

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-317

ADMINISTRATIVE DOCUMENTS

Bayer Corporation
Bayer Consumer Care Division

Extra Strength Bayer Migraine (500 mg buffered aspirin)
NDA 21-317

PATENT INFORMATION

In accordance with Section 505(b) and (c) of the Act and 21 C.F.R. §§ 314.50 – 314.53, Bayer Corporation states that it is unaware of any patent that claims the drug or a method of using the drug with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture use or sale of the drug product.

Request for Three-Year Exclusivity

Bayer Corporation, Consumer Care Division is requesting three-year marketing exclusivity from the date of approval of this application under the provisions of 21 CFR 314.108(b)(4). This request is based on the following:

- No drug product containing 500 mg aspirin with the same conditions of approval has been previously approved.
- The three new clinical investigations included in this application were conducted on humans, and meet the definition of "a new clinical investigation" set forth in 21 CFR 341.108(a). Bayer certifies that any such investigation has not been used by the Agency as part of the basis for a finding of substantial evidence of effectiveness for any previously approved new drug application or supplement.
- The three new clinical investigations included in this application are essential for approval, and meet the definition of "essential to approval" set forth in 21 CFR 341.108(a). The clinical investigations were sponsored by Bayer Corporation under IND: They are as follows:
 - Study No. S98-072- "A Multi-Center, Prospective, Randomized, Double-Blind, Parallel Group, Single-Dose, Placebo Controlled Study of the Efficacy of Extra-Strength Bayer Aspirin (1000 mg) in Subjects with Acute Migraine Attacks."
 - Study No. S98-073- "A Single Center, Prospective, Randomized, Double-Blind, Parallel Group, Single-Dose, Placebo Controlled Study of the Efficacy of Extra-Strength Bayer Aspirin (1000 mg) in Subjects with Acute Migraine Attacks."
 - Study No. S98-074- "A Multi-Center, Prospective, Randomized, Double-Blind, Parallel Group, Single-Dose, Placebo Controlled Study of the Efficacy of Extra-Strength Bayer Aspirin (1000 mg) in Subjects with Acute Migraine Attacks."

EXCLUSIVITY SUMMARY for NDA # 21-317 SUPPL # _____

Trade Name EXTRA STRENGTH
BAYER MIGRAINE Generic Name acetylsalicylic acid (aspirin)

Applicant Name BAYER CORPORATION
CONSUMER CARE DIVISION HFD- 560

Approval Date OCT 18, 2001

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 questions 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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9 (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.

Approved under OTC Monograph

YES / / NO / /

Aspirin

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

NDA # 16-030 (*Bayer Corporation*) *Aspirin* *Measurin - EXTENDED RELEASE CAPLETS*

NDA # _____

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 9. 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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:

- (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? If not applicable, answer NO.

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:

Investigation #1, Study # 598-072

Investigation #2, Study # 598-073

Investigation #3, Study # 598-074

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

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

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

Investigation #3 YES / / NO / /

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO //
Investigation #2 YES /___/ NO //
Investigation #3 YES /___/ NO /

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation # 1, Study # 598-072
Investigation # 2, Study # 598-073
Investigation # 3, Study # 598-074

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.

(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: _____

ISI
Signature of Preparer
Title: Regulatory Project Manager

10-10-01
Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

Bayer Corporation
Bayer Consumer Care Division

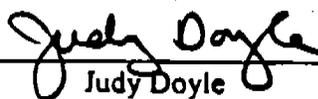
Extra Strength Bayer Migraine (500 mg buffered aspirin)
NDA 21-317

**BAYER CERTIFICATION IN COMPLIANCE WITH THE
NEW DRUG AND ABBREVIATED NEW DRUG
APPLICATIONS; PREAPPROVAL INSPECTION
REQUIREMENTS**

Bayer Corporation certifies that the documents contained herein are an identical copy to those submitted to FDA Division headquarters for review and approval.

12/13/00

Date



Judy Doyle

Associate Director Regulatory Affairs

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

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

NDA/PLA/PMA # 21317 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF _____ Trade and generic names/dosage form: aspirin (acetylsalicylic acid) 500mg Action: (AP)AE NA

Applicant Bayer Corporation
Consumer Care Division Therapeutic Class INTERNAL ANESTHESIC

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate

Proposed indication in this application N.A.

