AM
SE2-002
NDA SUPPL AMENDMENT

Extra

Pharmacia & Upjohn

ORIGINAL

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

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

August 28, 1997

Mark Goldberger, MD
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Center for Drug Evaluation
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Md 20850

Re: Amendment 5
NDA 50-680/S-002
Cleocin® Vaginal Cream
(clindamycin phosphate 2%)

Dear Dr. Goldberger,

We are amending the above referenced supplement in response to a not-approvable letter dated May 7, 1996. This submission contains an adequate and well controlled trial conducted in Europe in patients with bacterial vaginosis treated with either a 7 day or a 3 day regimen of Cleocin vaginal cream.

The body of the report, protocol and summary statistical tables are included in the first volume of the application. The last two volumes contain the case report forms for subjects who were discontinued due to an adverse event. There were no deaths in this study.

If you have any questions regarding this submission, please contact Donald R. Gieseker at (616) 833-8527. Please send correspondence addressed to Unit 0635-298-110.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Donald R. Gieseker

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

DRG:crdt
Attachments
cc: C. Chi, Ph.D.

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

Telephone (616) 833-4000

Contents

TR 9150-97-004

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

January 30, 1998

Mark Goldberger M.D. , Director
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,

Reference is made to a teleconference held between the Division and Pharmacia and Upjohn for the above referenced NDA supplement on Janauary 26, 1998. This letter is to confirm agreements made during and after the teleconference.

Pharmacia and Upjohn accepts modifying the Dosage and Adminsitration section of the package insert to - 3 or 7 day use of Cleocin vaginal cream in non-pregnant patients - as proposed by the Division.

The Division agreed to the Indication and Usuage section of the insert for pregnant patients to include "second and third trimester".

The Division agreed that in the Clinical Studies section of the package insert, the cure rates for BV, would be presented using the two criteria of absence of clue cells and amine odor.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shanaya for

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

DRG:kmv
Attachments

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

December 17, 1997

Mark Goldberger, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research HFD-590
Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 50-680/ S-002
Cleocin® Vaginal Cream
(clindamycin phosphate)

Amendment 006

Dear Dr. Goldberger,

Enclosed is the modified draft package insert for this supplement in support of the indication for the treatment of Bacterial Vaginosis using a 3 day regimen. The primary sections modified from the original draft insert submitted with the supplement are related to the adverse event section to include data from Protocol 0048 (Submitted in Amendment 005 on August 28, 1997 in response to a not approvable letter) and because of a new dictionary being used by Pharmacia and Upjohn to code adverse events. The clinical trials portion of the insert has also been modified to incorporate the cure rates for all 3 day cream studies using the criteria of the absence of clue cells and amine odor.

The supporting documentation for changes to the adverse event section and clinical trials are included in this amendment. The specific tables have been referenced in the annotated package insert. As requested, we have also included the four copies of labeling for the package and the tube which were previously approved in supplement 003 and the draft package insert in the archival copy.

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:kmv
cc: Christina Chi, Ph.D., CSO
Attachments

Pharmacia & Upjohn
Kalamazoo, MI 49001-0199
USA
Telephone (616) 833-4000

AM
SE2-002
NDA SUPPL AMENDMENT

Pharmacia & Upjohn

ORIGINAL

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

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

August 28, 1997

Mark Goldberger, MD
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Center for Drug Evaluation
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, Md 20850

Re: Amendment 5
NDA 50-680/S-002
Cleocin® Vaginal Cream
(clindamycin phosphate 2%)

Dear Dr. Goldberger,

We are amending the above referenced supplement in response to a not-approvable letter dated May 7, 1996. This submission contains an adequate and well controlled trial conducted in Europe in patients with bacterial vaginosis treated with either a 7 day or a 3 day regimen of Cleocin vaginal cream.

The body of the report, protocol and summary statistical tables are included in the first volume of the application. The last two volumes contain the case report forms for subjects who were discontinued due to an adverse event. There were no deaths in this study.

If you have any questions regarding this submission, please contact Donald R. Gieseker at (616) 833-8527. Please send correspondence addressed to Unit 0635-298-110.

Sincerely,

PHARMACIA & UPJOHN COMPANY

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

DRG:crdt
Attachments
cc: C. Chi, Ph.D.

