

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-676**

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Trade Name ActronGeneric Name KetoprofenApplicant Name BayerHFD # 550Approval Date If Known October 6, 1995**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 /

b) Is it an effectiveness supplement?

YES / NO /

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

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 / 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 / /

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

3 years

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 / /

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 / /

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 / / NO / /

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

NDA#	<u>19816</u>	<u>Orudis</u>
NDA#	<u>18,754</u>	<u>Oruvail</u>
NDA#	_____	_____

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 /___/

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 / / 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 / / 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 / /

(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 //

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:

S90-002

S90-008

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.

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 #	YES / <input checked="" type="checkbox"/> /	!	NO / ___ / Explain: _____
		!	_____
	Investigation #2	!	
IND #	YES / <input checked="" type="checkbox"/> /	!	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 / /

If yes, explain: _____

Signature

Title: Project Manager

Date

October 31, 1995

Signature of Office/
Division Director

Date

11/3/95

cc: Original NDA

Division File

HFD-85 Mary Ann Ward

ORIGINAL

Bayer 

**Pharmaceutical
Division**

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

September 11, 1995

N(XR)

Christina Fang, Medical Reviewer
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-499
Ketoprofen 12.5 mg tablet/caplet
REQUEST FOR NEW DRUG PRODUCT EXCLUSIVITY PURSUANT TO 21
CFR 314.108(b)(4)

Dear Dr. Fang:

Pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417) and 21 CFR 314.108(b)(4), Bayer Corporation hereby requests a three (3) year period of exclusivity for the above referenced product and submits the following information to show that the application contains "reports of new clinical investigations" that are "essential to approval of the application" and were "conducted or sponsored by the applicant" as set forth in 21 CFR 314.50(j):

- (i) I hereby certify that to the best of my knowledge, each of the clinical investigations sponsored by Bayer meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).
- (ii) Enclosed herewith is a list of all published studies or publicly available reports of clinical investigations known to me through a literature search that are relevant to the conditions for which Bayer Corporation is seeking approval. I hereby certify that I have caused the scientific literature to be thoroughly searched and, to the best of my knowledge, the list is complete and accurate.

Bayer submitted original NDA 20-499 demonstrating the safety and efficacy of ketoprofen 12.5 mg oral tablets/caplets, to be marketed over-the-counter, for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever.

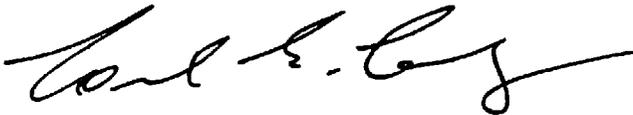
Wyeth-Ayerst obtained approval of Orudis® (ketoprofen) 25 mg, 50 mg, and 75

mg oral capsules in the United States for the treatment of acute or long-term signs and symptoms of rheumatoid arthritis and osteoarthritis in 1986 and 1987. The approved indications for Orudis® were expanded in 1988 to include mild-to-moderate pain and dysmenorrhea. Wyeth-Ayerst's patent for Orudis® expired on February 8, 1991. Generic formulations of ketoprofen 25 mg, 50 mg, and 75 mg oral capsules were approved for marketing in December 1992 and January 1993.

In my opinion, the published studies included in the enclosed comprehensive search are inadequate to establish the safety and efficacy of ketoprofen 12.5 mg tablets/caplets, to be marketed over-the-counter, for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever. Accordingly, Bayer Corporation conducted the new clinical investigations essential for approval under

- (iii) The applicant* was the sponsor named in Form FDA-1571 for under which the new clinical investigations that are essential to the approval of its application were conducted.

Sincerely,



Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs

* The name of the applicant changed 1 April 1995 from Miles Inc. to Bayer Corporation.

ORIGINAL



Consumer Care Division

ORIG AMENDMENT

Bayer Corporation
99 Cherry Hill Road
Parsippany, NJ 07054

August 24, 1995

N(SV)

Christina Fang, M.D.
Pilot Drug Evaluation Staff
Office of Drug Evaluation II (HFD-007)
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 9B-23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



**RE: NDA #20-499, Ketoprofen 12.5 mg Tablet/Caplet:
Safety Summary Update**

Dear Dr. Fang:

Pursuant to 21 CFR 314.50 (5) (vi) (b) Bayer Consumer Care Division is submitting, in triplicate, the Safety Summary Update for NDA #20-499, Actron®, Ketoprofen 12.5 mg Tablets/Caplets. This submission contains information obtained by Bayer since the 4-Month Safety Update Report, submitted on January 12, 1995.

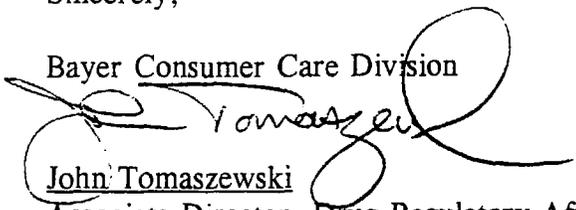
Included in this submission are the safety summary updates for clinical studies; Bayer Corp.
Study S95-001 Bayer AG Study 0296 Bayer AG Study 0297
and Bayer AG Study 0300

Tab I contains the individual study summaries of the above for all adverse drug experiences, and Tab II contains a tabulation of adverse drug experiences reported by Bayer AG, Leverkusen, Germany from 1986-1995.

If you need further assistance, please contact me at (201) 331-6707.

Sincerely,

Bayer Consumer Care Division


John Tomaszewski

Associate Director, Drug Regulatory Affairs



NDA 20-499

Food and Drug Administration
Rockville MD 20857

JUL 19 1995

Bayer Corporation
400 Morgan Lane
West Haven, Connecticut 06516-4175

Attention: Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs

Dear Mr. Calcagni:

Please refer to your July 15, 1994 new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actron (ketoprofen) OTC 12.5mg tablets.

We acknowledge receipt of your amendments dated April 10, May 3, and May 31, 1995.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit revised labeling for the drug in draft mock-up format incorporating the changes after they are agreed upon by the division.

Review of the Environmental Assessment has not been completed. We expect your continued cooperation to resolve any deficiencies that may occur.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

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 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

David Morgan
Consumer Safety Officer
Telephone: (301) 443-4250

Sincerely yours,

Reviewing Team
Pilot Drug Evaluation Staff
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Michael Weintraub, M.D.
Director, OTC

Robert Bedford, M.D.
Acting Director

Christina Fang, M.D.
Medical Officer

Richard A. Stein, Ph.D.
Statistician

Bart C. Ho, Ph.D.
Chemist

Almon Coulter, Ph.D.
Pharmacologist

Ruth Stevens, Ph.D.
Pharmacokineticist

cc:

Original NDA 20-499
HFD-007/Div. Files
HFD-2/M.Lumpkin
HF2-Med Watch
HFD-735/(DBarash)
HFD-009/JTreacy
HFD-009/LZwanziger
HFD-500
DISTRICT OFFICE
HFD-80
HFA-100
HFD-007/D.Morgan
HFD-007/CFANG *C.F 7/19/95*
HFD-007/RSTEIN/7-18-95 *R.S 7/19/95*
HFD-007/ACOULTER
HFD-007/BHO/7-18-95
HFD-007/RSTEVENS
HFD-240/S.Sherman (with draft labeling)
HFD-638 (with draft labeling)

Drafted: DM/June 30, 1995/20499AE
R/D Initials:CMoody/7-18-95
F/T By: POConnor/7-19-95

APPROVABLE

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

Bayer 

'L NEW CORRESP



Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

July 12, 1995

Mr. David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857

**RE: NDA #20-499, ketoprofen 12.5mg Tablets/Caplets:
Abnormal GI Histories**

Dear Mr. Morgan:

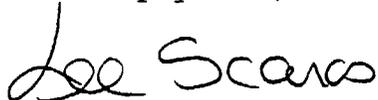
As requested by Dr. Fang, attached please find additional information regarding the distribution of abnormal gastrointestinal (GI) histories in the Consumer Use study.

Listed in the first line are the numbers and percentages of patients with histories of upper GI disease. The total number of patients with an abnormal GI history is used as the denominator.

The lower half of the table provides the number and percentages of patients by type of upper GI disease. The total number of patients with an abnormal GI history is used as the denominator. A patient may have reported more than one type of upper GI history; therefore the numbers and percentages are not additive.

Thank you for your attention to this NDA. Please do not hesitate to contact me at (203) 937-2693 if you have any questions regarding this submission.

Sincerely yours,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

Attachment

ORIGINAL



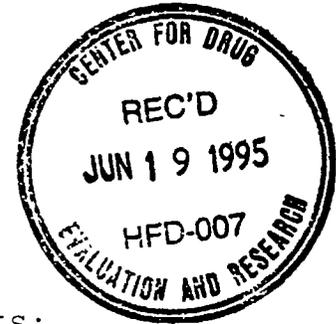
Pharmaceutical
Division

June 15, 1995

CRIS AMBROSE
N(BU)

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:
Color Copies of the Actron® Label

Dear Mr. Morgan:

Pursuant to the Pilot Drug Evaluation Division's June 9, 1995, request, fifteen color copies of the proposed Actron® label are enclosed.