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

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

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ___ Children (2-12yrs) ___ Adolescents(12-16yrs)

- ___ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- ___ 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- ___ 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - ___ c. The applicant has committed to doing such studies as will be required.
 - ___ (1) Studies are ongoing.
 - ___ (2) Protocols were submitted and approved.
 - ___ (3) Protocols were submitted and are under review.
 - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
 - ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- ___ 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- ___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___ No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader).

Signature of Preparer and Title /S/

Date 10-11-01

cc: Archival NDA/PLA/PMA # 21-317
HF 560 /Div File
NDA/PLA Action Package
HFD-104/Peds/T.Crescenzi

(revised 3/6/00)

Bayer Corporation
Bayer Consumer Care Division

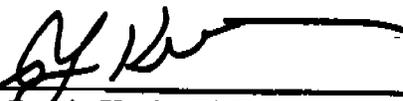
Extra Strength Bayer Migraine (500 mg buffered aspirin)
NDA 21-317

**BAYER CERTIFICATION IN COMPLIANCE WITH
THE GENERIC DRUG ENFORCEMENT ACT OF 1992**

Bayer Corporation, Consumer Care Division, certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in Connection with this application.

December 15, 2000

Date



Randy Koslo, Ph.D.

Director

Medical Affairs and Clinical Research

3 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.



MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

Date: September 21, 2001 *TS*

From: Charles J. Ganley, M.D.
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: Extra Strength Bayer Aspirin for Migraine Regulatory Action

To: NDA 21-317

NDA 21-317 was submitted by Bayer Corporation to support the use of Extra Strength Bayer Aspirin (ESBA) for the treatment of migraine headaches. Dr. Kevin Prohaska from the Division of Neuropharmacological Drug Products (HFD-120) completed the primary review of the clinical studies. In addition, Dr. Russ Katz and Dr. Armando Oliva provided summaries that include a recommendation that the application not be approved. The basis for their conclusions will not be repeated in detail in this memo but are based in part on the failure to establish benefit for the primary endpoint in subjects who had severe headaches at baseline. The studies also fail to support claims for the secondary symptoms of migraine. Thus, not having established benefit for the entire symptom complex of migraine, and benefit in pain intensity in all sub-populations of varying intensity at baseline, they recommend that the application is not approvable. They also note that granting a claim for pain of migraine is problematic.

Indications Limited to Migraine Pain

Three OTC analgesic products are currently approved for the treatment of migraine headache. The actual claims vary based on the data provided in each NDA. Motrin has a limited claim for the treatment of migraine pain whereas Advil and Excedrine have indications for the treatment of migraine (this includes the secondary symptoms of nausea, photophobia, phonophobia). The history of how this came to pass is complicated but started in 1997 with the initial approval of Excedrine "for the temporary relief of mild to moderate pain associated with migraine". It should be noted that the issue was taken before an advisory committee who supported a migraine type claim in an OTC market. Additional analyses were eventually submitted for Excedrine to support the secondary symptom claims and a general claim for treats migraine was born. During this time, development programs and NDA submissions for Motrin and Advil were based on the original claim given to Excedrine. Unfortunately, the Motrin application did not have the data to support the secondary symptom claims but the data in the Advil application supported it. Because the agency had already recognized pain of migraine as an acceptable OTC claim in the initial Excedrine approval, a similar claim was approved for Motrin. Without a sufficient basis for reversing the original decision made for Excedrine, it is difficult to not consider a limited claim for this application if the data support it. Although I may share Dr. Katz's and Oliva's uneasiness for the limited claim for pain, from a regulatory point of view a sufficient basis to not consider it has not been provided.

ESBA Clinical Data

The sponsor completed three clinical trials (S98-72, S98-73, S98-74) in a population of patients who had a history of migraine headache responsive to OTC therapy. The primary measure of efficacy was pain intensity and calculated as the percent responders at two hours. A responder was someone who experienced a two-point reduction in pain intensity using a four-point pain scale (0 - 3). As a consequence,

a subject could be a responder but still have symptoms of a migraine present at two hours. A responder did not have to achieve complete relief. The studies also evaluated the effect of treatment on the secondary symptoms associated with migraine (nausea, photophobia, phonophobia).