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

Telephone (616) 833-4000

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

Office of:
Kathy A. Steindler, B.A.
Regulatory Manager
Regulatory Affairs-US Market Company

Telephone No. (616) 833-8178
Facsimile No. (616) 833-0409

July 9, 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, MD 20850

Attn: Dr. Christina Chi

Re: NDA 50-680
CLEOCIN® Vaginal Cream
(clindamycin phosphate 2%)

General Correspondence

Dear Dr. Chi:

The Regulatory Manager, Peter J. DiRoma, has been your primary contact with Pharmacia & Upjohn (formerly The Upjohn Company) to date, concerning the product CLEOCIN Vaginal Cream (clindamycin phosphate 2%) and corresponding NDA 50-680. Please note that Kathy A. Steindler has assumed this responsibility as the primary contact. She can be contacted: by telephone at (616) 833-8178 or by fax at (616) 833-0409.

Thank you for your attention to this notification of change in responsibility.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Kathy A. Steindler
Regulatory Manager

KAS:SEH

[redacted] 091271 [redacted]

CBCAZN

ORIGINAL

Pharmacia & Upjohn

Office of:
Kenneth F. King, Ph.D.
Vice President
Regulatory Affairs

Telephone No. (616) 833-0856
Facsimile No. (616) 833-8237

June 26, 1996

NEW CORRESPONDENCE

Division of Anti-Infective Drug Products HFD-520
Center for Drug Evaluation and Research
Document Control Rooom
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

BEST POSSIBLE COPY

Re: NDA 50-680
CLEOCIN ® Vaginal Cream
(clindamycin phosphate)

COMPANY NAME CHANGE

Sir/Madam:

This is to notify you that, effective June 11, 1996, Pharmacia & Upjohn Company, K[illegible]azoo, Michigan, became the holder of the application cited above. Pharmacia & U[illegible]n Company is a new company formed as a result of the merger of the former Upjohn Company, Kalamazoo, Michigan and the former Pharmacia Inc, Dublin, Ohio. All applications at the Food and Drug Administration held by the two former companies are now held by the new company.

Consistent with 21 CFR §314.72, we wish to advise you that Pharmacia & Upjohn Company commits to any agreements, promises and conditions contained in the application cited above and is in possession of a complete copy of the approved application including supplements and records that are required to be kept under §314.81.

A copy of a completed form 356h, reflecting the new name, is provided for the file.

Please contact Robert A. Paarlberg at (616) 833-0646 if you have any questions about this notification.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Kenneth F. King, Ph.D.
Vice President
Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
LETTER NAI MEMO
INITIALS DATE

CENTER FOR DRUG
REC'D
JUN 28 1996
HFD
EVALUATION AND RESEARCH

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

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

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

May 9, 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%)

Attention: **Mary Fanning, M.D., Ph.D., FACP**

Dear Dr. Fanning:

This letter is in reference to your "not approvable" letter dated May 7, 1996 concerning NDA 50-680/S-002, submitted to the agency on May 4, 1995 with amendments on June 1, 1995, June 8, 1995, June 29, 1995, and July 7, 1995 and correspondence on February 8, 1996 and March 13, 1996.

We are notifying you under the provisions of 21 CFR 314.120 (a) that we intend to file an amendment to NDA 50-680/S-002. Likewise, we are requesting an opportunity to meet with you to discuss the rationale and decision to issue the "non approvable" letter. We are contacting the Project Manager, Dr. Christina Chi, to arrange such a meeting expeditiously.

Please contact Peter J. DiRoma at (616) 833-8070 should you have any questions concerning this correspondence.

Sincerely,

THE UPJOHN COMPANY

Peter Di Roma /for

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

cc: Christina H. Chi, Ph.D.

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

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

Telephone No. (616) 329-8516
Facsimile No. (616) 329-5409

signed off
Mar 15, 96

March 13, 1996

Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room #12B-30
5600 Fishers Lane
Rockville, MD 20857

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

REQUEST FOR TELECONFERENCE

Dear Sir/Madam:

We are requesting a teleconference with the FDA to discuss labeling for CLEOCIN® Vaginal Cream (clindamycin phosphate, 2%) NDA 50-680/S-002 now under review with the Division of Anti-Infective Drug Products.