As indicated in Bayer's May 31, 1995, submission to the Pilot Drug Division, the format of the enclosed label is similar to the label submitted in NDA #20-499. Bayer has reviewed the FDA draft guidance for OTC Analgesics/Antipyretics policy and sample draft labels. Since Bayer has not generated data regarding the readability and consumer's comprehension of the proposed OTC label format, Bayer believes that it is inappropriate to adapt this proposed OTC label format. Bayer wishes to collaborate with the Pilot Drug Evaluation and Nonprescription Drug Divisions to formulate a label which would best serve the needs of the consumer.

Thank you for your assistance with this issue. Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely yours,


Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

ORIGINAL



Pharmaceutical
Division

June 13, 1995

ORIG AMENDMENT
N(BM)

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:
Spontaneous reports of adverse events for Ketoprofen in the
FDA's Spontaneous Reporting System.

Dear Mr. Morgan:

On April 13, 1995, the Pilot Drug Evaluation Division requested a worldwide safety update for ketoprofen from 1969 through December 1994. Bayer submitted updated information on spontaneous reports of adverse events from the WHO Collaborating Center For International Drug Monitoring on May 30, 1995. No additional spontaneous reports of adverse events have been reported to the United Kingdom Medicine Control Agency since April 1993.

Under the Freedom of Information Act, Bayer has obtained updated information on adverse events for Ketoprofen in the FDA's Spontaneous Reporting System. The data now include 824 spontaneous reports on Ketoprofen, Orudis, Oruvail, and Profenid received at FDA from 3-18-86 through 3-22-95.

The denominator, from IMS data for 1986 through 1993, was 917 million total dispensed doses (including inpatient and outpatient hospital use). An updated usage estimate is pending.

The FOI data are summarized in 5 overview tables and fully presented in 4 listings, all designed and generated by Bayer Corporation Safety Assurance department. These are explained in detail in the key to listings.

The overview section summarizes the data from several perspectives. As shown in Overview Table 1, 87% of all reports were submitted through the manufacturer; health professionals (12%) were the major source of direct reports to FDA. Overview Table 2 shows the geographic origin of the reports; the largest

number are from New York (72 reports), California (63), and Texas (58); 40 reports from other countries are also included. Overview Table 3 reveals that 64% of patients were female; there were more reports for women aged 71 to 80 years than for any other decade of life, and more for men aged 61-70.

The largest numbers of events for a COSTART body system, as may be seen from the first pair of tables in Overview 4, were reported for the digestive system (508 events), the body as a whole (393), the skin (166), and the nervous system (154). The middle pair of tables in Overview 4 break down events by body system for patients under age 30, those aged 30-64 years, and those 65 or over; the event profiles for all groups are remarkably similar although there were somewhat more cardiovascular and digestive system events and fewer nervous system events in the oldest group than in the youngest. The bottom pair of tables in Overview 4 compare the event profiles of female and male patients; no meaningful differences are apparent, at least at the body system level.

Finally, Overview Table 5 lists the most frequently reported events, headed by abdominal pain (113), diarrhea (82), nausea (80), GI hemorrhage (60), rash (52), dyspepsia (31), dyspnea (29), dizziness (29), urticaria (26), and allergic reaction (25).

The four data listing are: 1) index to events grouped by body system, 2) index to all COSTARTs alphabetically, 3) index to medications and comedications alphabetically, and 4) the main listing of spontaneous reports arranged by FDA control number. Refer to the Key to Listings for further guidance and examples.

Please do not hesitate to call me at (203) 937-2693 if you have any questions.

Sincerely yours,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

ORIGINAL



Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000
Fax: 203 937-0708

June 26, 1995

NEW CORRESP

C



Mr. David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:
Ketoprofen International Registration Status

Dear Mr. Morgan:

As requested by the Pilot Drug Evaluation Division, enclosed please find the international registration status of ketoprofen. Also enclosed are lists of countries where ketoprofen 12.5 mg and ketoprofen 25 mg applications have been submitted by Bayer for prescription marketing.

On March 30, 1995, Bayer submitted an application for 25 mg ketoprofen for OTC marketing to the authorities in Norway. Other than Norway and the United States, no other applications for OTC ketoprofen have been submitted by Bayer.

Please do not hesitate to call me at (203) 937-2693 if you have any questions.

Sincerely yours,

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

Attachments

ORIGINAL

Bayer 

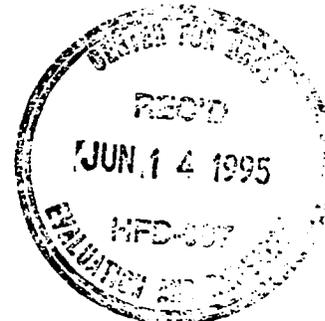
NEW CORRESP

Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

June 9, 1995

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:

Dear Mr. Morgan:

Pursuant to the Pilot Drug Evaluation Division's June 9, 1995, request regarding amendments to the June 7 1995, submission, the attached materials are provided for your review.

We think the statistical differences or trends seen in this table mostly reflect the similar trends observed in the overall population, rather than differences specific to noncompliance or overdose. The impact of multiple testing is also a concern.

Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely yours,

A handwritten signature in cursive script that reads "Lee Scaros".

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

ORIGINAL

Bayer 

Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

NEW CORRESP

C

June 15, 1995

Mr. David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:
Incidence of Adverse Events by Age

Dear Mr. Morgan:

As requested by the Pilot Drug Evaluation Division on June 14, 1995, attached please find the incidence rates of adverse events by age (<65 years v. \geq 65 years) within treatment group and across treatment with the associated p-values requested by the FDA. Note that the p-values within treatments are both less than 0.10 indicating a trend toward significant differences in adverse events between younger and older patients regardless of treatment. As stated earlier, caution should be employed because of the number of statistical tests made in this study.

Please do not hesitate to call me at (203) 937-2693 if you have any questions.

Sincerely yours,


Lee Scaros, Pharm.D.

Associate Director, Regulatory Affairs

/LS

Attachments

ORIGINAL

Bayer 

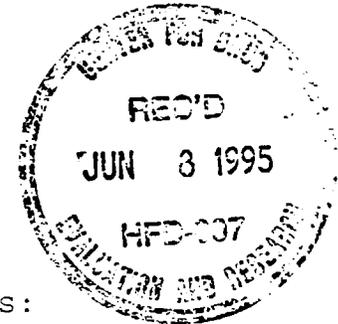
Pharmaceutical
Division

June 7, 1995

NEW CORRESP

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

Mr. David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:
Consumer-Use Study #S90-003

Dear Mr. Morgan:

Reference is made to Exhibit D (summary tables from consumer-use study #S90-003 for non-compliance and overdose in the valid patient population and in those valid patients with adverse events) of Bayer's March 16, 1995, submission to NDA 20-499. Consumer-Use study #S90-003 was designed to characterize consumer use patterns and was sized to detect infrequent adverse events. This large sample size (>3000 patients/treatment group) has the potential to result in statistically significant differences between treatment groups which are not clinically relevant.

Pursuant to the Pilot Drug Evaluation Division's May 31, 1995, request, p-values have been provided for the comparisons indicated. In the case of the ketoprofen male vs. female comparison, a p-value of 0.016 is calculated. This calculation does not include any adjustment for multiple tests performed and pertains to an overall adverse event difference that is small (7.2% vs. 9.9%) and not clinically relevant. Further, the difference between genders in the ketoprofen group (2.7%) is not statistically significantly different from the difference between genders in the ibuprofen group (0.6%, p=0.144).

Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely,

William E Maguire

for L.S.

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS
Attachments

ORIGINAL
N(SU)



ORIG AMENDMENT

**Pharmaceutical
Division**

May 31, 1995

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

Mr. David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:
Worldwide Safety Update

Dear Mr. Morgan:

Pursuant to the Pilot Drug Division's request, please find enclosed an update of the worldwide safety data for ketoprofen.

Three sets of spontaneous adverse event data were submitted in NDA #20-499 on July 15, 1994, volume 92; page 08-11-0000456 through 08-11-0001074:

1. Spontaneous adverse event reports to Bayer for ketoprofen 25mg and 50mg between October 1, 1985, and December 31, 1993.
2. Spontaneous adverse event reports to the United Kingdom Medicines Control Agency for all ketoprofen preparations between November 1, 1974, and December 31, 1993.
3. Spontaneous adverse event reports to the FDA for any ketoprofen preparation between March 18, 1986, and December 28, 1993.

On April 13, 1995, the Pilot Drug Evaluation Division requested a worldwide safety update for ketoprofen from 1969 through December 1994. Enclosed please find data which are currently available to Bayer. Additional data will be forwarded to the Pilot Drug Division as it becomes available.

WHO Collaborating Center For International Drug Monitoring:

Spontaneous adverse event reports collected by the WHO as of April 28, 1995, are enclosed.

