered in urine as clindamycin (Cleocin-T Package Insert).

Distribution

In man, clindamycin is widely distributed in many fluids and tissues, including bone (Sande, 1985). No significant levels of clindamycin are attained in the cerebrospinal fluid even in the presence of inflamed meninges. Clindamycin readily crosses the placental barrier. Orally and parenterally administered clindamycin has been reported to appear in breast milk (Cleocin T Package Insert).

Ninety percent or more of clindamycin is bound to plasma proteins (Gordon, 1973; Sande, 1985). Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of 1% clindamycin phosphate solution for 4 weeks was 0.60µg/mg of comedonal material (range 0-1.49) (Guin, 1982). For most patients treated with clindamycin hydrochloride, the antibiotic was present in deeper layers of the comedo as well as in those layers closer to the follicular wall(Guin, 1980) as early as 2 weeks after it was first applied.

Metabolism

Clindamycin phosphate is rapidly hydrolyzed *in vivo* to clindamycin (Cleocin T Package Insert). This conversion takes place in blood (Flaherty, 1988) and in the skin including comedones (Guin, 1982). Following parenteral administration, the decay of clindamycin phosphate levels in serum was rapid, with virtually 100% of the phosphate eliminated within the first 1.5 hr following the dose (Plaisance,1989). Approximately 0.35% of the dose was recovered in the urine as clindamycin phosphate.

Human metabolites of clindamycin which have been identified include N-demethylclindamycin, clindamycin 1-sulfoxide, N-demethylclindamycin 1-sulfoxide, and clindamycose (Brodasky, 1977).

Excretion

In man, only about 10% of administered clindamycin is excreted unaltered in the urine, and small quantities are found in feces (Sande, 1985). The serum disappearance half-life of active clindamycin is about 2.7 hr. The disappearance half-life is increased slightly in patients with markedly reduced renal or hepatic function. After parenteral therapy with clindamycin was stopped, antimicrobial activity persisted in feces for 5 or more days; growth of sensitive microorganisms in colonic contents remained suppressed for up to 2 weeks (Sande, 1985).

6.4.2 Benzoyl Peroxide

Description

Benzoyl peroxide is an oxidizing agent.

Mechanism of Action

The exact mechanism of action is unknown, but oxidation of bacterial proteins is likely. The concentration in sebaceous follicles is reported at bactericidal levels. Benzoyl peroxide causes skin irritation and desquamation.

Absorption and Distribution

The absorption and biodisposition of ^{14}C-benzoyl peroxide was studied *in vitro* with excised human skin. In 8 hours, 1.9% of the labeled drug was recovered as benzoic acid on the dermal side, 1.3% was benzoic acid within the skin, 1.3% was benzoyl peroxide within the skin, and the remaining labeled drug was benzoyl peroxide on the skin surface (Nacht, 1981).

An investigation in humans of the absorption of benzoyl peroxide from leg ulcers following application of a 20% benzoyl peroxide formulation demonstrated elevated plasma levels of benzoic acid which were never higher than 610 µg/L (Fed Reg, 1982).

Metabolism and Excretion

There is evidence to support the theory of rapid conversion of benzoyl peroxide to benzoic acid, especially when applied to skin. When benzoyl peroxide was applied to human forearms, benzoyl peroxide and benzoic acid were recovered in a chloroform wash in a ratio of 1.5 to 1 four hrs after application, indicating conversion to benzoic acid (Fed Reg, 1982).

After oral ingestion in humans, in rhesus monkeys, and in certain other mammalian species, benzoic acid was conjugated with glycine as hippuric acid in the liver and excreted in urine (Nacht, 1981).

6.4.3 BENZOYL PEROXIDE 5% AND CLINDAMYCIN 1% (CLINDOXYL™ GEL)

The sponsor presents no pharmacologic or pharmacokinetic data concerning this new combination product, based upon the assumption that the clindamycin phosphate would not affect the formation of free radical oxygen from benzoyl peroxide, and that benzoyl peroxide would not inhibit the hydrolysis of clindamycin phosphate to clindamycin (the active moiety). Moreover, the sponsor has not discussed the possible oxidation of clindamycin-2-phosphate to other metabolites. The sponsor has not characterized the oxidation products of clindamycin phosphate, nor described their detectability in Clindoxyl™ Gel.