Issue #1: CLEOCIN® Vaginal Cream (CVC) was approved by the FDA for treatment of bacterial vaginosis (BV) on August 11, 1992. The NDA contained four clinical studies establishing the efficacy of a 7-day regimen of CVC to treat BV (protocols M/1115/009, 0010, 0011, and 0017) Subsequently, a supplemental NDA was submitted on December 29, 1992 to support a labeling change for the use of CVC to treat BV during the second trimester of pregnancy. This supplement contained clinical data from protocol M/1115/006 which established the safety and efficacy of a 7-day regimen to treat BV during the second trimester of pregnancy. In an amendment to this supplement dated January 27, 1995 we provided a table comparing overall treatment outcome for pregnant patients (protocol M/1115/006) vs nonpregnant patients from the original NDA (protocols M/1115/009, 0010, 0011, and 0017) for the first and second follow-up visits. This table (appendix 1) shows that pregnant patient outcome is comparable to the nonpregnant patient outcome when comparing parallel data. Per the February 28, 1995 approvable letter for this supplement, the clinical cure rate for pregnant patients was revised upward to 50% (65/129) which was based on cure at second follow-up. This supplement was approved by the FDA on October 5, 1995.

Supplemental NDA 50-680/S-002 was submitted to the FDA on May 4, 1995 to support a labeling change from 7 day to a "3 to 7" consecutive day dosage regimen. This supplement was submitted while the use in pregnancy supplement was under FDA

review. Safety and efficacy of CVC in a 3-day regimen was evaluated in two placebo controlled studies and one active controlled study comparing the 3-day CVC regimen with the approved 7-day regimen of CVC. Pregnant women were not included in the above studies. In this supplement, we provided a table comparing overall treatment outcome from the 3-day pivotal studies with the 7-day arm of protocol 0020 (appendix 2). These data indicate, based on the overall treatment outcome, CVC administered once daily for 3 days is statistically more effective than placebo and equivalent in efficacy to the 7-day CVC regimen for the treatment of BV.

A safety update for the pending labeling supplement was submitted on February 8, 1996. The safety update consisted primarily of medical event data collected from an ongoing non-IND study to evaluate the safety of a 3-day regimen of CVC in pregnant women (protocol # M/1115/0025). Observed medical events did not differ from those reported in the pending 3-day supplement and the observed medical events judged to be associated with CVC do not present a substantial risk to pregnant patients. A line listing of drug related medical events by treatment groups for pregnant women (appendix 3) was included in the safety report. Out of the 182 pregnant patients treated with CVC for 3 days 15 (8.2%) had at least one medical event related to treatment. For comparison, safety data from protocol M/1115/006 (appendix 4) reported that 40 of 180 (22%) pregnant patients treated with CVC for 7 days had at least one medical event related to treatment. It is likely that exposure to medication for a longer period of time (7 days rather than 3 days) accounts for the higher incidence of drug-related medical events.

Additionally, available literature indicates that the same change in vaginal flora associated with BV occurs both in pregnant and non-pregnant patients (appendix 5-8). Since there is similar microbial pathology, 3-day therapy of CVC should be effective against organisms associated with BV in both pregnant as well as nonpregnant patients.

Question #1: Does the FDA agree that the data discussed above support the safety and efficacy of a 3-day treatment regimen of CVC for the treatment of BV in both pregnant and nonpregnant patients?

*Question #2: Will the FDA agree not to restrict the 3-day regimen to non-pregnant patients in the **DOSAGE and ADMINISTRATION** section?*

Issue #2: We have reviewed CFR 201.57 (i) which pertains to specific requirements and formats for labeling when a drug is used during pregnancy. The regulation indicates that if clinical studies have failed to demonstrate a risk to patients during the first trimester and there is no evidence of risk in later trimesters, labeling can indicate studies have not shown the specific drug increases risk of fetal abnormalities if administered during all trimesters. We believe the scientific basis for this labeling format is applicable to current CVC labeling. No evidence of risk to patients when CVC is used during the second trimester was demonstrated in clinical data contained in the supplemental NDA approved by the FDA. We do not believe there is evidence of additional risk when the drug is used during the 3rd trimester.

Question # 3: Will the FDA agree to our request to extend the labeling in the

INDICATIONS AND USAGE *section to include second and third trimester?*

We request the opportunity to discuss our labeling proposal and rationale with the FDA at your earliest possible convenience.

Please contact Peter J. DiRoma at (616) 329-8070 or (616) 833-8070 to schedule a teleconference.