United Kingdom, Medicines Control Agency:

No additional spontaneous adverse events have been reported to the Medicine Control Agency since April 1993. Therefore, the data presented in NDA #20-499 is current.

Mr. David Morgan, Project Manager
Page Two
May 31, 1995

United States, Food and Drug Administration:
A request for an update through F.O.I. is pending.

Please do not hesitate to call me at 203 (937-2693) if you have any questions.

Sincerely,

A handwritten signature in black ink that reads "Lee Scaros". The signature is written in a cursive, flowing style.

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

Attachments

**APPEARS THIS WAY
ON ORIGINAL**

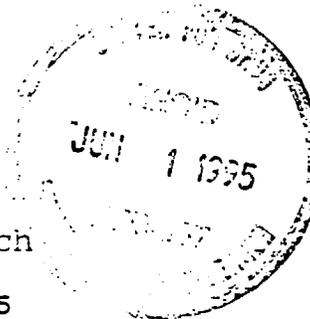
ORIGINAL



Pharmaceutical
Division

May 31, 1995

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

ORIG AMENDMENT

Morgan

RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:
Additional requests regarding Bayer's May 22, 1995,
submission.

Dear Mr. Morgan:

Pursuant to the Pilot Drug Evaluation Division's May 26, 1995,
request for additional data regarding Bayer's May 22, 1995,
submission entitled, "Frequency of Adverse Events In Females And
The Elderly, the following information is enclosed for the
Division's review.

Exhibit A:

A table of the frequency of adverse events in females and the
elderly for all U.S. adequate and well-controlled trials,
including another category for Age \geq 55. Please refer to page 10
of the May 22, 1995, submission.

Exhibit B:

For the dental pain studies, a column with baseline mean pain
intensity for each trial by treatment group was added. Please
refer to page 19 of the May 22, 1995, submission.

Exhibit C:

For the three dysmenorrhea studies, the column, mean baseline
intensity for each trial by treatment was added. Please refer to
page 22 of the May 22, 1995, submission.

Please do not hesitate to call me at (203) 937-2693 if you have
any questions regarding the enclosed materials.

Sincerely yours,

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

ORIGINAL



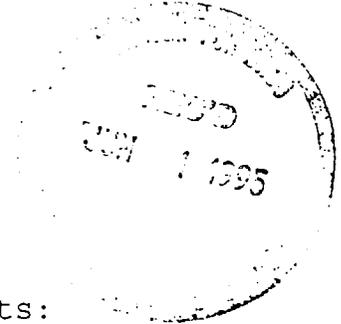
Pharmaceutical
Division

May 31, 1995

ORIG AMENDMENT
N(BL)

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets:
Proposed label

Dear Mr. Morgan:

Pursuant to the Pilot Drug Evaluation Division's May 16, 1995, request, the proposed label for ketoprofen 12.5mg Tablets/Caplets is enclosed.

The format of the enclosed label is similar to the label submitted in NDA #20-499. Bayer has reviewed the FDA draft guidance for OTC Analgesics/Antipyretics policy and sample draft labels. Since Bayer has not generated data regarding the readability and consumer's comprehension of the proposed OTC label format, Bayer believes that it is inappropriate to adapt this proposed OTC label format. Bayer wishes to collaborate with the Pilot Drug Evaluation and Nonprescription Drug Divisions to formulate a label which would best serve the needs of the consumer.

Thank you for your assistance with this issue. Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely yours,

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

ORIGINAL



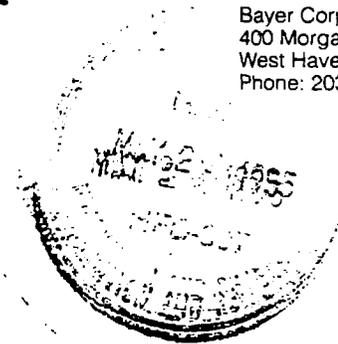
Pharmaceutical
Division

May 22, 1995

ORIG AMENDMENT
NCBM)

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

Mr. David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 Ketoprofen 12.5mg Tablets/Caplets.

- Frequency of adverse events in females and elderly (Pilot Drug Evaluation Division's May 10, 1995, facsimile)
- Summary table (Pilot Drug Evaluation Division's May 15, 1995, facsimile)

Dear Mr. Morgan:

Reference is made to the Pilot Drug Evaluation's facsimiles dated May 10, 1995 and May 15, 1995.

Enclosed please find:

- | | |
|-----------|--|
| Exhibit A | Pilot Drug Division's May 10, 1995 & May 15, 1995 facsimiles |
| Exhibit B | Adverse event rates in females and the elderly based on the pool of U.S. adequate and well-controlled trials |
| Exhibit C | Adverse event rates in females and the elderly not included in the pool of adequate and well-controlled trials |
| Exhibit D | Summary table (Pilot Drug Evaluation Division's May 15, 1995, facsimile) |

Adverse event rates in females and the elderly based on the pool of U.S. adequate and well-controlled trials (Exhibit B):

As requested, in the May 10, 1995, facsimile, the frequency of adverse events in females and the elderly are provided for the Division's review.

Mr. David Morgan, Project Manager
Page Two
May 22, 1995

The following studies are included in the pool of adequate and well-controlled clinical studies.

Dental	Dysmenorrhea	Fever	Consumer Care
S90-002	S92-001	S92-002 (INDUCED FEVER)	S90-003
S91-008	S92-004	S92-003 (NATURAL FEVER)	
S92-008	S92-012		
S92-009			

Please note that for dysmenorrhea studies:

rate = # of events /# at risk, where:

of events = # of patients reporting the events at any time from the first dose of that treatment to 7 days after the last dose of that treatment.

at risk = # of patients who were exposed to that treatment.

However, for all other studies:

rates are incidence rates = # of events/ # at risk, where:

of events = # of patients reporting the event during treatment with greater intensity than was reported during pretreatment.

at risk = # of patients who were exposed to that treatment.

Adverse event rates in females and the elderly not included in the pool of adequate and well-controlled trials (Exhibit C):

The following studies are included in the pool of clinical studies other than the adequate and well-controlled studies.

Mr. David Morgan, Project Manager
Page Three
May 22, 1995

Clinical Pharmacology	Dental Pain (using old formulation)	Foreign	
91-5	88-1	0280A	0284
89-12	88-2	0280B	0286
90-5		0281	0287
D90-041			

Summary Table (Exhibit D):

On May 15, 1995, the Pilot Drug Division requested that for those patients who received study medication, Bayer provide a table specifying:

- Information on age, gender and race for each treatment group.
- The number of dropouts and the reason for the dropout, based on the criteria defined by the protocol.
- The number of patients who received study medication but either pain relief, pain intensity or both were excluded from the efficacy analysis.
- The classification of patients based on their baseline pain intensity for each treatment arm.

This summary table is also provided for the Division's review.

As follow-up to the May 19, 1995, submission (Adverse events expressed in COSTART terms), only 2 patients had adverse events of unknown drug relationship. One patient reported a headache while on ketoprofen and the other patient reported ecchymosis while on ibuprofen.

Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

Attachments

**Pharmaceutical
Division**

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

ORIGINAL

ORIG AMENDMENT

May 19, 1995

N. (BM)

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets.
Adverse events expressed in COSTART terms.

Dear Mr. Morgan:

Reference is made to the Pilot Drug Evaluation's May 10, 1995, facsimile to the Bayer Corporation. As requested, adverse events, including lab abnormalities, expressed in COSTART terms and grouped into 12 body systems (Issue #2 of the Division's May 10, 1995, facsimile) are enclosed for the Division's review. During the May 18, 1995, conference call Bayer and the Pilot Evaluation Drug Division agreed that it is appropriate to pool the adverse event rates by body system for the adequate and well-controlled trials separately from other studies.

Enclosed please find:

- Exhibit A The Division's May 10, 1995, facsimile
- Exhibit B Rates of adverse events by body system based on the pool of all adequate and well-controlled trials
- Exhibit C Rates of adverse events by body system not included in the pool of adequate and well-controlled trials

Rates of adverse events by body system based on the pool of all adequate and well-controlled trials

The following tables are based on the pool of all adequate and well-controlled US studies:

Table 1	Table 2	Table 3
Rates of Adverse Events by Body System and Treatment for Patients Valid for Safety Analysis	Rates of Drug-Related Adverse Events by Body System and Treatment for Patients Valid for Safety Analysis	Rates of Severe Adverse Events by Body System and Treatment for Patients Valid for Safety Analysis

The following studies are included in this pool of adequate and well-controlled studies:

Dental:	Dysmenorrhea:	Fever:	Consumer Use:
S90-002	S92-001	S92-002	S90-003
S91-008	S92-004	S92-003	
S92-008	S92-012		
S92-009			

Please note that for dysmenorrhea studies:

- Rates = # of events/ # at risk, where:

of events = # of patients reporting the event at any time from the first dose of that treatment to 7 days after the last dose of that treatment.

at risk = # of patients who were exposed to that treatment.