Study 72 and 74 show a significant treatment effect for the primary measure of efficacy. Study 73 did not show a significant treatment effect. For the secondary measures of efficacy, nausea was not significantly improved with ESBA in any of the trials whereas photophobia and phonophobia are significantly improved with ESBA in study 72 and 74. In view of the findings for the primary endpoint and secondary symptoms in study 73, this study fails to provide any support to this application.

In study 72, subjects with either moderate or severe headaches at baseline appear to have a benefit from therapy. Baseline pain severity does not matter. In study 74, all of the benefit appears to be derived in the sub-group with moderate headaches at baseline. The percentage of responders in the severe sub-group is not different between treatment groups. Study 73 is somewhat of an anomaly compared to the other two because it already failed on the primary endpoint and all of the secondary symptom endpoints. The failure of this study may not be solely attributable to the response in patients with severe headaches at baseline.

The issues raised by Dr. Oliva regarding the baseline severity are interesting but are not conclusive. There are clearly other rational subgroup analyses that can be conducted based on a variety of factors such as gender, age, race, headache frequency, use of chronic suppression therapy, etc. It is not clear how severity at baseline should take precedent and be raised to a higher importance. Consequently, it is difficult to interpret the results of any subgroup analysis unless they were clearly pre-specified as pivotal to the overall interpretation of the study. That was not done in this case.

Additionally, it is unclear whether an OTC therapy is required to establish effectiveness in all subgroups. For the OTC monograph drug review, 21 CFR 330.10 defines effectiveness as a reasonable expectation that, in a target population, the pharmacological effect of the drug, when used under adequate directions of use and warnings against unsafe use, will provide clinically significant relief of the type claimed. There are clearly conditions of use in the OTC market where severe symptoms may not be responsive to the OTC therapy (e.g. insomnia, heartburn). In these cases, the consumer is generally directed to see their physician.

Recommendations

- Study 72 and 74 showed a significant treatment effect for the primary endpoint of pain but they failed to show a benefit for the secondary symptoms of migraine. There is sufficient data to support a claim for migraine pain but not a general claim for migraine.

• _____

MEMORANDUM

DATE: August 1, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-317

SUBJECT: Division Recommendation for Action on NDA 21-317, for the use of Extra Strength Bayer Aspirin in patients with Migraine

This NDA, submitted by Bayer Corporation, contains the results of 3 randomized, controlled trials, adequate by design to examine the effectiveness of Extra Strength Bayer Aspirin (ESBA) as an acute treatment for migraine. The data have been reviewed by Dr. Prohaska, medical officer, HFD-120, Dr. Yeh-Fong Chen, statistician, HFD-710, and Dr. Armando Oliva, Neurology Drugs Team Leader, HFD-120. Drs. Prohaska and Chen have concluded that the data support certain effectiveness conclusions; for example, they conclude that ESBA is effective for the headache of migraine, as well as for the photophobia and phonophobia of migraine.

Dr. Oliva, on the other hand, while essentially agreeing with Drs. Prohaska and Chen about the basic findings, recommends that the application not be approved; that is, he concludes that the evidence supports no claims. He bases his conclusion on the fact that, because a consistent effect on nausea has not been demonstrated, ESBA cannot be considered a bona fide treatment for "migraine". As he notes, a similar finding was the basis for the Agency's lack of approval for Motrin as a treatment for migraine; in that case, Motrin was granted a claim for the pain of migraine.

Dr. Oliva also points out that the data strongly suggest that there is no reproducible effect of ESBA on severe headaches. He does point out that there is no requirement for such a demonstration, but even in the Motrin NDA there was a trend in favor of drug for severe headaches; in this application, there is clearly no such trend in Studies 73 and 74. This strongly suggests that the lack of any demonstrable effect on severe headaches in these 2 studies is not due to a lack of power to detect such an effect. Further, Dr. Oliva points out that in Study 73, which was "negative" on its primary outcome, there was a nominally significant finding for moderate headaches. This does suggest, as he points out, that whatever effect on migraine pain this product may have, it seems to be related to an effect on moderate headaches.