Very truly yours,

THE UPJOHN COMPANY

Peter DiRoma

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

Appendix

1. Table 1. Overall Treatment Outcome pregnant vs nonpregnant patients, Table 2. Outcomes at First and Second Follow-up Visits for Protocols 006, 009, 011 and, 0017; Amendment No.2 NDA 50-680/S-001 submitted January 27, 1995

2. Table 8.D-6. 3-Day Studies: Overall Treatment Outcome; from supplemental NDA 50-680/S-002; Item 8, Vol. 1, p. 28 submitted May 4, 1995

3. Table A-10; Clindamycin Vaginal Cream, Safety Update Report; Item 9, Vol. 1, pp.107-109 submitted February 8, 1996

4. Table 8.D-25. Medical Event Summary in Pregnant Women; Item 8, Vol. 1, p. 59 in NDA 50-680/S-002 submitted May 4, 1995

5. Gale B. Hill, PhD, and Charles H. Livengood III, MD; Bacterial vaginosis-associated microflora and effects of topical intravaginal clindamycin

6. Sharon L. Hiller, Marijane A. Krohn, Ph.D, Robert P. Nugent, Ph.D. and Ronald S. Gibbs, MD , for the Vaginal Infections and Prematurity Study Group; Characteristics of three vaginal flora patterns assessed by Gram stain among pregnant women; Am. J. Obstet Gynecol, pp. 938-944, March 1992

7. H.M. McDonald, J.A.O'Loughlin, P.Jolley, R.Vigneswaran, P.J.McDonald; Prenatal microbial risk factors associated with preterm birth; British Journal of Obstetrics and Gynecology, March 1992, Vol 99, pp 190-196

8. Helen M. McDonald, John A. O'Laughlin, Patricia T.Jolley, Rasiah Vigneswaren, and Peter J.McDonald; Changes in Vaginal Flora during Pregnancy and Association with Preterm Birth; Journal of Infectious Diseases, Vol 170 p724-728, 1994

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

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

Telephone No. (616) 329-8516
Facsimile No. (616) 329-5409

February 8,1996

Division of Anti-Infective Drug Products
HFD-520
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville MD 20850

ATTN: Dr. Christina Chi

SAFETY UPDATE

RE: NDA 50-680/S-002

CLEOCIN® Vaginal Cream
(clindamycin phosphate 2%)

Dear Dr. Chi:

As required by 21 CFR 314.50(d)(5)(vi)(b), we are submitting a safety update for our supplemental NDA 50-680/S-002, CLEOCIN® Vaginal Cream (clindamycin phosphate 2%). This submission contains updated safety information as requested.

This safety update focuses primarily on medical event data collected from one ongoing study which evaluates the safety of the 3-day regimen in pregnant women (M/1115/0025). Data provided are cumulative, representing all demographic and medical event data collected from the beginning of the study through the date tables were produced on February 5, 1996. Additional supportive safety data is provided from six additional ongoing studies which use other than a 3-day dosing regimen. Worldwide spontaneous medical event data and published medical literature are also provided.

The most frequently reported adverse medical event reported in protocol 0025 and the worldwide spontaneous medical event database occurs in the genital tract, gastrointestinal system, and in the dermatologic body system. This does not differ from that reported in the Supplemental NDA. The observed medical events judged to be associated with clindamycin vaginal cream do not present substantial risk to patients. The safety data continue to demonstrate that clindamycin vaginal cream is a

well-tolerated and safe therapy for the treatment of bacterial vaginosis.

This submission consists of a total of four volumes

Item 9	Safety Update - 2 Volumes
Item 12	Case Report Forms - 2 Volumes

Please contact Peter DiRoma at (616) 329-8070 if you have any questions regarding the contents of this submission.

Sincerely yours,

Peter DiRoma for

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

cc: Dr. Joseph K. Winfield

THE UPJOHN COMPANY

7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001-0199, U.S.A.