However, for all other studies:

- Rates are incidence rates = # of events/ # at risk, where:

of events = # of patients reporting the event during treatment with greater intensity than was reported during pretreatment.

at risk = # of patients who during pretreatment either did not report the event, or reported it with less than severe intensity.

David Morgan, Project Manager
Page Three
May 19, 1995

In all studies, for the category "any event" within a body system, all patients were considered at risk.

Rates of adverse events by body system not included in the pool of adequate and well-controlled trials.

The following tables are based on the pool of all studies not included in the pool of adequate and well-controlled US studies:

Table 1	Table 2	Table 3
Rates of Adverse Events by Body System and Treatment for Patients Valid for Safety Analysis	Rates of Drug-Related Adverse Events by Body System and Treatment for Patients Valid for Safety Analysis	Rates of Severe Adverse Events by Body System and Treatment for Patients Valid for Safety Analysis

The following studies are included in this pool:

Clinical Pharmacology:	Dental Pain (using old formulation)	Foreign:	
91-5	88-1	0280A	0284
89-12	88-2	0280B	0286
90-5		0281	0287
D90-041			

Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS
Attachments

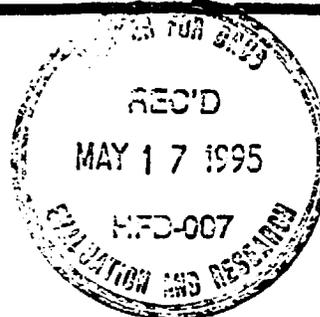
ORIGINAL

Bayer 

May 15, 1995

OTIC AMENDMENT

N(BM)



Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets.
• Literature Search Comparing the Safety of Ketoprofen to Other NSAIDs.

Dear Mr. Morgan:

Reference is made to the Pilot Drug Evaluation's April 11, 1995, facsimile to the Bayer Corporation. As requested, a literature search of published clinical data from 1986 to April 1995 comparing the safety of ketoprofen to another nonsteroidal anti-inflammatory drug is provided.

Enclosed please find the Division's April 11, 1995, facsimile; a listing of abbreviations used in the tables; and retrospective epidemiology studies, controlled clinical studies, and uncontrolled clinical studies. Selected uncontrolled clinical studies were included only if they provided data on a substantial cohort (> 500) of patients exposed to ketoprofen. Although lacking a control, large databases such as these add to the safety profile of ketoprofen and can be compared to similar data from other nonsteroidal anti-inflammatory agents. Following the tables, the individual references are provided.

Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

Attachment

ORIGINAL



Pharmaceutical
Division

L NEW CORRESP

May 17, 1995

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

C

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #20-499 Ketoprofen 12.5mg Tablets/Caplets.
Premature Termination Due To Adverse Events or Concurrent Illness

Dear Mr. Morgan:

Reference is made to the Pilot Drug Evaluation's May 10, 1995, facsimile to the Bayer Corporation. As requested, a table of premature terminations due to adverse events or concurrent illness (Issue #1 of the Division's May 10, 1995, facsimile) is enclosed for the Division's review. Bayer intends to forward Issue #2 to the Division on Thursday or Friday. Issue #3 will be forwarded to the Division next week.

Please do not hesitate to call me at (203) 937-2693 if you have any questions. Thank you for your attention to this NDA.

Sincerely,

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

Attachment



ORIGINAL

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000
Fax: 203 937-0708

April 28, 1995

Mr. David Morgan, Project Manager
Pilot Drug Evaluation
Office of Drug Evaluation II (HFD-007)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: DOCUMENT CONTROL ROOM 9B-23
5600 Fishers Lane
Rockville, MD 20857



- RE: NDA #20-499; ketoprofen 12.5mg Tablets/Caplets.
- Summary statistics obtained from analysis of covariance for the induced-fever study #S92-002.
 - Summary statistics obtained from analysis of variance for natural fever study #S92-003.
 - Summary of the number of patients re-medicating within 4 hours for the dysmenorrhea studies.
 - Estimated duration of analgesian (time-to-remedication) graphs.

As discussed during our telephone conversation on April 20, 1995, the following materials are enclosed for the Division's review:

Induced-Fever Study #S92-002:

- Table 3.1, summary statistics obtained from analysis of covariance based on the population of patients valid for analysis of efficacy for FDA requested variables. This table has been revised from that issued on April 10, 1995, as follows:
 1. Raw means and ranges have been included
 2. Tests for baseline and baseline-by-treatment interaction have been made and p-values displayed
 3. Indications of significant treatment differences similar to analgesic studies have been provided
 4. Actual pairwise comparison p-values have been removed
 5. All related footnotes have been modified

Mr. David Morgan, Project Manager
Page Two
April 28, 1995

Natural Fever Study #S92-003:

- Table 11.1a, summary statistics obtained from analysis of variance based on the population of patients valid for analysis of efficacy for FDA requested variables. This table has been revised from that discussed on April 20, 1995, to include raw means.
- Table 11.1 is also provided. This is the same table as table 11.1a except that it is based on the population valid for efficacy analysis according to the FDA criteria. (Please refer to Exhibit A; Dr. Fang's January 27, 1995, comments regarding "patients excluded from any part of the efficacy analysis.")

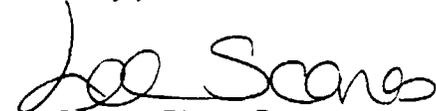
Dysmenorrhea Studies #S92-001, #S92-004 and #S92-012:

- A summary of the number of patients re-remedicated within 4 hours by treatment group, cycle and study for all three dysmenorrhea studies.

Dysmenorrhea Studies #S92-012 and #S92-001:

- Estimated duration of analgesia (time-to-remedication) graphs including median time to remedication, 95% confidence intervals and Wilcoxon and Log rank tests for patients valid for FDA duration of analgesia based on first period only. Please note from the table above that no patients re-remedicated during the first cycle in the #S92-004 study, therefore this page is not provided for this study.

Sincerely yours,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

LS:pc

Attachments

ORIG AMENDMENT

Pharmaceutical
Division

April 10, 1995

ORIGINALBayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000
Fax: 203 937-0708

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857

N (BM)



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets.

Dear Mr. Morgan:

As discussed during telephone conversations on April 4 and 5, 1995, the following materials are enclosed for the Division's review:

- Drug by stratum P-values for (1) 6-hour & 8-hour temperature reduction AUC, (2) 6-hour & 8-hour maximum temperature decrease, and (3) 6-hour & 8-hour temperature AUC for the natural fever study #S92-003 based on the model with drug, center, stratum and drug by stratum interaction.
- 0 to 6 hours temperature difference AUC, 0 to 8 hours temperature difference AUC, 0 to 6 hours maximum temperature difference and 0 to 8 hours maximum temperature difference summary statistics for fever study #S92-002.
- 6-hr and 8-hr temperature AUCs summary results for natural fever study #S92-003.
- 6-hr and 8-hr temperature reduction AUCs summary results for natural fever study #S92-003.
- 6-hr and 8-hr maximum decrease in temperature summary results for natural fever study # S92-003.
- Baseline pain intensity (valid patients) for dysmenorrhea studies
- Baseline pain intensity (valid patients) for dental pain studies
- List of deviated and missing data for dental pain studies
- List of deviated and missing data for dysmenorrhea studies

David Morgan
Page Two
April 10, 1995

Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely yours,

A handwritten signature in cursive script that reads "Lee Scaros".

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

Attachment

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

MILES 

Pharmaceutical Division

March 16, 1995

Miles Inc.
400 Morgan Lane
West Haven, CT 06516-4175
Phone 203-937-2000

NEW CORRESP

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg Tablets/Caplets.

- A list of missing and deviated data for dysmenorrhea studies S92-001, S92-004, and S92-012.
- Adjusted analyses for dental pain studies S90-002, S91-008, S92-008 and S92-009, applying the January 1995 guideline.
- Adjusted analysis for dental pain study S92-008, based on a sample size of 50 patients per treatment group.
- Additional Consumer-Use analyses.

Dear Mr. Morgan:

Reference is made to the minutes of the February 14, 1995, conference call, which were submitted to the Division on February 23, 1995. As requested during this conference call, the following exhibits are enclosed for the Division's review:

Exhibit A: A list of missing and deviated data for dysmenorrhea studies S92-001, S92-004, and S92-012. All patients with at least one difference in pain intensity or pain relief between the analyses presented in the NDA and the analyses applying the January 1995 guideline are provided.

Miles is generating the analyses of the dysmenorrhea studies applying the January 1995 guideline and will make these available as soon as possible, but no later than the end of March.

Exhibit B: The analyses for dental pain studies S90-002, S91-008, S92-008 and S92-009 applying the January 1995 guideline.

David Morgan
Page Two
March 16, 1995

Please note, that in regard to missing and deviated data for dental pain studies, only S92-009 had patients with a difference in pain intensity or pain relief between the analyses presented in the NDA and the analyses applying the January 1995 guideline. A listing of these patients and data was provided in the March 3, 1995 submission.

Exhibit C: The analysis of dental pain study S92-008, reconstructed based on a sample size of 50 patients per treatment group.