Systemic absorption after topical administration of clindamycin in a variety of vehicles is minimal, however, the bioavailability of clindamycin may be dependent upon the other components in the gel. The topical and systemic tolerance to the bioavailability of clindamycin from a 1gm application of Clindoxyl™ Gel after a single application **HAS NOT** been established by the sponsor.

Reviewer Comment: *The sponsor should characterize the bioavailability of the 1% clindamycin /5% benzoyl peroxide combination which it proposes to market. The sponsor should provide information which characterizes the metabolic products of clindamycin phosphate, and demonstrates that they are not present in Clindoxyl™ Gel. The sponsor should also establish that the combination product provides no greater absorption of clindamycin than clindamycin phosphate alone. This is particularly important due to the known incidences of pseudomembranous colitis and interaction with neuromuscular blocking agents, which are both attributed to clindamycin.*

6.5 OTHER RELEVANT BACKGROUND INFORMATION

The studies submitted with this NDA were completed under ———— . The sponsor did not request either a preIND meeting or an End of Phase 2 meeting.

6.6 DIRECTIONS FOR USE

Proposed Statement on the Label: Clindoxyl™ Gel should be applied once daily in the evening, or as directed by physician, to affected areas after the skin has been ————washed, rinsed with warm water and gently patted dry.

"Instructions to patients" used in clinical trials:

You should use this gel once daily in the evening for 11 weeks. Apply the gel 10 to 20 minutes after washing and drying your face. Apply a thin layer of the gel to your entire face each time you use the gel. Wash your hands after applying the gel. Do not apply too much gel as the excessive use of the gel may irritate your skin. Avoid applying the gel to lips, mouth, eyes, or open wounds.

Reviewer Comment: *The proposed labeling statement is consistent with the instructions to patients used in the clinical trials.*

7. DESCRIPTION OF CLINICAL DATA SOURCES

The clinical trials submitted by the sponsor are summarized below.

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Chart to follow
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STUDY	PURPOSE	DESIGN	N	EXPOSURE
153	PHOTOTOXICITY	UNCONTROLLED UNBLINDED SINGLE CENTER NON-RANDOMIZED	10	48HRS
154	PHOTOALLERGY	UNCONTROLLED UNBLINDED SINGLE CENTER NON-RANDOMIZED	28	3 WKS
155	CONTACT SENS.	UNCONTROLLED UNBLINDED SINGLE CENTER NON-RANDOMIZED	26	3WKS
150 PROTOCOL 9401	EFFICACY AND SAFETY	CONTROLLED DOUBLE BLIND PARALLEL RANDOMIZED SINGLE CENTER	120	QD X 11 WKS
151 PROTOCOL 9405	EFFICACY AND SAFETY	CONTROLLED DOUBLE BLIND PARALLEL RANDOMIZED MULTICENTER(5)	273	QD X 11 WKS
152 PROTOCOL 9406	EFFICACY AND SAFETY	CONTROLLED DOUBLE BLIND PARALLEL RANDOMIZED MULTICENTER(2)	280	QD X 11 WKS

8. CLINICAL STUDIES

There were six studies conducted with Clindoxyl™ Gel. Three of these studies (#150, #151, #152) were controlled clinical trials which included 4 arms: Clindoxyl™ Gel, 5% benzoyl peroxide gel, 1% clindamycin phosphate gel, and vehicle gel. Study duration was for 11 weeks, with evaluations at 2, 5, 8 and 11 weeks. The pivotal trials were studies 151 and 152, as these were both multicenter trials and had the largest number of subjects involved. Study 150 was a single investigator trial. Results at Site 152B were generally significantly inconsistent with those at Site 152A and the other two studies. Accordingly, the sponsor proposes that the results of Site 152B are to be disregarded in drawing conclusions from these three studies. [1]

Reviewer Comment: The results of a study cannot be disregarded simply due to untoward outcomes. Studies 151 and 152, in their entirety, remain the pivotal trials for this submission.

The other three studies (#153, #154, #155) were clinical patch test safety studies to evaluate the potential of Clindoxyl™ Gel to cause phototoxicity, photocontact sensitization (photoallergy) or contact sensitization. These are reviewed under Section 10.2.3 (Special Studies).

