CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050680/S002

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Chi 520

NDA 50-680/S-002

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison
The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001-0199

MAY 7 1996

Dear Dr. de Koning Gans:

Please refer to your May 4, 1995 supplemental new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Cleocin[R] 3 Vaginal Cream (clindamycin phosphate cream 2%).

We acknowledge receipt of your amendments and correspondences dated June 1, June 6, June 29, July 7, August 25, 1995 as well as February 8 and March 13, 1996.

This supplemental application provides for a 3-day dosing regimen of clindamycin phosphate cream 2% in the treatment of bacterial vaginosis.

We have completed our review of this supplemental NDA and find that the information provided is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CRF 314.125(b). The reasons for the Agency's decision and the deficiencies in your application are summarized as follows:

In your supplemental application, you have provided results from Studies 0021 and 0027 which compare the shortened 3-day clindamycin phosphate cream 2% regimen to a placebo control. These studies demonstrated that the clindamycin cream regimen was superior to placebo.

In addition, Study 0020 compared the shortened 3-day clindamycin phosphate vaginal cream 2% regimen to the standard 7-day clindamycin phosphate vaginal cream 2% regimen. The results obtained from our analysis of this study showed that the 3-day clindamycin phosphate regimen is statistically inferior to the 7-day regimen in the treatment of patients with bacterial vaginosis.

The convenience and the safety profile seen in the above studies with the 3-day regimen do not outweight the clinically and statistically-significant inferior efficacy relative to the 7-day regimen.

According to the Division's POINTS TO CONSIDER document (page 28), for a drug to receive approval for the "treatment of infections with dosing regimen durations less than generally approved for that infection...two statistically adequate and well-controlled trials" should be provided.

For approval of a shorter dosing regimen, such as your proposed 3-day bacterial vaginosis treatment regimen, the Division usually requires that two adequate and well-controlled clinical trials be conducted comparing the proposed shortened regimen (e.g., 3-day regimen) to a currently-approved standard treatment regimen for that indication (e.g., the 7-day regimen). The results from these trials should demonstrate clinical and statistical equivalence using the 95% confidence interval.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CRF 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should contain a complete response to the above deficiencies. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact:

Christina H. Chi, Ph.D.
Project Management Staff
Telephone: (301) 827-2125.

Sincerely yours,

/S/ for 5/7/96

Mary Fanning, M.D., Ph.D., FACP
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc: Orig. NDA 50-680

HFC-130/JAllen
HFD-2/MLumpkin
HFD-80
HFD-638
HFD-735
HFD-520
HFD-520/DepDivDir/RAlbrecht
HFD-520/SMO/BLeissa /S/ 5/7/96
HFD-520/MO/JWinfield /S/ 5/7/96
HFD-520/Pharm/AEllis
HFD-520/Micro/HSilver
HFD-520/PM/CChi
HFD-830/SPagay
HFZ-440
CChi 4/6/96

NOT APPROVABLE

Concurrence Only:

HFD-520/DivDir/MFanning
HFD-520/SPM/JBona for /S/ 5/7/96

APPEARS THIS WAY
ON ORIGINAL

Pharmacia & Upjohn

Office of:
Donald R. Gieseker, Pharm.D.
Associate Director
U.S. Regulatory Affairs

Telephone No. (616) 833-8527
Facsimile No. (616) 833-8237

February 27, 1998

Mark Goldberger, M.D. , Director
Divsion of Special Pathogens and Immunologic Drug Products HFD-590
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

DESK COPY

Re: NDA 50-680, S-002
CLEOCIN® Vaginal Cream
(Clindamycin Phosphate Vaginal Cream USP)

Dear Dr. Goldberger,

In response to a fax sent from the Division on February 25, 1998 and a telephone contact on February 27, 1998, we are providing the text of the package insert (dated 2/27/98) for the above referenced supplement.

If you have any questions regarding this submission, please contact Donald R. Gieseker at (616) 833-8527. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Donald R. Gieseker, Pharm.D.
Associate Director
U.S. Regulatory Affairs

cc: Christina Chi, Ph.D., CSO

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

Pharmacia & Upjohn

Office of:
Donald R. Gieseker, Pharm.D.
Associate Director
U.S. Regulatory Affairs

Telephone No. (616) 833-8527
Facsimile No. (616) 833-8237

February 5, 1998

Mark Goldberger, M.D
Division of Special Pathogens and Immunologic Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 50-680, S-002
Cleocin® Vaginal Cream
(clindamycin phosphate)

General Correspondence

Dear Dr. Goldberger,

Enclosed, as requested during a teleconference held between Pharmacia and Upjohn and the Division on January 26th, 1998, are the text and supporting tables in Word 6.0 from amendment 006 submitted on December 17, 1997 to the above referenced NDA supplement. The disks have been checked for viruses and are virus free. There are two disks.