Office of:
DONALD A. EGGE, *Director*
Regulatory Affairs - Marketed Products
Telephone No. (616) 329-8097
Facsimile No. (616) 329-5409

August 25, 1995

Division of Anti-Infective Drug Products
Center for Drug Evaluation II, HFD-521
Room#12B-05
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

General Correspondence:
Letter to correct August 14, 1995
Correspondence

Dear Sir/Madam:

Please disregard the August 14, 1995 communication. On August 4, 1995 a teleconference was made by The Upjohn Company (Ilze Antons and Peter DiRoma) with Dr. Christina H. Chi, Project Manager, Division of Anti-Infective Drug Products. Upjohn requested that submission of the Safety Update for NDA 50-680/ S-002 for CLEOCIN Vaginal Cream ® (Clindamycin phosphate 2%) could be deferred until notification from the FDA. Dr. Chi agreed with this proposal and indicated that the Anti-Infective Drug Division will coordinate the request for the Safety Update with review of the submission.

If you have any questions, please contact Peter DiRoma at (616) 329-8070.

Very truly yours,

THE UPJOHN COMPANY

Peter DiRoma for

Donald A. Egge, Director
Regulatory Affairs - Marketed Products

cc: Dr. Christina H. Chi, Project Mgr.
Division of Anti-Infective Drug Products

Peter Di Roma, Regulatory Manager

THE UPJOHN COMPANY

7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001-0199, U.S.A.

Office of:
DONALD A. EGGE, *Director*
Regulatory Affairs - Marketed Products
Telephone No. (616) 329-8097
Facsimile No. (616) 329-5409

August 4, 1995

Christina H. Chi, Ph.D.
Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drug Evaluation II, HFD-520
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 50-680
CLEOCIN® Vaginal Cream
(Clindamycin Phosphate 2%)

General Correspondence

Dear Dr. Chi:

Per your request of August 2, 1995, I would like to inform you that I am assuming regulatory responsibility from Ilze Antons for NDA 50-680 CLEOCIN® Vaginal Cream (Clindamycin phosphate 2%). I may be contacted at the above address and my phone number is (616) 329-8070. Please do not hesitate to call me if I can assist the FDA with review of our supplements to this NDA.

Thank you for the opportunity for Ilze and me to talk with you on August 2. I look forward to working with you in the future.

Best regards,

Peter DiRoma for

THE UPJOHN COMPANY

Donald A. Egge, Director
Regulatory Affairs - Marketed Products

cc:: Ilze K. Antons

THE UPJOHN COMPANY

7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001-0199, U.S.A.

Stat. data

Office of:
DONALD A. EGGE, *Director*
Regulatory Affairs - Marketed Products
Telephone No. (616) 329-8097
Facsimile No. (616) 329-5409

July 7, 1995 **DESK COPY**

Division of Anti-Infective Drug Products
Center for Drug Evaluation II, HFD-520
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

AMENDMENT #4

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

Dear Sir/Madam:

This correspondence is in response to your June 16, 1995 facsimile requesting Chemistry, Microbiology and Statistical information to support fileability of our May 4, 1995 submission to NDA 50-680 which provides for a 3-day dosing regimen for the treatment of Bacterial vaginosis.

On June 27, 1995 we were notified via telephone that our May 4 submission was separated into two supplements and that the *efficacy* portion should be contained within S-002. On June 29, 1995 we provided responses to Issues 2,3,4 and 6 for the statistical information requested in your June 16 correspondence as Amendment #3 to the NDA 50-680/S-002. We are now providing datasets requested in Issue 1 and the complete response to Issue 5 as promised in our June 29 correspondence.

Should you have any additional questions concerning the contents of this amendment, please contact Ilze K. Antons at 616-329-8008.

Sincerely,

THE UPJOHN COMPANY

Ilze K. Antons for.

Donald A. Egge, Director
Worldwide Regulatory Affairs-Marketed Products

Desk Copies: Division of Anti-Infective Drug Products
[redacted]

Amendment 4

THE UPJOHN COMPANY

7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001-0199, U.S.A.

DESK COPY

Office of:
DONALD A. EGGE, *Director*
Regulatory Affairs - Marketed Products
Telephone No. (616) 329-8097
Facsimile No. (616) 329-5409

June 29, 1995

Division of Anti-Infective Drug Products
Center for Drug Evaluation II, HFD-520
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

AMENDMENT #3

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

Dear Sir/Madam:

This correspondence is in response to your June 16, 1995 facsimile requesting Chemistry, Microbiology and Statistical information of our May 4, 1995 submission to NDA 50-680 to provide for a 3-day dosing regimen for the treatment of Bacterial vaginosis.