Exhibit D: From the Consumer-Use study S90-003, additional information concerning non-compliance and overdose in the valid patient population and in those valid patients with adverse events.

Please do not hesitate to call me at (203) 937-2693 if you have any questions regarding the enclosed materials.

Sincerely yours,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/LS

Attachment

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

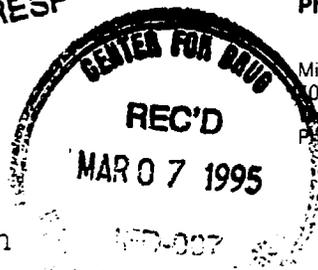
MILES 

NEW CORRESP

Pharmaceutical Division

March 3, 1995

Christina Fang, Medical Reviewer
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



Miles Inc.
100 Morgan Lane
West Haven, CT 06516-4175
Phone 203 937-2000

RE: NDA #20-499 ketoprofen 12.5mg tablets/caplets.
A list of missing and deviated data and analyses as per the
January 1995 guideline.

Dear Dr. Fang:

Reference is made to the minutes of the February 24, 1995,
conference call, which were submitted to the Division on February
27, 1995. During this conference call, the Division suggested
that Miles' submit at least one dental pain study (the study with
the most deviations) to ensure that the data presentation is
acceptable. The Division indicated that they would like to see:

- 1) A list of missing and deviated data
- 2) Analyses as per the January 1995 guideline
 - 1 page for PR
 - 1 page for PID
 - 1 page for PRID
 - 1 page for duration of relief
 - 1 page for onset of relief

Please find attached as Exhibit A, a list of missing and deviated
data for dental pain study S92-009. All patients with at least
one difference in pain intensity or pain relief between the
analyses presented in the NDA and the analyses applying the
January 1995 guideline for study S92-009 are provided.

Please note, the column entitled, "Outside Window (min)"
specifies the number of minutes between the "scheduled time" and
the "actual time". The column entitled, "Difference" specifies
(by a *) a difference between the CRF value and the January 1995
guideline value with interpolation only or the difference between
the original interpolation\extrapolation value and the January
1995 guideline interpolation\extrapolation value.

Exhibit B contains the analyses as per the January 1995 guideline for PR, PID, PRID, duration of relief and onset of relief.

Please do not hesitate to call me at (203) 937-2693 if you have any questions or amendments to these minutes.

Sincerely yours,

A handwritten signature in cursive script that reads "Lee Scaros". The signature is written in black ink and is positioned below the text "Sincerely yours,".

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

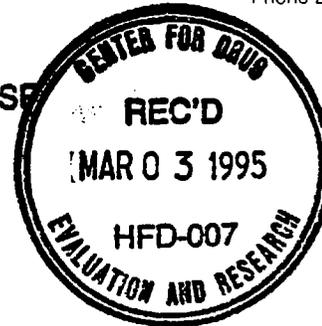
**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

March 1, 1995

NEW CORRESPONDENCE

Christina Fang, M.D., Medical Reviewer
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499 ketoprofen 12.5mg tablets/caplets.
Procedures used for interpolation and extrapolation of data for
the adequate and well-controlled dysmenorrhea and dental pain
trials.

Dear Dr. Fang:

As requested during the February 14, 1995, conference call, the procedures which were used for interpolation and extrapolation of data for the adequate and well-controlled dysmenorrhea and dental pain trials are provided for your review. Since the Division and Miles agreed that fever is not an analgesic model and the January 1995 draft guidelines for single-dose analgesic studies do not apply, the interpolation and extrapolation procedures for fever study S92-002 and S92-003 are not provided. The Division and Miles concluded that Miles would not modify the fever analyses presented in the NDA. Please refer to the February 14, 1995, conference call minutes submitted to the Division on February 23, 1995.

The following tables present the NDA volume and page number which contains the interpolation and extrapolation procedures for the adequate and well-controlled dysmenorrhea and dental pain trials. Exhibits A and B contain the pages from the protocols and medical reports which describe the interpolation and extrapolation procedures. Please note, within each indication the actual interpolation and extrapolation procedures applied are identical.

Tables 1 presents the volume and page number of the interpolation and extrapolation procedures presented in the protocols and medical reports for dysmenorrhea studies #S92-001, #S92-004 and #S92-012. Exhibit A contains the pages which are referenced from the protocol and medical report for study #S92-001. The procedures presented in studies S92-004 and S92-012 are identical.

Table 1

	Planned Procedure (as defined in the protocol)		Actual procedure (as defined in the medical report)	
	VOL	PAGE #	VOL	PAGE #
DYSMENORRHEA STUDY #S92-001				
Interpolation method	44	Not defined in protocol. Defined prior to breaking the blind.	44	08-08-0000043 08-08-0000190
Extrapolation method	44	08-08-0000094	44	08-08-0000043 08-08-0000190
DYSMENORRHEA STUDY #S92-004				
Interpolation method	48	Not defined in protocol. Defined prior to breaking the blind.	48	08-08-0001487 08-08-0001696
Extrapolation method	48	08-08-0001578	48	08-08-0001487 08-08-0001696
DYSMENORRHEA STUDY #S92-012				
Interpolation method	53	Not defined in protocol. Defined prior to breaking the blind.	53	08-08-0003544 to 3545 08-08-0003709
Extrapolation method	53	08-08-0003633	53	08-08-0003544 to 3545 08-08-0003709

Tables 2 presents the volume and page number of the interpolation and extrapolation procedures presented in the protocols and medical reports for dental pain studies #S90-002, #S91-008, # S92-008 and #S92-009. Exhibit B contains the pages which are referenced from the protocol and medical report for studies #S90-002 and S91-008. The procedures presented in studies #S92-008 and S92-009 are identical to S91-008.

Table 2

	Planned Procedure (as defined in the protocol)		Actual procedure (as defined in the medical report)	
	VOL	PAGE #	VOL	PAGE #
DENTAL PAIN STUDY #S90-002				
Interpolation method	30	Not defined in protocol.	30	Not applicable.
Extrapolation method	30	08-06-0000293	30	08-06-0000178
DENTAL PAIN STUDY S91-008				
Interpolation method	34	Not defined in protocol.	34	Not applicable.
Extrapolation method	34	08-06-0001725	34	08-06-0001678 08-06-0001790
DENTAL PAIN STUDY S92-008				
Interpolation method	35	Not defined in protocol.	35	Not applicable.
Extrapolation method	35	08-06-0002204	35	08-06-0002148 08-06-0002278
DENTAL PAIN STUDY S92-009				
Interpolation method	36	Not defined in protocol.	36	Not applicable.
Extrapolation method	36	08-06-0002523	36	08-06-0002474 08-06-0002587

Christina Fang, M.D.
Page Four
March 1, 1995

Please do not hesitate to call me at (203) 937-2693 if you have any questions or amendments to these minutes.

Sincerely yours,

A handwritten signature in cursive script that reads "Lee Scaros".

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

\LS

Attachments

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

Pharmaceutical Division

February 27, 1995

~~SUPPL NEW CORRESP~~Miles Inc.
400 Morgan Lane
West Haven, CT 06516-4175
Phone 203 937-2000

C

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499
Ketoprofen 12.5mg Tablets/Caplets
February 24, 1995, Conference Call Minutes

Dear Mr. Morgan:

On February 22, 1995, the Pilot Drug Division sent Miles Inc. a facsimile regarding a table for summarizing the number of patients with deviated or missing data. This table prompted a question from the Division concerning the format of dental pain studies 88-1 and 88-2. On February 23, 1995, Miles Inc. submitted, to the Pilot Drug Division, a request for clarifications of additional analyses for the adequate and well-controlled dysmenorrhea studies.

The Division and Miles agreed to conduct a conference call on Friday, February 24, 1995, to discuss Miles' request for clarifications of additional analyses for the adequate and well-controlled dysmenorrhea studies and the format of dental pain studies 88-1 and 88-2. Highlights and conclusions from this conference call are presented below:

Participants:

The following individuals participated in the conference call:

Pilot Drug Division:

David Morgan	-	Project Manager
Christina Fang, M.D.	-	Medical Reviewer
Richard Stein, Ph.D.	-	Statistician

Miles, Inc.:

Steven Jungerwirth, M.D.	-	Medical Affairs
Lee Scaros, Pharm.D.	-	Regulatory Affairs
Tim Shannon, M.D.	-	Medical Affairs
JoAnn Shapiro	-	Statistic & Data Systems

Miles opened the conference call by explaining that the purpose of the call was to discuss the following two issues:

- 1) Miles' February 23, 1995, facsimile regarding clarification of additional analyses for the dysmenorrhea studies.
- 2) The format of dental pain studies 88-1 and 88-2.