Disk 1 contains the text and the supporting tables for safety and efficacy. Under the main directory of NDA50680 are subdirectories for efficacy (301kb) and safety. The safety subdirectory is further subdivided into nonpreg (non-pregnant patients - 412kb) and preg (pregnant patients - 185kb). These would correspond to the data contained in appendices C, A and B, respectively, of the document submitted on December 17, 1997. The tables in each of these appendices are then listed under the appropriate subdirectory by the table number as it appeared in the original paper submission. One additional Table has been added to the non-pregnant data to provide the information on placebo adverse events which are included in the revised draft package insert. The text portion (27kb) of the 12/17/97 document is a file under the main directory.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

NDA 50-680
February 5, 1998
General Correspondence

Disk 2 includes the draft package insert which has been revised based on discussions at the January 26, 1998 teleconference. We are providing the document both as a paper copy and the electronic file (214kb) in Word 6.0.

If you have any questions regarding this submission, please contact Donald R. Gieseker at (616) 833-8527. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Donald R. Gieseker, Pharm.D.
Associate Director
U.S. Regulatory Affairs

DRG:law

Attachments

APPEARS THIS WAY
ON ORIGINAL

JUL 2 1998

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 2, 1998

FROM: Christina H. Chi, Ph.D. /S/

SUBJECT: Summary basis of approval of NDA 50-680 S Cleocin®3 Vaginal Cream

TO: The NDA file

The summary basis of approval of the second efficacy supplement of NDA 50-680 Cleocin® 3 Vaginal Cream is recorded in the Medical (clinical) Review section, page 36 (see attachment).

APPEARS THIS WAY
ON ORIGINAL

Conclusion

In this clinical study, Clindamycin Vaginal Cream 2% administered as a 5-gram dose once daily for three consecutive days, appear to be therapeutically equivalent to 5 grams of clindamycin vaginal cream administered once daily for 7 consecutive days in treating patients with bacterial vaginosis. Both regimens appear to be safe; in this study there was no clinically-significant difference in the incidence of adverse events between the two regimens although drug-related medical events were reported more frequently among patients treated for 3 days.

The results of this study suggest that a 3-day regimen of clindamycin is an appropriate therapy for the treatment of bacterial vaginosis however it does no offer an advantage to the consumer in either efficacy or safety when compared to the approved 7-day regimen.

Recommendation: The Applicant requests approval for the use of clindamycin vaginal cream for 3 or 7 days in treating non-pregnant patents with bacterial vaginosis. Based on the results of this clinical study and the results obtained in the US study that was submitted and analyzed previously, I recommend approval of this supplement to NDA 50-680 provided the labeling appropriately reflect the results obtained in both clinical studies.

/S/

Joseph K. Winfield, M.D.
Reviewing Medical Officer

cc: NDA 50-680
HFD-340
HFD-590
HFD-590-Dep/Dir/RAlbrecht
HFD-590/MO/JKWinfield
HFD-590 MO/DDavis
HFD-725/Stat/Dixon
HFD-590-/TmLdr/BLeissa /S/ 7/2/98
HFD-590/cs.file

Concurrence Only:
HFD-590/Div/Dir/MGoldberger /S/

DEBARMENT CERTIFICATION FOR NDA 50-680/S-002

CLEOCIN® Vaginal Cream Supplement

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Ann L Buckley

Ann L. Buckley
Executive Director,
Worldwide Regulatory Compliance

4 May 95
Date

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

BLA # 50-680 Supplement # 002 Circle one: SE1 (SE2) SE3 SE4 SE5 SE6

HFD 590 Trade and generic names/dosage form: Cleocin Vaginal Cream Clindamycin Phosph. Action: AP AE NA

Applicant Pharmacia & Upjohn Therapeutic Class Antifungals

Indication(s) previously approved Bacterial Vaginosis, 7 day treatment regimen

Pediatric information in labeling of approved indication(s) is adequate __ inadequate ✓ not supplied.