I agree with Dr. Oliva's recommendation. Our approach with all proposed migraine treatments has been that such a claim must be supported by significant findings on the 3 major associated symptoms of nausea, photophobia, and

phonophobia. All treatments granted a "migraine" claim have demonstrated such effects. In this application, no such effect is seen in any of the three controlled trials in the analyses that we ordinarily perform. Indeed, the analyses performed by the sponsor to address this question (in which the data from only those patients who had nausea at baseline is analyzed) also did not demonstrate any effect on nausea. None of the analyses document any reasonable numerical trends in favor of the drug for this outcome.

Further, I agree with Dr. Oliva's conclusion that the data seem to support the conclusion that the effect on migraine pain is accounted for by an effect on moderate pain, and that this would be an inappropriate OTC (or Rx) claim (I also agree with Dr. Oliva's larger point that granting a claim for the "pain of migraine" is problematic).

Finally, one very small point about the analysis that we prefer of the major associated symptoms. All 3 members of the review team suggest that one reason for not relying upon an analysis of only those patients who had the symptom of interest at baseline is that this represents a subset of patients that is not randomized. I disagree. I believe that randomization is preserved in this subset, given that it is defined by a baseline (pre-randomization) characteristic. It is true, given that it is smaller than the total randomized sample, that randomization may not have been as "successful" as it might have been in the total sample, but this is an entirely different point. However, I still agree with the review team that our preferred analysis (in which all patients are included) is appropriate, because patients may develop the symptom at any time during the assessment period.

/s/

Russell Katz, M.D.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
8/1/01 03:52:21 PM
MEDICAL OFFICER



MEMORANDUM

Date: July 24, 2001
From: Armando Oliva, MD
To: Russell Katz, MD
Subject: Team Leader Memorandum for NDA 21-317, Bayer Migraine

Bayer Corporation submitted an NDA for Bayer Migraine and Midol Migraine (acetylsalicylic acid, or aspirin) on 12/19/2000 to the Division of Over the Counter Drug (OTC) Products. The proposed indication is the temporary relief of migraine headache and associated symptoms (nausea, photophobia, and phonophobia) in adults 18 years and older. The marketed formulations will each contain 500mg of aspirin. The proposed therapeutic dose is 1,000mg given as a single dose.

Currently, Extra Strength Bayer Aspirin 500mg, is marketed and indicated for "relief of headache, painful discomfort, and fever of colds, muscular aches and pains, temporary relief of minor pains of arthritis, toothache and pain following dental procedures and dental pain" in adults and children 12 years and older. The recommended dose is 1 to 2 tablets every 4 to 6 hours as needed. The maximum daily dose is 4 grams.

Professional labeling already exists for a wide range of peripheral and cardiovascular conditions, and rheumatologic diseases. I do not discuss these further.

This NDA contains the results of three adequate and well controlled trials that used a single dose of unbuffered aspirin 1,000mg to treat an acute migraine of moderate/severe intensity. It also contains a bioequivalence study that compared two different formulations (buffered vs. unbuffered), as well as the sponsor's review of global safety.

By mutual agreement between our Division and the Division of OTC, their Division is the principal review division and we are acting as consultants. We agreed to review the results of the three controlled trials, and the single PK study. The Division of OTC would review the global safety of the product.

I divide my memo into three sections:

- a review of the short-term studies (as performed by Dr. Prohaska, the medical officer, and Dr. Yeh-Fong Chen, the biostatistician),
- a review of the PK study (as performed by Dr. Hong Zhao), and
- my discussion and recommendation.

There were no disagreements between the medical and statistical reviews with regard to which analyses did or did not reach statistical significance.

Acute Migraine Studies

The sponsor refers to the three controlled studies as S98-072, S98-073, and S98-074. In this memo, I refer to them as studies 072, 073, and 074. All three studies shared a similar design with the exception that study 073 took place at a single center, and the other two were multi-center trials.

The three trials were randomized, double-blind, placebo-controlled, parallel-group studies. They enrolled patients that met the International Headache Society (IHS) criteria for migraine with or without aura. Patients were at least 18 years of age, and received a diagnosis of migraine prior to the age of 50. They had to have a history of migraine of at least one year at screening, and have 1-6 migraines per month. In addition, subjects should have been able to distinguish migraine from other types of headaches, and have no more than 15 headache days per month.

