CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-015

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

JUL 21 1994

Review of Final Printed Labeling

NDA 19-537/S-013
NDA 19-537/S-015

DATE OF SUBMISSION: June 9, 1994,

REVIEW STARTED: June 24, 1994
REVIEW COMPLETED: June 24, 1994
REVIEW REVISED: July 20, 1994

APPLICANT: Miles Inc. Pharmaceutical Division.
West Haven, CT 06516

DRUG: Generic - ciprofloxacin
Trade - CIPRO(R)

DOSAGE FORM: Tablets

ROUTE OF ADMINISTRATION: Oral

Description of Submission:

Final printed labeling (FPL) submitted in response to approvable letters issued June 4, 1993, for S-013; and April 16, 1993, for S-015.

Review and Comments:

DOSAGE AND ADMINISTRATION

It was requested in the April 16, 1993, approvable letter that the third paragraph, under the **DOSAGE AND ADMINISTRATION** section, be revised to read:

> "The recommended adult dosage for infectious diarrhea — typhoid fever is 500 mg every 12 hours."

Applicant's revision:

> "The recommended adult dosage for Infectious Diarrhea or Typhoid Fever is 500 mg every 12 hours."

The use of the word "or" instead of '—' is acceptable; however, the names of the infections should be in lower case.

In paragraph six, sentence five ("Infectious Diarrhea may be treated for 5-7 days."), the word diarrhea should be change to lower case for consistency.

Recommendation:

An approval letter should be issued informing the applicant that the FPL is approved. However, at the next FPL printing the following should be done:

1. Under the **DOSAGE AND ADMINISTRATION** section, the third paragraph, "Infectious Diarrhea" and "Typhoid Fever" should be written in lower case. Also, in the sixth paragraph, sentence five, the word "Diarrhea" should be written in lower case.

2. Under the **ADVERSE REACTIONS** section, the last paragraph, "pseudomembranous colitis" should be moved to the end of the list of adverse reactions and followed by the following new sentence: "The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment."

7/25/94
Pauline Fogarty
Project Manager

cc:Orig NDA 19-537
HFD-520
HFD-520/MO/MBlum MB 7/21/94
HFD-520/Micro/PDionne
HFD-520/Chem/VShetty
HFD-520/Pharm/LBuko
HFD-521/PM/PFogarty
fogarty7/20/94
APPROVAL

Concurrence only:
HFD-520/ActDivDir/LGavrilovich
HFD-520/SMO/MAlbuerne
L. L. G. 7/21/94
HFD-521/APM/PDeSantis 7/21/94

APPEARS THIS WAY
ON ORIGINAL

HFD-520

EXCLUSIVITY SUMMARY FOR NDA # 19,537 SUPPL # S-015

Trade Name CIPRO Generic Name Ciprofloxacin

Applicant Name Miles, Inc. HFD # 520

Approval Date If Known July 21, 1994

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19,537 Cipro (Ciprofloxacin) Tablets

NDA# 19,847 Cipro (Ciprofloxacin) vial

NDA# 19,857 Cipro (Ciprofloxacin) D5W

19,858 Cipro (Ciprofloxacin) .9% NS

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study D84-052-02

Study D87-054

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study D84-052-02 _____

Study D87-054 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 21,804 YES /X/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

/S/

Signature
Title: Project Manager

September 1, 1994
Date

/S/

Signature of
Division Director

9/14/94
Date

APPEARS THIS WAY
ON ORIGINAL

ORIG

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date OCT 30 1991

NDA No. 19-537

20.1

Pharmaceutical Division
Miles Inc.
400 Morgan Lane
West Haven, CT 06516-4175

Attention: Carl E. Calcagni, R.Ph.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Cipro Tablets

NDA Number: 19-537

Supplement Number: S-015

Date of Supplement: October 23, 1991

Date of Receipt: October 29, 1991

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research, HFD-520
Attention: Document Control Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

/S/

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