Proposed indication in this application Bacterial Vaginosis for 3 or 7 day treatment regimen

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply) None

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use. → No

__a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,

__ (2) Protocols were submitted and approved.

__ (3) Protocols were submitted and are under review.

__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from 3/1/1998 Proj. Mngr. (e.g., medical review, medical officer, team leader)

/S/ 3/1/1998

Signature of Preparer Date

Orig NDA/BLA #_____

HF_____/Div File

NDA/BLA Action Package

HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date MAY 11 1995

NDA No. 50-680

Donald A. Egge
The Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Attention: Donald A. Egge

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Cleocin Vaginal Cream

NDA Number: 50-680

Supplement Number: S-002

Date of Supplement: May 4, 1995

Date of Receipt: May 8, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

/S/

for: Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research

FORM FDA 3217d (12/91)

Extra

Pharmacia & Upjohn

Office of:
Hendrik J. de Koning Gans, M.D.
Director, Worldwide Regulatory Liaison

Telephone No. (616) 833-8516
Facsimile No. (616) 833-0409

1 July 1996

Division of Anti-Infective Drug Products
HFD-520
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 50-680/S-002
CLEOCIN® Vaginal Cream
(clindamycin phosphate 2%)

ATTN: Mary Fanning, M.D., Ph.D., FACP

Dear Dr. Fanning:

We are requesting a teleconference with Joseph Winfield M.D. (Medical Reviewer), Nancy Paul Silliman Ph.D. (Biomedical Statistician, Biometrics IV), and Daphne Lin Ph.D (Acting Team Leader, Biometrics IV) to discuss the non-approvable letter for CLEOCIN® Vaginal Cream (clindamycin phosphate, 2%) NDA 50-680/S-002 dated 7 May 1996.

At this meeting, we will address the issues of relative efficacy of the 3-vs 7-day regimens in pivotal study M/1115/0020 and the "Points to Consider Document" in regards to our clinical development program for the 3-day regimen of clindamycin phosphate vaginal cream.

Issue 1: Relative efficacy of 3-day vs 7-day regimens in pivotal study M/1115/0020.

Medical Officers (MO) Assessment: In regards to pivotal study M/1115/0020: "Comparison of Two Dosing Regimens of 2% Clindamycin Vaginal Cream for the Treatment of Bacterial Vaginosis - 3 Days vs 7 Days", the non-approvable letter states "The results obtained from our analysis of this study showed that the 3-day clindamycin phosphate regimen is statistically inferior to the 7-day regimen in the treatment of patients with bacterial vaginosis." The basis for this conclusion was discussed in detail in the MO's (Medical Officer) assessment report dated 7 May 1996, which stated all evaluable patients were assessed as being either cured or failures.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

The MO states "all patients who were considered as improved by the Applicant were assessed as a cure or failure by the MO. Additionally, to be considered a cure, all patients must have had a discharge that was negative for clue cells and negative for "fishy" amine odor with or without the pH returning to 4.5 or less." Treatment outcome using the above diagnostic criteria resulted in a cure rate of 74% and 86% for the 3-day and 7-day therapy respectively (see MO report, p. 37). Based on this analysis, the MO indicated there is a statistically-significant difference between the cure rates for the 3-day vs 7-day regimens.

P&U Response:

We do not agree with the MO's rationale to assess improved patients as being cured based on only two criteria ie. odor and clue cells. McCutchan[1] has reported in *Guidelines for the Evaluation of Anti-Infective Drug Products* that "For bacterial vaginosis, the resolution of symptoms (odor and/or discharge)and of microscopic abnormalities (clue cells) and the restoration of vaginal pH to <4.7 constitute a successful outcome." When the analysis for clinical outcome in pivotal study 020 is performed using all three diagnostic criteria (odor, pH<4.5, and clue cells) returning to normal and patient evaluability as defined in the protocol, the 3-day vs 7-day cure rate was determined to be 58.8% vs 62.5% respectively (Table 1). Our analysis indicate there is no statistical difference in the cure rate between the 3-day vs 7-day regimen. Additionally, when the analysis is performed using intent-to-treat (ITT), the 3-day vs 7-day cure rate was determined to be 48.8% vs 50.5% respectively (Table 1). Our analysis indicate there is no statistical difference in the cure rate between the 3-day vs 7-day regimen.