Excluded were subjects whose headaches didn't respond historically to over-the-counter medication and/or prescription medication. The sponsor also excluded subjects who experienced vomiting in greater than twenty percent of their migraines, or experienced unusual migraine variants such as basilar or ophthalmoplegic migraine. The goal was to enroll subjects who were likely to take OTC therapies for their migraines. These exclusion criteria are similar to those that other sponsors used to develop other OTC products for migraine, and one can assume it resulted in a population of "milder" migraine sufferers (at least milder than the migraine population recruited for typical triptan studies, which did not contain these exclusionary criteria).

Study 072 used a random telephone screening procedure to recruit subjects. Studies 073 and 074 identified potential subjects using private practice records, research databases, referrals, and local advertising (*i.e.*, conventional recruiting). This is similar to the recruiting methods used in previous NDA's involving other OTC migraine products.

The sponsor powered the studies to achieve 85% power to detect a 15% difference in the primary endpoint (percent responders at 2 hours) between ASA and placebo, using a two sided $\alpha = 0.05$.

Investigators randomized subjects either to 1,000mg of aspirin, or placebo. They instructed subjects to treat a single migraine of moderate or severe intensity within eight weeks of randomization. Rescue medication was permitted after two hours. Those taking rescue prior to two hours were considered treatment failures. A second dose of study medication was not used to treat either persistent or recurrence (although subjects could use open-label Extra Strength Bayer Aspirin 1,000mg as rescue).

The patients recorded efficacy variables in the headache diary at various time points out to six hours, with the exception of headache recurrence which they assessed out to 24 hours. The investigators assessed safety by having the patients record adverse events in the patient diary through hour 24, and by patient interview at the follow-up visit (which occurred within 7 days of treatment).

The primary efficacy analysis compared the percentage of patients who responded at two hours between drug and placebo. The sponsor defined a response in the traditional manner: subjects responded to treatment if they had moderate or severe pain at baseline, mild or no pain at two hours, and didn't require rescue in the interim. Important secondary analyses included the prevalence of nausea, photophobia, and phonophobia at two hours.¹

At this point, I'd like to describe in some detail the various populations that were analyzed for efficacy because the sponsor's ITT population differed from the definition we typically use. Ordinarily, we include in the ITT population any patient who took study medication and who recorded at least one post-treatment observation. Instead, the sponsor's ITT population (labeled ITT_{CM} in Dr. Prohaska's review) included just those patients who treated a "confirmed migraine." It is not clear why the sponsor chose this population for their analysis, but based on the interaction that took place with CDER prior to NDA filing, I believe I understand their misunderstanding.

During pre-NDA discussions, we had raised the possibility that some patients might treat a headache other than a migraine. This was based on our experience with the Motrin Migraine Pain application in which this became an important issue. If this occurred frequently, then we would have difficulty interpreting the results of these studies, given that aspirin is already approved for the treatment of headache in general. Therefore, we recommended they use an algorithm to identify probable migraines, and to analyze the subset of migraineurs that actually treated a probable or "confirmed migraine."² We intended this as a secondary analysis that would, hopefully, support the primary ITT analysis. We never intended that this analysis replace the traditional ITT analysis. There must have been a confusion in communication, since they reported this analysis as primary.

The sponsor also performed efficacy analysis on the safety population (*i.e.*, all patients who took study medication). This included 10 patients who did not meet the criteria for "confirmed migraine" as well as an additional 11 patients who took study medication but failed to provide any post-treatment efficacy data (which the sponsor treated as treatment failures for their analysis).

It is clear that the ITT_{CM}, ITT, and the safety population were all very similar (Table 1, adapted from the medical review tables 3 and 15) and, as Dr. Prohaska reports in his review, the efficacy results do not meaningfully differ among the various populations.

¹ Dr. Prohaska describes in his review additional secondary analyses that the sponsor performed (*e.g.*, PID, SPID, recurrence, time to recurrence, severity of associated symptoms, vomiting, functional ability). Although they are of clinical interest, I don't describe them further in this memo and instead I refer the reader to the clinical review.