[1] Summary of efficacy, Vol 1.16, Page 209

8.1 INDICATION # 1: ACNE VULGARIS

8.1.1 REVIEWER'S TRIAL # 1 STUDY #150 SPONSOR'S PROTOCOL 9401

TITLE: A DOUBLE-BLIND CLINICAL COMPARISON OF THE EFFICACY AND SAFETY OF CLINDOXYL™ GEL, CLINDAMYCIN PHOSPHATE GEL, BENZOYL PEROXIDE GEL, AND VEHICLE GEL IN THE ONCE DAILY TREATMENT OF ACNE VULGARIS FOR 11 WEEKS.

INVESTIGATOR:

D.K. Chalker, M.D. (STUDY DATES: 18 MAR 94 TO 29 JUNE 94)
Georgia Dermatology and Skin Cancer Center
420 Charter Blvd, Suite 205
Macon, Georgia 31210-4831

8.1.1.1 OBJECTIVE/RATIONALE

The primary objective of this study is to determine the relative efficacy of the use of Clindoxyl™ Gel, clindamycin phosphate gel, benzoyl peroxide gel, and vehicle gel in the topical treatment of acne vulgaris. Secondarily, the relative safety of these gels will be determined.

8.1.1.2 DESIGN

This study was a single center, double blind, parallel, vehicle controlled design.

8.1.1.3 PROTOCOL

8.1.1.3.1 POPULATION

120 patients ranging in age from 13 to 30 years were enrolled in the study, 46 females and 74 males.

Entry Criteria:
Inclusion

1. Age: 13 to 30 years.
2. Sex: Males and females.
3. Race: No specific requirement.
4. Diagnosis: Patients with a diagnosis of acne vulgaris of the face and a minimum of 12 inflammatory lesions, a minimum of 12 noninflammatory lesions, and no more than 3 facial nodulocystic lesions.
5. Motivation and Consent: All patients should be properly motivated to participate in the entire study program and would provide written informed consent.

Exclusion:

1. Medicated cleansers or shampoos used during one week prior to the study
2. Acne treatment of any type, systemic or topical antibiotics, systemic or topical corticosteroids or any medication that might have interfered with the study results within one month of admission to the study.
3. Treatment with oral isotretinoin within six months of admission to the study.
4. Known hypersensitivity or idiosyncratic reactions to benzoyl peroxide, clindamycin, lincomycin, or any of the components of the study medication.
5. Patients who would require any significant concomitant medication.
6. Patients with severe systemic diseases or any other diseases which might have affected the evaluation of the study medication .
7. Patients with a history of regional enteritis, ulcerative colitis, or antibiotic - associated colitis.
8. Female Patients:

   Pregnant and/or lactating women were excluded from the study.

   All females patients were required to use an effective form of birth control (which could include abstinence) for a period of 3 months before, throughout, and for one month after stopping use of study medication. Oral contraceptives (except anti-androgen compounds) were allowed provided that the same contraceptive was used 6 months before and throughout the study period.

***Reviewer Comment**: The protocol does not specifically exclude concomitant antibiotic treatment, although this could be included under #5. The requirement to use birth control and exclude pregnant women is not necessary, unless the sponsor wishes to include this birth control requirement in the labeling of the product*

Study Procedures:

Patients were instructed to apply the study medication to the entire face once a day, in the evening for a period of 11 weeks. Examinations of the patients were performed initially (week 0), and at therapy weeks 2, 5, 8, and 11. Variation of this schedule of approximately ± five days was permitted provided that the investigator assured himself that use of the test medication had been continued.

Evaluation of efficacy was made by counting inflammatory and noninflammatory lesions of the entire face at all visits and grading global improvement at all visits after baseline. Evaluation of safety was made by reporting adverse events; scoring of local tolerance for erythema, peeling, and burning at all visits; and, scoring of overall tolerance at the final visit. Erythema, peeling, and burning were evaluated on a scale of 0 to 3 where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The overall tolerance for study medication was rated on a scale of 0 to 3 where 0 = poor, 1 = fair, 2 = good, and 3 = excellent. These study procedures are summarized in the following table:

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Chart to follow

	WEEK 0 (VISIT 1)	WEEK 2 (VISIT 2)	WEEK 5 (VISIT 3)	WEEK 8 (VISIT 4)	WEEK 11 (VISIT 5)
Demographic data	X				
Entry Criteria	X				
Pregnancy Test	X				X
Informed Consent	X				
Dispense Medication	X	X	X	X	
Return Medication		X	X	X	X
Medication Accountability	X	X	X	X	X
Instructions for med use	X				
Initiate treatment	X				
Patient Compliance		X	X	X	X
Lesion Counts	X	X	X	X	X
Grade Local Tolerance	X	X	X	X	X
Grade Global Improvement		X	X	X	X
Grade Overall tolerance					X
Adverse Events		X	X	X	X
End treatment					X

8.1.1.3.2 ENDPOINTS

Efficacy

Efficacy parameters included **counts of inflammatory** and **non-inflammatory** lesions, and an **investigator's global assessment** of percentage improvement from baseline. These are the primary efficacy variables presented by the sponsor.