For consistency with the MO's analysis of protocol 020, we also assessed patients in the improved category as either cured or failure based on two diagnostic criteria. However, we assessed patients as being cured if both the presence of clue cells and pH returned to normal. Our decision to use pH and clue cells instead of odor and clue cells (as done by the MO) is based on relevant literature addressing selectivity of these methods for the diagnosis of bacterial vaginosis. Kaufman[2] reports that "A pH within the range essentially eliminates the possibility of trichomoniasis or G. *vaginalis* (bacterial vaginosis)." Amsel[3] also has reported that a pH of above 4.5 was found to best discriminate the normal from the abnormal state. Additionally, P-G Larsson [4] has reported that the detection of amine odor for the diagnosis of bacterial vaginosis to be a very subjective criterion in the clinical setting . False positives can be seen postcoitally possibly due to the fact that semen contains putrescine an amine present in vaginal secretions in women with BV[4]. When we reanalyzed pivotal study 0020, determining patient evaluability as described in the protocol, the cure rate was determined to be 59.5% and 63.3% for the 3-day and 7-day therapies respectively (Table 2). Again, there was no statistical difference in the two regimens. Additionally, when the analysis is performed using intent-to-treat (ITT), the 3-day vs 7-day cure rate was determined to be 49.8% vs 52.0% respectively (Table 2). Our analysis indicate there is no statistical difference in the cure rate between the 3-day vs 7-day regimen.

The efficacy of the 3-day and 7-day regimens as reported in Tables 1 & 2 are more in line with historical values for overall treatment outcome for pivotal 7-day clindamycin phosphate vaginal cream registration studies submitted in NDA 50-680[2]. Protocols M/1115/0010 and M/1115/0009 compared the 7-day therapy vs placebo and triple sulfonamide respectively. The observed clinical cure rates of 35% and 49% respectively are significantly lower than the 86% cure rate reported in the MO's assessment report. Clinical cure rates for the 7-day regimen are reported in the current package insert as 35% and 58% respectively[3]. We are therefore at a loss to explain why a 86% cure rate for the 7-day therapy (see p 87 MO's assessment report) should be considered reasonable based on previous pivotal studies and current product labeling.

Issue 2: Points to Consider Document

The non-approvable letter states that for a drug to receive approval for a shortened dosage regimen, two adequate and well controlled trials vs current therapy are needed. We were specifically referred to the *Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products*(p 28).

P&U Response:

In regards to this issue, the guideline states "Likewise, applications for treatment of infections with dosing regimen durations less than generally approved for that infection should ordinarily contain two statistically adequate and well-controlled trials." The guidance document does not specifically indicate that two adequate and well controlled trials comparing the current vs shortened therapy are required for approval. For our clinical program we referred to the current FDA Guideline for *The Format and Content of The Clinical and Statistical Sections for New Drug Application*, which require at least two adequate and well controlled studies. Pivotal studies 0020 and 0027 have both demonstrated the safety and effectiveness of the 3-day regimen of clindamycin phosphate vaginal cream. Additionally, we also refer to the Gynecologic infections section of the *Points to Consider* document which states "One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested." As discussed above, our analysis of pivotal study 0020 has demonstrated the 3-day vs 7-day therapies are statistically equivalent.

Conclusions

Our analysis of protocol M/1115/0020 assessing patients as cured if all three diagnostic criteria (pH, clue cells and odor) returned to normal, indicate the 3-day vs 7-day regimens are statistically similar. When patients in the improved category are assessed using pH and clue cells as diagnostic criteria, there is no statistically significant difference between the 3-day vs 7-day therapies. Additionally, pivotal study M/1115/0027 has demonstrated the 3-day therapy of clindamycin phosphate to be safe and effective. Therefore, per the current FDA Guidelines we have

demonstrated safety and efficacy of clindamycin vaginal cream in two adequate and well controlled clinical studies in support of the 3-day dosing regimen. We therefore request approval of NDA 50-680/S-002.

We wish to arrange a teleconference for the week of July 8, 1996. Please contact me at (616) 833-8516 regarding dates and times that are suitable to the Division. Thank you for your consideration of our request.

Sincerely,

Hendrik deKoningGans, M.D.
Pharmacia & Upjohn
Regulatory Liaison Manager

APPEARS THIS WAY
ON ORIGINAL

References:

1. J. Allen McCutchan, Allan R. Ronald, Lawrence Corey, and H.Hunter Handafield; Evaluation of New Anti-Infective Drugs for the Treatment of Vaginal Infections; Clinical Infectious Diseases 1992; 15(Suppl 1):S115-22 (Appendix 1).

2. Kaufman, RH; Establishing a correct diagnosis of vulvovaginal infection; Am J Obstet Gynecol 1988; 158:986-8 (Appendix 2).

3. Richard Amsel et. al; The American Journal of Medicine; Vol 74, p. 14-22 (1983); Nonspecific Vaginitis-Diagnostic Criteria and Microbial and Epidemiologic Associations (Appendix 3).