² This algorithm is based on a modification of the IHS diagnostic criteria for migraine disorders (with and without aura) that I developed during the course of my reviews of the Advil Migraine and Motrin Migraine Pain NDA's. We provided them a copy of the algorithm that we had used in the past.

Table 1: Analysis Populations

	S98-072		S98-073		S98-074		Pooled	
	ASA	PBO	ASA	PBO	ASA	PBO	ASA	PBO
Randomized	243	242	224	222	240	242	707	706
Safety Population	205	204	199	183	192	208	596	595
ITT (traditional)	204	202	197	181	191	205	592	588
ITT _{CM}	201	200	197	180	188	204	586	584

Each study treated approximately 400 patients, which were roughly evenly divided between drug and placebo. The demographics described here relate to the safety population, as defined above. Across all studies, 79% were female (which is typical of outpatient adult migraine trials). The vast majority were Caucasian (79%) and the mean age was 36.6 years. This is slightly lower but similar to other migraine studies, where the mean age tends to be around 40. There were no subjects under the age of 18 and only 9 subjects were ≥ 65 years of age. Age, sex, and race distributions were similar among the treatment groups in the three studies (table 4 in the medical review), with the exception of study 73, where the placebo group was significantly younger (mean 29.6) compared to the aspirin group (31.8). I doubt this represents a clinically meaningful difference.

Regarding baseline migraine characteristics, 68% reported treating a moderate headache. This is typical compared to previous migraine studies where usually two-thirds of the attacks are rated as moderate at baseline. These were evenly distributed between treatment groups in each study. Similarly, the secondary symptoms of nausea, photophobia, and phonophobia were also evenly distributed at baseline. Of note, 78% of the headaches treated in study 074 were moderate. This was higher than in the other two studies (62-64%).

I show the primary analysis (percent responders at 2 hours) in Table 2 (table 15 of the medical review). Dr. Prohaska used a last post-treatment observation carried forward (LOCF) approach to impute missing data. The results are almost identical to those obtained by the statistical reviewer, Dr. Yeh-Fong Chen (tables 10-12 of the statistical review pages 21-22, the only difference was that she counted 55 placebo responders in study 074 to Dr. Prohaska's 56, but the p-values for the three studies are the same).

Table 2: Percent Responders at Two Hours Post-Dose

Study	ESBA	Placebo	p-value*
S98-072	112/204 (54.9%)	72/202 (35.6%)	<0.001
S98-073	97/197 (49.2%)	76/181 (42.0%)	0.158
S98-074	76/191 (39.8%)	56/205 (27.2%)	0.007

*CMH, stratified by Investigator

The results show that study 072 and 074 both demonstrated a significant treatment effect in favor of aspirin at two hours.³ Study 073 (the single center study) was negative on its primary analysis. The sponsors analysis using the "confirmed migraine" population confirms these results (table 7 of the medical review).

³ I note again that 072 used random telephone screening, and 074 used standard recruiting methods.

Dr. Prohaska performed a subgroup analysis by baseline pain intensity using the ITT population (Table 3, medical review table 16). Patients who had a moderate pain at baseline benefited from aspirin treatment in all three studies.

Table 3: Percent Responders at Two Hours Post-Dose (by baseline pain intensity)

Study	Baseline Severity	ASA	PBO	p-value
S98-072	Moderate	69/123 (56.1%)	50/127 (39.4%)	0.008
	Severe	43/81 (53.1%)	22/75 (29.3)	0.003
S98-073	Moderate	78/125 (62.4)	55/116 (47.4)	0.020
	Severe	19/72 (26.4%)	21/65 (32.3%)	0.448
S98-074	Moderate	65/146 (44.5%)	44/161 (27.3%)	0.002
	Severe	11/45 (24.4%)	11/44 (25.0)	0.927

*CMH, stratified by Investigator

However, those with severe pain benefited in study 072, but not in the other two studies. In fact, treatment of severe migraine pain with aspirin was associated with a numerically lower prevalence of responders at 2 hours in the aspirin group in study 073, and there was essentially no difference when compared with placebo in study 074. The sponsor's analysis using the "confirmed migraine" population gave almost identical results (medical review table 8). There was no consistent, reproducible effect of aspirin treatment on severe pain. The statistical reviewer's findings were identical (pages 27, 28, 29 of the statistical review), with a severity by treatment interactions of $p=0.48$, 0.04 , and 0.09 for studies 072, 073, and 074, respectively.