Inflammatory and noninflammatory lesions were counted on the entire face. These counts were presented as reduction in lesions and as percent reduction in lesions from baseline at weeks 2,5,8, and 11.

The *percent reduction from baseline in total lesion counts* was requested by the division. These were provided by the sponsor as an amendment.

Global assessment was defined by the following ordinal scale: 0 = worsening, 1 = 0-25% improvement (poor), 2 = 26-50% improvement (fair), 3 = 51-75% improvement (good), 4 = 76-100% improvement (excellent). The global improvement score at week 11 was simplified by the sponsor to the dichotomous variable Success (global improvement scores of good and excellent) versus Failure (global improvement scores of fair, poor, and worsening). The global improvement scores at all weeks were summarized as an AUC measure. The collapsed global improvement score at week 11 is a primary variable, and the AUC of global improvement is secondary, as the untransformed scores at all weeks.

Safety

The sponsor assessed the safety of Clindoxyl™ Gel by collecting data concerning **scoring of overall tolerance, scoring of local tolerance** and reporting **adverse events**. Overall tolerance

is the primary safety variable selected by the sponsor. Secondary variables include changes from baseline of local tolerance scores for erythema, peeling, and burning and adverse event frequency .

Overall tolerance for study medication was determined on the final visit, and was rated on a scale of 0 = poor, 1 = fair, 2 = good, 3 = excellent.

Local tolerance was recorded by evaluating erythema, peeling, and burning at each visit on a scale of 0 = absent, 1 = mild, 2 = moderate, 3 = severe. The case report form also includes a space for "other" under local tolerance, but this does not appear to have been used extensively by the sponsor. The sponsor evaluated the patient's erythema, peeling and burning at baseline (prior to medication exposure), then compared the "treatment emergent" signs and symptoms to this baseline score.

Adverse events were recorded on a CRF page titled Adverse Events. The protocol (Appendix C) defines an adverse event as any untoward medical occurrence in a patient causing a change in his medical status while enrolled in the study. The information collected included a brief description of the event, start and stop dates, frequency, severity, study drug relationship, cause, corrective drug treatment, and outcome. Appendix C of the protocol describes for the investigator the procedures for Handling and Reporting Adverse Events, and is very comprehensive.

Reviewer Comment:

Choice of primary safety variable. The sponsor chose final overall tolerance as a primary safety variable. This variable is undefined in the protocol, and subject to investigator bias due to its lack of definition. Adverse events and local tolerance would be better primary safety variables, with overall tolerance as a secondary variable.

Lack of Definitions of Scales. The sponsor does not define any of the safety ordinal scales (overall tolerance, local tolerance) in the protocol, which should have been clearly defined so that all investigators at all sites could be consistent.

Problems with tabulation method for local clinical reactions. At each visit the investigator reports the signs/symptoms of local tolerance such as erythema, burning, and peeling, on the CRF -and may add in a blank space any additional s/s such as dryness and pruritus. However, these same clinical events can also be collected under the adverse event tabulation and eventually reported as rash erythematous(i.e. erythema), paraesthesia(i.e. burning), peeling(peeling), skin dry(dryness), and pruritus(pruritus). It will be demonstrated later in the review (Summary of Safety, Study 150) that these categories can be mutually exclusive - a patient may be dropped from the study with an AE report of rash caused by direct contact with the medication, but have no notation on the CRF that there was any change in local tolerance. This is partly due to a defect in the design of the CRF, in which there is no specific form for Final Treatment Visit other than the week 11 visit.

Problems with baseline evaluation of local tolerance. The sponsor has many subjects that scored above 0 on the baseline score for local tolerance. This in effect biases the subsequent reporting of local tolerance, as the underlying condition may mask the emergence of local effects from the medication.