Clarification of the Additional Analyses for the Dysmenorrhea Studies:

Because of the manner in which Miles handled missing data or data not within windows, within the valid for efficacy population, there are a few patients with non-evaluable visits (e.g. Visit 3.0 with more than 2 consecutive time points outside of windows) followed by a repeat visit which was evaluable (Visit 3.1 with time points within windows). Visit 3.1 was used in the valid for efficacy analysis while both visits were included in the intent-to-treat analysis. Retrospectively implementing the January 1995 draft guidelines would make both visits evaluable. Miles' proposal is to use the repeat visit in such cases. The justification is that the use of the repeat visit would represent data within the time points (although the windows are 15 minutes) and would not require the use of interpolation. The Division agreed that Miles' proposal is appropriate.

One other individual issue is in need of clarification. In study S92-004, patient #2021 had Visit 4.0 deemed non-evaluable because the patient re-medicated with study medication 2 hours after initial dosing. By Miles' original methods, this was not considered rescue medication. The visit was repeated (Visit 4.1), and the patient completed 4 hours of evaluation without rescue medication or re-medication. Visit 4.1 was used in the valid for efficacy analysis; both visits were used in the intent-to-treat analysis. Miles asked which visit the Division would like included in the new analyses. The Division indicated that Miles should use the second visit.

The Format of Dental Pain Studies 88-1 and 88-2:

Miles explained that these two trials utilized a different formulation than the formulation proposed for marketing and used in the adequate and well-controlled trials. These trials are seven years old. The investigators who completed the trials also generated the reports. The data generated by these trials were not handled according to Miles' traditional procedures. Miles further explained that the Division and Miles had come to an understanding on how to handle these trials during pre-NDA discussions. The Division requested that Miles forward to the Division minutes from these meetings. Miles agreed to review the Regulatory files and forward to the Division minutes which may have been generated from these pre-NDA discussions. The Division suggested that this issue should be re-visited after Miles faxes minutes from the pre-NDA discussions.

Subsequent to the conference call, Lee Scaros reviewed the Regulatory files and determined that formal minutes of these discussions were not generated. However, outlines of the Integrated Summary of Efficacy and Safety sections of the NDA and a table of all pertinent investigations, were submitted to the Agency on March 22, 1994, in preparation for the May 25, 1994, meeting to discuss the proposed NDA outline and the CANDAs. These outlines were sent to the Division on February 24, 1995. These proposed outlines and Miles' internal contact reports revealed that it was discussed that the non-adequate and well-controlled trials (including study 88-1 and study 88-2) would not be provided in an electronic format.

The rationale for not considering studies 88-1 and 88-2 as pivotal studies is as follows:

1. Studies 88-1 and 88-2 used a different formulation compared to the studies Miles have deemed adequate and well-controlled studies, all of which used the [redacted] formulation. The [redacted] formulation is the formulation for which Miles is seeking approval and the one that will be marketed.
2. The pharmacokinetic profiles of the two formulations are very different (see clinical pharmacology study S90-5). The pharmacokinetic profile of [redacted] formulation was a factor in choosing it as the formulation to develop and market. There are no clinical efficacy studies directly comparing the two formulations.
3. The efficacy of ketoprofen in the wet granulation formulation has been demonstrated in the adequate and well-controlled studies in which it was used (dental pain studies S90-002, S91-008, S92-008, S92-009; dysmenorrhea studies S92-001, S92-004, S92-012; fever studies S92-002, S92-003). Studies 88-1 and 88-2 are supportive in this regard, but not critical to the claim of efficacy.

Since studies 88-1 and 88-2 were analyzed and reported by the investigators, Miles does not have sufficient data in the electronic database to produce the retrospective re-analyses the Division requested using the January 1995 draft guidelines.

**APPEARS THIS WAY
ON ORIGINAL**

The Division suggested that Miles submit at least one study (the study with the most deviations) to ensure that data presentation is acceptable. The Division would like to see:

- 1) A list of missing and deviated data
- 2) Analyses as per the January 1995 guidelines
 - 1 page for PR
 - 1 page for PID
 - 1 page for PRID
 - 1 page for duration of relief
 - 1 page for onset of relief

Miles will submit the analysis for one of the dental pain studies next week.

Dr. Stein indicated that he had a small issue with fever study #92-003. The value which was carried forward for patient 1005 was not the last value. JoAnn Shapiro indicated that the interpolation/extrapolation policy used for that study is found on page 08-07-0000950 of volume #40 of the ketoprofen NDA (see attachment #1). If the patient rescued, then the highest temperature recorded (including the temperature measured at 15 minutes prior to dosing and immediately prior to rescue) was used for each post-rescue time point. The data listing for patient 1005 is provided as attachment #2.

Miles thanked the Division for their assistance and attention to the ketoprofen NDA. The Division reiterated that Miles should call if they have any questions.

Conclusions:

- For patients with a previously non-evaluable visits followed by a repeat visit which was evaluable, the repeat visit will be used in the valid for efficacy analysis.
- For study S92-004 (patient #2021) Visit 4.1 will used in the valid for efficacy analysis.
- The format of dental pain studies 88-1 and 88-2 will be discussed after the Division reviews the materials which Miles faxed to the Division of Friday, February 24, 1995.
- Miles will submit the analyses for dental pain study S92-009 by Friday, March 3, 1995.

David Morgan
Page Five
February 27, 1995

Please do not hesitate to call me at (203) 937-2693 if you have any questions or amendments to these minutes.

Sincerely yours,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

/ls

Attachments

**APPEARS THIS WAY
ON ORIGINAL**

February 23, 1995

Miles Inc.
400 Morgan Lane
West Haven, CT 06516-4175
Phone 203 937-2000

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #20-499
Ketoprofen 12.5mg Tablets/Caplets
February 14, 1995, Conference Call Minutes

Dear Mr. Morgan:

On October 14, 1994, the Pilot Drug Division and Miles, Inc. discussed, via conference call, several format and analysis issues regarding NDA #20-499. On October 17, 1994, the Division requested that Miles create a table of patients who were excluded from any part of the efficacy analysis for all of the adequate and well-controlled trials. Miles submitted this table to the Division on November 16, 1994. Miles and the Division agreed that the format and analysis issues identified during the October 14, 1994, conference call would not be finalized by Miles until the Division provided comments regarding the table of patients excluded from any part of the efficacy analysis for all of the adequate and well-controlled trials. The Division provided comments regarding this table on January 27, 1995. Miles submitted, to the Division, an initial response to these comments on February 10, 1995.

The Division and Miles agreed to conduct a conference call on Tuesday, February 14, 1995, to reach an agreement on how to resolve the analysis and format issues discussed on October 14, 1994. Highlights and conclusions from this conference call are presented below.

The following individuals participated in the conference call:

Pilot Drug Division:

David Morgan	-	Project Manager
Christina Fang, M.D.	-	Medical Reviewer
Richard Stein, Ph.D.	-	Statistician

Miles Inc.:

Lee Scaros, Pharm.D.	-	Regulatory Affairs
Tim Shannon, M.D.	-	Medical Affairs
JoAnn Shapiro	-	Statistic & Data Systems

Fever Study:

The Division indicated that Miles' approach for the analysis of fever study #D92-003 is adequate. Miles proposed that because fever is not an analgesic model, it is not necessary to apply the January 1995 draft guidelines for single-dose analgesic studies to the adequate and well-controlled fever studies. Miles does not plan to modify the analyses that were provided in the NDA. The two patients which the Division asked to be included in the analysis of study #D92-003 were the only two patients excluded from the valid for efficacy population. These two patients were included in the intent-to-treat analyses, and therefore, Miles feels that the intent-to-treat analyses provides the information requested.

Dental Pain Studies:

The Division indicated that Miles' proposal to submit the requested changes for the adequate and well-controlled dental pain studies by mid-March is acceptable.

Miles indicated that there still are some questions regarding the calculations to be used in adjusting the sample size of the one dental pain study which has enrolled around 60 patients. Joann Shapiro will discuss this issue later with Dr. Stein. Miles reiterated that for those dental pain studies which enrolled close to 50 patients (i.e. 50 - 52 patients) the analyses would not be modified. The Division agreed.

Analytical Procedure For Interpolation, Extrapolation, And Missing Data:

The Division indicated that they would like to see all data presented as described in the January 1995 guideline. The Division would look at the analyses from both the January 1995 guideline and the original analyses provided in the NDA.

The Division requested that Miles provide a list of the procedures, as defined in the protocols, which were used for interpolation and extrapolation of data for all the adequate and well-controlled trials. Miles explained that the Efficacy Summary presents Miles' global interpolation and extrapolation policy and that these procedures may not have been described in each of the original protocols. The Division reiterated that they would like to see the list of interpolation and extrapolation procedures used in each of the adequate and well-controlled trials, as well as, the data generated by the January 1995 guideline's interpolation and extrapolation procedures. Miles indicated that this request requires extensive reprogramming. Miles indicated that a list of the procedures, as defined in the protocols, which were used for interpolation and extrapolation of data for all the adequate and well-controlled trials will be submitted by March 1, 1995.