On June 27, 1995 we were notified via telephone that our May 4 submission was separated into two supplements and that the *efficacy* portion should be contained within S-002. As a result, we are now providing responses to Issues 2,3,4 and 6 for the statistical information requested in your June 16 correspondence as Amendment #3 to the NDA 50-680/S-002. Please note that the datasets requested in Issue 1 and the complete response to Issue 5 of your June 16, 1995 correspondence will be provided to you as soon as they have been finalized. We expect this task to be completed within the next two weeks.

Under separate cover we will submit the Chemistry and Microbiology responses as Amendment #1 to NDA 50-680/S-003.

Should you have any questions concerning the contents of this amendment, please contact Ilze K. Antons at 616-329-8008.

Sincerely,

THE UPJOHN COMPANY

for

Donald A. Egge, Director
Worldwide Regulatory Affairs-Marketed Products

Desk Copies: Division of Anti-Infective Drug Products
attn: Ms. Christina Chi, CSO

Christina

ORIGINAL

To: Winfield
Bioptram
Sheldon

THE UPJOHN COMPANY

7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001-0199, U.S.A.

Office of:
DONALD A. EGGE, *Director*
Regulatory Affairs - Marketed Products
Telephone No. (616) 329-8097
Facsimile No. (616) 329-5409

June 8, 1995

Division of Anti-Infective Drug Products
Center for Drug Evaluation II, HFD-520
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

S 002
SUPPL NEW CORRES

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

Dear Sir/Madam:

Under the provisions of 21CFR§314.70, on May 4, 1995 we submitted a supplement to NDA 50-680 to provide for a 3-day dosing regimen for the treatment of Bacterial vaginosis consisting of 40 volumes that included the Application Summary, pertinent container-closure information, labeling and the supportive clinical documentation. In a telephone conversation on May 25, 1995 with Christina Chi, CSO, we were requested to provide Items 5 and 7 for review as soon as possible. Item 5 was sent to the FDA on June 1, 1995. On June 7, we were requested to also provide Item 6. Enclosed is the following documentation:

VOLUME NO.	ITEM
1.4B	6. Review of published data from date of original submission to present. No in-house data has been generated for this section of the NDA since the original submission of NDA 50-680.
1.4C	7. Review of published data from date of original submission to present. No in-house data has been generated for this section of the NDA since the original submission of NDA 50-680.

Should you have any questions concerning the contents of this supplement, please contact Ilze K. Antons at 616-329-8008.

Sincerely,

THE UPJOHN COMPANY

Donald A. Egge, Director
Worldwide Regulatory Affairs-Marketed Products

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 12 1995
HFD-520

Desk Copies: Division of Anti-Infective Drug Products
attn: Ms. Christina Chi, CSO (Items 6 and 7, Vols. 1.4B and 1.4C)
Mr. James Bona (Item 6, Vol. 1.4B)
Dr. Al Sheldon (Item 7, Vol. 1.4C)

THE UPJOHN COMPANY

7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001-0199, U.S.A.

Office of:
DONALD A. EGGE, *Director*
Regulatory Affairs - Marketed Products
Telephone No. (616) 329-8097
Facsimile No. (616) 329-5409

June 1, 1995

Division of Anti-Infective Drug Products
Center for Drug Evaluation II, HFD-520
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

AMENDMENT #1

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

Dear Sir/Madam:

Under the provisions of 21CFR§314.70, on May 4, 1995 we submitted a supplement to NDA 50-680 to provide for a 3-day dosing regimen for the treatment of Bacterial vaginosis consisting of 40 volumes that included the Application Summary, pertinent container-closure information, labeling and the supportive clinical documentation. In a telephone conversation on May 25, 1995 with Christina Chi, CSO, we were requested to provide Items 5 and 7 for review as soon as possible. Enclosed is the following:

VOLUME NO.	ITEM
1.4A	5. Review of in-house and published data from date of original submission to present.

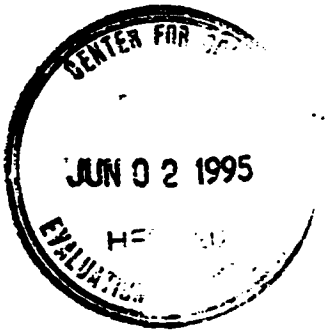
We will be providing Item 7 as soon as we have completed the requested review of both in-house and published data.