There appeared to be no effect of gender or race on the efficacy results. There were too few people over the age of 65 to make any conclusions regarding efficacy in the elderly.

Patients rated nausea, photophobia, and phonophobia on a 4 points scale (none, mild, moderate, severe). The sponsor analyzed these associated migraine symptoms using two methods that we don't ordinarily use: mean difference from baseline using the least square means, and the proportion reporting resolution of symptoms using the Cochran-Mantel-Haenszel test for row mean scores. They only included patients who had the symptom at baseline. We don't favor this approach because it uses a non-randomized subgroup for the analysis, and ignores subjects that may develop the symptoms over the course of treatment. Instead, we favor an analysis that compares the prevalence of each symptom in the ITT population at two hours.

Dr. Prohaska describes the sponsor's analyses in his review, but he also performs the analysis that we generally prefer. I only present Dr. Prohaska's analysis here, and describe the differences (if any) from the sponsor's conclusions. Table 4 shows the prevalence of associated symptoms at baseline and at two hours (tables 17 and 18 from Dr. Prohaska's review). Dr. Chen's statistical review was again in agreement with Dr. Prohaska's findings. Although there were slight differences in her p-values in some cases, there were no disagreements with regards to which analyses did or did not reach nominal significance (tables 10-12 of the statistical review, pages 21-22).

Table 4: Prevalence of Migraine Associated Symptoms at Baseline and Two Hours

Study		Nausea	Phonophobia	Photophobia
Baseline				
S98-072	ASA	116/204 (56.9%)	198/204 (97.1%)	196/204 (96.1%)
	PBO	110/202 (54.5%)	195/202 (96.5%)	194/202 (96.0%)
	p-value*	0.654	0.734	0.959
S98-073	ASA	124/197 (62.9%)	187/197 (94.9%)	193/197 (98.0%)
	PBO	108/181 (59.7%)	172/181 (95.0%)	176/181 (97.2%)
	p-value*	0.514	0.963	0.641
S98-074	ASA	122/191 (63.9%)	176/191 (92.2%)	185/191 (96.9%)
	PBO	137/205 (66.8%)	189/205 (92.2%)	198/205 (96.6%)
	p-value*	0.593	0.917	0.925
Two-Hours				
S98-072	ASA	81/204 (39.7%)	130/204 (63.7%)	134/204 (65.7%)
	PBO	70/202 (34.7%)	159/202 (78.7%)	164/202 (81.2%)
	p-value*	0.299	<0.001	<0.001
S98-073	ASA	80/197 (40.6%)	136/197 (69.0%)	152/197 (77.2%)
	PBO	85/181 (47.0%)	138/181 (76.2%)	151/181 (83.4%)
	p-value*	0.214	0.118	0.127
S98-074	ASA	100/191 (52.4%)	130/191 (68.1%)	140/191 (73.3%)
	PBO	107/205 (52.2%)	167/205 (81.5%)	175/205 (85.4%)
	p-value*	0.870	0.002	0.003

*CMH, stratified by Investigator

The prevalence of nausea, photophobia, and phonophobia were reasonably balanced among the various treatment groups at baseline. Between half and two-thirds of the patients had nausea at baseline across all treatment groups, which is typical of migraine studies of this type. The vast majority (in excess of 90%) had phonophobia and photophobia at baseline.

The prevalence of nausea at two hours was not significantly affected by aspirin treatment. Numerically, aspirin treatment was associated with a lower prevalence of nausea at two hours in study 073 (which lost on pain), but nausea was actually numerically higher with aspirin treatment in study 072, and was no different from placebo in study 074. The sponsor's analyses were consistent with this finding (table 9 in the medical review, not shown here). The sponsor also performed a pooled analysis on nausea which resulted in a nominally significant p-values at later time points (*i.e.*, 3 hours or greater, which are confounded by use of rescue that included additional open label doses of aspirin), but was still not significant at 2 hours.⁴ Dr. Yeh-Fong Chen concludes on page 22, and I agree, that the p-value from this type of pooled analysis is not suitable for decision making.