Since all three of the dysmenorrhea studies are affected by the January 1995 guideline's interpolation policy, the Division suggested that an efficient manner of handling the reanalyses may be for Miles to select the most problematic dysmenorrhea study (a study

which seems to have a larger number of data points outside the windows or missing data). Miles expressed concern that the reanalysis of the dysmenorrhea studies may become rate limiting. Subsequent to the conference call, Miles determined that the reanalyses of the dysmenorrhea studies are so similar that it may be more efficient to submit all the reanalyses of the dysmenorrhea studies by March 30, 1995. Prior to submitting these reanalyses for the dysmenorrhea studies, feedback on the data handling policies will be elicited from the Division (as per the Division's request) through the comparison of data applying extrapolation, interpolation and missing data procedures.

Since only one dental pain study is effected by the interpolation policy outlined in the January 1995 guideline, Miles and the Division agreed that all the dental pain studies should be submitted at one time.

Conclusions:

- Miles will submit a list of the procedures, as defined in the protocols, which were used for interpolation and extrapolation of data for all the adequate and well-controlled trials, by March 1, 1995.
- Miles will submit the adjusted analyses for the dental pain studies per the August 1994 and January 1995 guidelines by mid-March 1995.
- Miles will submit the additional consumer-use analyses by mid-March 1995.
- Miles will submit (by mid-March) a comparison of data applying the extrapolation, interpolation and missing data procedures for the dysmenorrhea studies submitted in the NDA with the data generated per the January 1995 guideline. This listing will include all data for patients for which the methods generate different pain intensity and pain relief values.
- Reanalyses of the dysmenorrhea studies will be submitted by March 31, 1995.

Please do not hesitate to call me at (203) 937-2693 if you have any questions or amendments to these minutes.

Sincerely yours,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs
ls/jmd

ORIGINAL

MILES 

Pharmaceutical Division

February 23, 1995

Miles Inc.
400 Morgan Lane
West Haven, CT 06516-4175
Phone 203 937-2000

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM 9B-45
5600 Fishers Lane
Rockville, MD 20857

. NEW CORRESP

C



RE: NDA #20-499
Ketoprofen 12.5mg Tablets/Caplets
Clarification of additional analyses for the adequate and well-controlled
dysmenorrhea studies

Dear Mr Morgan:

Miles requests further clarification regarding the additional analyses for the adequate and well-controlled dysmenorrhea studies. We have received (January 27, 1995, by fax) input from Dr. Fang, regarding inclusion of certain patients who were excluded from our valid for efficacy analysis and are able to comply with her requests in regard to those patients.

Because of the manner in which we handled missing data or data not within windows, within our valid for efficacy population, there are a few patients with non-evaluable visits (e.g. Visit 3.0 with more than 2 consecutive time points outside of windows) followed by a repeat visit which was evaluable (Visit 3.1 with time points within windows). Visit 3.1 was used in our valid for efficacy analysis while both visits were included in the intent-to-treat analysis. Retrospectively implementing the 1995 draft guidelines would make both visits evaluable. We need to decide which visit should be included in the additional analyses that we will be sending to you. Our proposal would be to use the repeat visit in such cases. The justification is that the use of the repeat visit would represent data within the time points (although our windows are 15 minutes) and would not require the use of interpolation.

To further clarify the issue, we have included data from a patient where we have encountered this problem (Attachment 1). After the Division's review, we would like to come to an agreement as to how these situations should be handled.

Another individual issue is in need of clarification. In study S92-004, patient #2021 had Visit 4.0 deemed non-evaluable because the patient re-medicated with study medication 2 hours after initial dosing. By our original methods, this was not

David Morgan, Project Manager
Pilot Drug Evaluation (HFD-7)
NDA #20-499
Ketoprofen 12.5mg Tablets/Caplets

February 23, 1995
Page 2

considered rescue medication. The visit was repeated (Visit 4.1), and the patient completed 4 hours of evaluation without rescue medication or remediation. Visit 4.1 was used in our valid for efficacy analysis; both visits were used in the intent-to-treat analysis. We need to know which visit the Division would like included in the new analyses we will be sending to you.

Clarification of these issues are required as soon as possible for Miles to provide the additional analyses to the Division in a timely manner. We look forward to discussing these issues with the Division as soon as possible.

Sincerely,



Lee Scaros, Pharm.D.
Associate Director

ls/jmd

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

MILES 

Pharmaceutical Division

Miles Inc.
400 Morgan Lane
West Haven, CT 06516-4175
Phone 203 937-2000

ORIG AMENDMENT

January 12, 1995

N (54)

Christina Fang, M.D.
Medical Reviewer
Pilot Drug Evaluation
Office of Drug Evaluation II (HFD-007)
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 9B-23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #20-499
Actron®, ketoprofen 12.5 mg Tablet/Caplet
4-Month Safety Update

Dear Dr. Fang:

Please refer to NDA #20-499 for ketoprofen 12.5 mg Tablet/Caplet (Actron®). Pursuant to 21 CFR 314.50 (d) (vi) (b), Miles Inc., Pharmaceutical Division, hereby submits a 4-Month Safety Update report.

If you have any questions regarding this information, please contact me at (203) 937-2693.

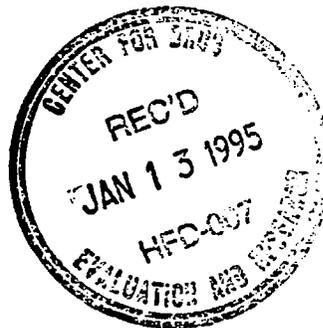
Sincerely,



Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

LS/pc

Attachments



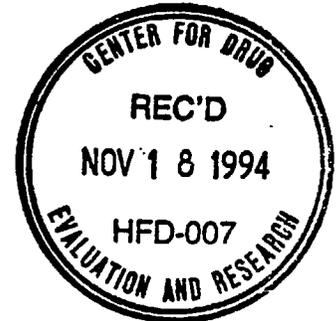
. NEW CORRESP

Pharmaceutical Division

November 16, 1994

ORIGINALMiles Inc.
400 Morgan Lane
West Haven, CT 06516-4175
Phone 203 937-2000

Christina Fang, M.D.
Medical Reviewer
Pilot Drug Evaluation
Office of Drug Evaluation II (HFD-007)
Center for Drug Evaluation and Research
Attention Documentation Control Room 9B-23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: **NDA #20-499:**
Request for clarification of data on patients excluded from any part of the efficacy analysis for all adequate and well-controlled studies.

Dear Dr. Fang:

Please find attached a table listing all patients excluded from any part of the primary efficacy analysis for all adequate and well-controlled studies within the dental pain, fever and dysmenorrhea indications for NDA #20-499. This table is consistent with the Division's October 17, 1994, facsimile and the October 27, 1994, conference call. The intent of this table is to illustrate, for patients excluded from any part of the primary efficacy analysis, those analyses for which the patient is excluded and those analyses for which data on the patient is available.

During the Thursday, October 27, 1994, conference call the Division and Miles agreed that Miles would submit this table to the Division prior to addressing the analysis issues identified during the October 14, 1994, conference call. Upon the Division's request, members of Miles' Medical Affairs, Statistical & Data Systems and Regulatory Affairs departments are available to meet with the Division to discuss this table or any other ketoprofen issues.

Thank you for your attention to this NDA. Please do not hesitate to call me at (203) 937-2693 if you have any questions.

Sincerely,



Lee Scaros Pharm.D.
Associate Director, Regulatory Affairs

ORIGINAL

MILES 

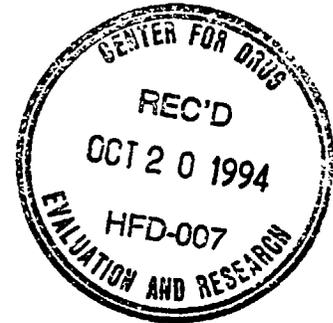
Pharmaceutical Division

NEW CORRESP

October 18, 1994

Miles Inc.
400 Morgan Lane
West Haven, CT 06516-1175
Phone 203 937-2000

David Morgan
Project Manager
Pilot Drug Evaluation Staff
Office of Drug Evaluation II (HFD-007)
Center for Drug Evaluation and Research
Attention Documentation Control Room 9B-23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: NDA #20-499
October 14, 1994, Ketoprofen Teleconference

Dear Mr. Morgan:

It was a pleasure to discuss the ketoprofen NDA# 20-499 on Friday, October 14, 1994. For your review, a summation of the conclusions from our October 14, 1994, teleconference is provided. The teleconference participants are listed below:

Participants from the Pilot Drug Division:

Christina Fang, M.D. - Medical Reviewer
David Morgan - Project Manager
Richard Stein, Ph.D. - Statistician
Rudy Widmark, M.D. - Medical Reviewer

Participants from Miles, Inc.:

Steven Jungerwirth, M.D. - Director, Cardiopulmonary/Self-Medication
Lee Scaros, Pharm.D. - Associate Director, Regulatory Affairs
Tim Shannon, M.D. - Deputy Director, Pulmonary/Self-Medication
JoAnn Shapiro - Associate Director, Statistics and Data Systems

Onset of Analgesia:

The Division indicated that the onset of analgesia should be calculated as shown on page 5 and 6 of the draft guideline entitled, "Presentation of Efficacy Results of Single-Dose Analgesics For Studies Using Acute Pain Models" (referred to throughout this letter as "the guideline"). This draft guideline

was dated August 1994, subsequent to submission of the ketoprofen NDA. It was agreed that the Abbreviated Study Reports will be amended to include tables, as originally provided in the complete research report, in the format found on page 8 of the guideline.