Should you have any questions concerning the contents of this supplement, please contact Ilze K. Antons at 616-329-8008.

Sincerely,

THE UPJOHN COMPANY

Donald A. Egge, Director
Worldwide Regulatory Affairs-Marketed Products



Desk Copy: Division of Anti-Infective Drug Products
attn: Ms. Christina Chi, CSO

DUPLICATE

THE UPJOHN COMPANY

7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001-0199, U.S.A.

Office of:
DONALD A. EGGE, *Director*
Regulatory Affairs - Marketed Products
Telephone No. (616) 329-8097
Facsimile No. (616) 329-5409

May 4, 1995

Division of Anti-Infective Drug Products
Center for Drug Evaluation II, HFD-520
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 50680 REF. NO. _____
SE1

SUPPLEMENT

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

Dear Sir/Madam:

Under the provisions of 21CFR§314.70, we are submitting a supplement to NDA 50-680 to provide for a 3-day dosing regimen for the treatment of Bacterial vaginosis. This supplement consists of 40 volumes as described below:

VOLUME NO.	ITEM
1.1	Cover Letter *Attachments:* Form FDA 356h User Fee Cover Sheet Field Copy Statement Debarment Statement Pagination System 1. Overall Table of Contents 2. Application Summary
1.2-1.3	3. Information is provided for a supplement to NDA 50-680 for CLEOCIN™ Vaginal Cream which describes tubes of a smaller size to be used for the 3-day treatment, as well as tubes for product samples. The composition and specifications of these container-closure systems as well as stability data are provided.
1.4	4. Draft labeling for the insert, label and carton
1.5-1.21	8. Three clinical trials were completed to support the 3-day dosing regimen with Clindamycin Vaginal Cream for the treatment of Bacterial vaginosis. A total of 687 women with Bacterial vaginosis were enrolled in the three 3-day trials and 685 received study drug; 339 were randomized to the 3-day

Clindamycin Vaginal Cream regimen and 346 were randomized to the control arms. In the control arms, 142 patients received placebo in Protocols 0021 and 0027, and 204 patients received the 7-day CVC regimen as the active control in Protocol 0020. All 687 patients are included in the analysis of safety.

1.22-1.38 10. Duplicate of Item 8.

1.39 11. Case report tabulations for the 3 registration studies are provided.

1.40 12. Case report forms are provided for patients who discontinued treatment due to a medical event or who experienced a serious medical event in the 3 registration studies.

We are providing an archival copy of all volumes listed above and review copies for ITEMS 3,4,8,and 10. Only archival copies are being provided for ITEMS 11 and 12. Copies of the Index/Application Summary volume (Volume 1.1) are found in Volumes 1.3, 1.21 and 1.38.

Should you have any questions concerning the contents of this supplement, please contact Ilze K. Antons at 616-329-8008.

Sincerely,

THE UPJOHN COMPANY

for

Donald A. Egge, Director
Worldwide Regulatory Affairs-Marketed Products

Desk Copy: Division of Anti-Infective Drug Products
attn: Ms. Christina Chi, CSO

Ch.
520

NDA 50-680/S-002

MEMORANDUM OF TELECON

DATE : May 8, 1996

DRUG : Cleocin® Vaginal Cream
(clindamycin phosphate 2%)

BETWEEN : FDA : Division of Anti Infective Drug Products
James Bona, R.Ph., M.P.H., Sup. Proj. Mngr.
Christina Chi, Ph. D., Project Manager.

Sponsor : Upjohn Company
Peter DiRoma, Regulatory Manager

SUBJECT : NDA 50-680/S-002 Action letter.

The Agency informed the sponsor that their application had been reviewed and that a nonapproval letter was issued yesterday, May 7, 1996. The reasons for the Agency's decision and the deficiencies were described in the letter. A copy of the letter would be faxed while the original one would be sent through regular mail.

The Agency would be glad to accommodate questions and requests of explanation at a future date.

The telecon was concluded with the understanding that the sponsor would inform us of their decision.

APPEARS THIS WAY
ON ORIGINAL

/S/

Christina H. Chi, Ph.D.

cc: Orig. NDA

HFD-520
Participants
HFD-520/SPM/JBona
HFD-520/PM/CChi (2)
Record of Telecon
CChi:5/8/96

Concurrence Only:

HFD-520/SPM/JBona 5/10/96