4. Bacterial Vaginosis: Diagnosis, treatment and significance in gynecological practice, P-G Larsson; Linkoping University Medical Dissertations, No. 339 (1991) p. 28.

5. Original NDA for Cleocin Vaginal Cream; NDA 50-680, Item 8, Volume 1, p 38, Table 8.D-14 (Appendix 4).

6. Current Package Insert for CLEOCIN Vaginal Cream (clindamycin phosphate, 2%) (Appendix 5).

Table 1
Clindamycin phosphate vaginal Cream
Pivotal Study M/1115/ 0020
3-day vs 7-day regimens
(Using pH, Clue Cells and Amine Odor for Defining Clinical Outcome)

Diagnostic Criteria	Patient Subset	Clinical Outcome	3-Day Cream	7-Day Cream	95% 2-Sided CI for Difference
			n (%)	n (%)	
pH, CC, AO	P&U Eval	Cured	77/131 (58.8%)	80/128 (62.5%)	(-16.4, 8.9)
		Failed	54/131 (41.2%)	48/128 (37.5%)	
	FDA Eval	Cured	93/159 (58.5%)	94/152 (61.8%)	(-14.9, 8.2)
		Failed	66/159 (41.5%)	58/152 (38.2%)	
	ITT	Cured	100/205 (48.8%)	103/204 (50.5%)	(-11.9, 8.5)
		Failed	105/205 (51.2%)	101/204 (49.5%)	

pH (cure if ≤ 4.5), CC = Clue Cells (cure if absent), AO = Amine Odor (cure if absent)
The FDA Eval subset is an approximation (allows follow-up visits within +/- 7 days of schedule and nonconfirmatory pretreatment gram stain results)
ITT=Intent to Treat

Elevated pH, ≤ 4.5 is the least important, then (discharge) odor
Clue cells is the most important determinant

all 3 → cured
2 → improved
1 or more: failure

APPEARS THIS WAY
ON ORIGINAL

If there is: Clue cells → failed
" " + odor → failed

Table 2
Clindamycin phosphate vaginal Cream
Pivotal Study M/1115/ 0020
3-day vs 7-day regimens
(Using pH and Clue Cells for Defining Clinical Outcome)

Diagnostic Criteria	Patient Subset	Clinical Outcome	3-Day Cream n (%)	7-Day Cream n (%)	95% 2-Sided CI for Difference
pH, CC	P&U Eval	Cured	78/131 (59.5%)	81/128 (63.3%)	(-16.4, 8.9)
		Failed	53/131 (40.5%)	47/128 (36.7%)	[redacted]
	FDA Eval	Cured	94/159 (59.1%)	97/152 (63.8%)	(-16.1, 6.8)
		Failed	65/159 (40.9%)	55/152 (36.2%)	[redacted]
	ITT	Cured	102/205 (49.8%)	106/204 (52.0%)	(-12.4, 8.0)
		Failed	103/205 (50.2%)	98/204 (48.0%)	[redacted]

pH (cure if≤ 4.5), CC = Cure Cells (cure if absent)
The FDA Eval subset is an approximation (allows follow-up visits within +/- 7 days of schedule and nonconfirmatory pretreatment gram stain results).
ITT=Intent to Treat

Clue cells is the most important determinant.

PHARMACIA & UPJOHN, INC. FACSIMILE

7000 Portage Road
Kalamazoo, MI 49001
Facsimile #: (616) 833-0409

60-1982 11/95

TO: Dr. Christina Chi
FDA
Division of Anti-Infective Drug Products

DATE: July 2, 1996

FACSIMILE #: (301) 827-2325

SUBJECT: CLEOCIN® Vaginal Cream - NDA 50-680/S-002
Request for Teleconference

FROM: Peter DiRoma

PHONE: (616) 833-8070

MESSAGE:

Dear Dr. Chi:

Please find enclosed a copy of the cover letter that was sent to Mary Fanning M.D., Ph.D. , FACP at The Division of Anti-Infective Drug Products on 1 July 1996 regarding the non-approvable letter for NDA 50-680/S-002 dated 7 May 1996. We are requesting a teleconference for the week of July 8th to discuss the Division's rationale for non-approval.

Please contact me at (616) 833-8070 or Kathy Steindler at (616) 833-8178 regarding scheduling of this teleconference.

Thank you for your consideration of our request.

Sincerely,

Peter DiRoma

Peter DiRoma
Regulatory Affairs