The Division indicated that in the calculation for onset of analgesia, only patients with data for at least 1 hour should be included. Patients whose data has been extrapolated should not be included in this calculation. Miles indicated that the onset of analgesia calculation only utilizes patients who had data through the 1 hour time-point. PRID at 30 minutes includes valid for efficacy patients only and one of the criteria for valid patients is that they have evaluations up to the first hour.

Duration of Analgesia\Remedication:

The Division referenced page 10 of the guideline. The Division asked that Miles use the exact times of remedication if available and place the table and figure on the same page. The Division commented that they liked the "A" and "B" flags used in the table (on page 08-05-000025 of the NDA) entitled, "Number Terminating For Inadequate Pain Relief". The Division stated that they would like to add these flags to the table on page 10 of the guideline. However, the Division indicated that in the calculation of time-to-remedication, all patients should be included even if they remedicated before 1 hour.

Miles indicated that the figure (on page 08-05-000028 of the NDA) entitled, "Survival Distribution Function For Time To Rescue", does use the actual time. But to be valid for the efficacy analysis the patients must not remedicate prior to the 1 hour time-point. Both the table and graph regarding time-to-remedication uses the valid for efficacy population. It was agreed that Miles will examine the need to create an intent-to-treat analysis which examines patients who remedicated prior to the 1 hour time-point.

PRID:

The Division asked that we refer to page 4 of the guideline and page 08-05-000024 of the NDA. The Division requested that the P-value for the treatment group be labeled as "treatment p-value" and that the baseline value be included in the model and the treatment by baseline interaction p-values tested and displayed, even though the studies were stratified by baseline severity and were comparable across treatments within studies.

The Division requested that where the sample size was larger than 50, the standard analysis be adjusted to 50. Miles explained that the study #S92-008 study was an exception. It was sized larger than the FDA preferred size of 50 because it was designed to evaluate onset of relief and therefore required a larger

sample size. The Division commented that they already made this adjustment and it did not change the conclusion. Miles asked that, given these two facts, would it still be necessary to adjust the analysis for this study. The Division responded "yes" and to "spread the word". Richard Stein agreed to send JoAnn Shapiro an Excel® spread sheet with the suggested methods. Miles proposes that only study #S92-008 with the sample size of approximately 60 per treatment group will be modified in this way. Other studies with sample sizes 51 - 52 or less will not be modified.

Demography:

The Division requested the Miles create a composite demography table across all pain models by study. Miles explained that such a table exists in the NDA.

Post-Meeting Follow-up:

For the ease of the Division's review a composite demography table is attached.

Duration of Relief:

Miles asked if the Division had considered Miles' analyses of duration of relief. Dr. Stein asked for specifics. JoAnn Shapiro said she would fax him a copy of the methods. Dr. Stein agreed he would send his methods.

Post-Meeting Follow-up:

Miles faxed page 29 of study #S92-008 research report and page 2 of appendix 13.8 of study #S92-008 research report, with notations on October 14, 1994.

Advisory Committee:

The Miles staff indicated that there has been some discussion regarding the possibility that the ketoprofen NDA may go to an Advisory Committee. The Miles staff asked if the Division could comment on the possible timing and format of the Advisory Committee. The Division replied that they were not prepared to discuss the Advisory Committee at this time. Miles asked if the format will be similar to the Pilot Drug Divisions's NDA days or the advisory meetings which have been conducted by other Divisions in the past. The Division replied that it will probably be a combination of both.

Conclusion:

It was agreed that the above modifications will be incorporated into the Abbreviated Study Reports and directed to the Division

as soon as possible.

Thank you for your attention to this NDA. Please do not hesitate to call me at (203) 937-2693 if you have any questions or comments.

Sincerely,

A handwritten signature in cursive script that reads "Lee Scaros".

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-499

Food and Drug Administration
Rockville MD 20857

Miles Inc.
Consumer Healthcare Products
400 Morgan Lane
West Haven, Connecticut 06516

AUG 26 1994

Attention: Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs

Dear Mr. Calcagni:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Actron (ketoprofen) 12.5 mg tablet/caplet OTC

Therapeutic Classification: S

Date of Application: July 15, 1994

Date of Receipt: July 19, 1994

Our Reference Number: NDA 20-499

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 17, 1994 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact me at (301) 443-4250.

Sincerely yours,

David Morgan
Project Manager
Pilot Drug Evaluation Staff
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Orig. NDA 20-499

HFD-007/Div File

HFD-80

HFD-007/DMorgan/8-5-94

R/D init.by: *CPM*

F/T by: trh/8/10/94

for CPM 8.26.94

Doc:Wd :A:ACTRON1

ACKNOWLEDGEMENT - AC

**APPEARS THIS WAY
ON ORIGINAL**

Miles Inc.
400 Morgan Lane
West Haven, CT 06516-4175
Phone 203 937-2000

July 15, 1994

Food and Drug Administration
Center for Drugs and Biologics
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852



Re: Actron®, ketoprofen 12.5 mg Tablet/Caplet
NDA #20-499

Dear Sir or Madam:

Pursuant to Title 21, CFR Subpart B 314.50 and 314.54, Miles Inc., Pharmaceutical Division, hereby submits a 505(b)(2) original New Drug Application #20-499 in duplicate for ketoprofen 12.5 mg oral tablets/caplets. This 505(b)(2) New Drug Application contains information required to support modifications of the listed drug Orudis® (ketoprofen) 25 mg, 50 mg and 75 mg oral capsules, NDA #18-754. Wyeth-Ayerst obtained approval of Orudis® in the United States for the treatment of acute or long-term signs and symptoms of rheumatoid arthritis and osteoarthritis in 1986. The approved indications for Orudis® were expanded in 1988 to include mild-to-moderate pain and dysmenorrhea. Wyeth-Ayerst's patent for Orudis® expired on February 8, 1991. Generic formulations of ketoprofen 25 mg, 50 mg and 75 mg oral capsules were approved for marketing in December 1992 and January 1993. Table #1, attached, summarizes the product and patent information for the ketoprofen products marketed in the United States. Oral formulations of ketoprofen are marketed in 27 countries worldwide. The ketoprofen 25 mg dose has been available without prescription in Belgium, Brazil and Finland since 1992 and in Italy since 1990.

Miles has completed a clinical program to demonstrate the safety and efficacy of ketoprofen 12.5 mg oral tablets/caplets, to be marketed over-the-counter, for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever. The nonclinical pharmacology/toxicology section of this submission is based on information in the public domain.

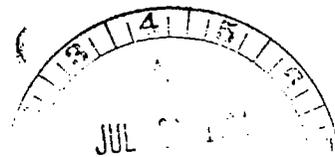


Table #1

Applicant	Wyeth-Ayerst	Biocraft	Lederle
Dosage Form; Route of Administration	Oral Capsules	Oral Capsules	Oral Capsules
	25mg	25mg	25mg
	50mg	50mg	50mg
	75mg	75mg	75mg
Trade or Generic Name	Orudis	Ketoprofen	Ketoprofen
Final Approval Date	25mg - 07/31/87	25mg - 12/22/92	25mg - 01/29/93
	50mg - 01/09/86	50mg - 12/22/92	50mg - 01/29/93
	75mg - 01/09/86	75mg - 12/22/92	75mg - 01/29/93
Patent Number	3641127	N/A	N/A
Patent Expires	2/08/91	N/A	N/A
Applicant number and product number	25mg = N18754 001	25mg = N73515 001	25mg = N74014 001
	50mg = N18754 002	50mg = N73516 001	50mg = N74014 002
	75mg = N18754 003	75mg = N73517 001	75mg = N74014 003

Food Drug Cosmetic Law Reports: Approved Drug Products With Therapeutic Equivalence Evaluations, 14th Edition; Chicago
II.CCH Incorporated. Report 1655, June 16, 1994

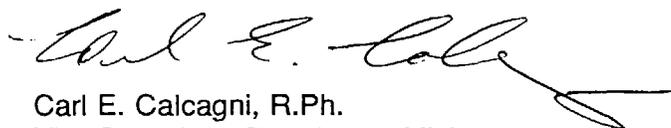
July 15, 1994

Please find enclosed in the archival and clinical copies of Volume #1B and #1C, thirteen diskettes which contain the clinical database and five diskettes which contain the consumer use data, respectively.

This portion of the submission was presented to the Pilot Drug Division on May 25, 1994. In addition, the archival and chemistry copies of Volume #1 contain the stability database on one diskette.

If any questions should arise with regard to this original 505(b)(2) New Drug Application, please contact Lee Scaros, Pharm.D. at (203) 937-2693.

Sincerely Yours,



Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs

LS/jmd

**APPEARS THIS WAY
ON ORIGINAL**