Treatment with aspirin was associated with a nominally significant decrease in prevalence of both photophobia and phonophobia in two of the three studies (072 and

⁴ ISE tables C-10 and C-10a, pages 77, 78, not shown here.

074, which are also the two that won on pain), and the prevalence of each was in the right direction for study 073. The sponsor's analyses were consistent with these findings (tables 10 and 11 in the medical review).

In summary, aspirin, when given as a single unbuffered 1,000mg dose, appeared to be effective in the treatment of headache associated with migraine, but the treatment effect appeared to result largely from the subgroup of patients who treated a moderate headache. Aspirin was not effective for the treatment of nausea, but seems to be effective against photophobia and phonophobia. I elaborate further on these findings in the discussion section below.

The sponsor collected safety data from the three controlled efficacy trials, plus the one PK study. The PK study (discussed in the next section of this memo) treated 51 subjects with two formulations of aspirin. Patients in that study reported only one adverse event (migraine); therefore, the sponsor did not include it in the integrated safety summary.

There were no deaths, and only three serious adverse events. Two of the three SAE's occurred in patients who never took study medication (brain tumor, gastrointestinal hemorrhage). The third event was a ruptured appendix that occurred two weeks following ingestion of placebo. Clearly none of these events can be attributed to study medication. There were no adverse dropouts, which is not unusual for a single attack study where the opportunity to discontinue due to an adverse event is small.

Overall, 11% of aspirin patients and 8% of placebo patients reported at least one adverse event. As can be expected, the most commonly occurring AE's in the aspirin group were gastrointestinal in nature. Most were mild or moderate and resolved without sequelae. The most commonly occurring AE in the aspirin group was nausea (2%, vs. 1% for placebo). Other commonly occurring AE's (occurring $\geq 1\%$ and greater than placebo) were asthenia, insomnia, and somnolence. There were no identifiable gender differences.

The sponsor collected no additional safety data (*e.g.*, laboratory, ECG, etc.).

In summary, there was little in the safety database to suggest any safety concerns with the dosing regimen used to treat migraine in this population.

Clinical Pharmacology Study

The sponsor conducted a single bioequivalence study (S99-102) that compared the PK of commercial extra-strength Bayer Plus Buffered Aspirin and commercial Extra-Strength Bayer Aspirin Caplets in healthy adults under fasting conditions. Dr. Hong Zhao from OCPB reviewed this study. The goal is to compare the formulation used in the clinical trials (the unbuffered caplets) with the buffered formulation.

The study treated 25 healthy volunteers (11 males, 14 females), ages 19-45 years. The majority (84%) were Caucasians, and the remaining were Hispanic. Subjects received a single 500mg oral dose of both formulations using a crossover design and a 7-day washout period between doses.

Since acetylsalicylic acid is rapidly converted in the body to salicylic acid via first-pass hepatic metabolism (73% in 30 minutes), the sponsor measured salicylate levels for their PK analysis. I show the results in Table 5 (unnumbered biopharm review table, page 3).

Table 5: Study 102 – PK Results

N=25 Parameter	T (Buffered)	R (Unbuffered)	Geometric Mean	
	Mean±SD	Mean±SD	Ratio (T/R)	90% CI
C _{max} (µg/ml)	34.8±8.6	33.2±7.8	1.045	99.8-109.4
AUC _t (µg.h/ml)	190±64	183±64	1.038	100.5-107.3
AUC _{inf} (µg.h/ml)	199±73	191±72	1.038	100.3-107.4
T _{max} (h)	1.7±0.5	1.9±0.9		
T _{1/2} (h)	2.1±0.5	2.1±0.4		

Means were derived from least squares means.

These data demonstrate that the buffered formulation is bioequivalent to the unbuffered (reference) formulation. Since the intended use is the acute treatment of migraine, we have always looked at T_{max} very carefully to insure that the test product has a T_{max} that is not delayed compared to the reference product. This table shows that the T_{max} of the buffered formulation is, if anything, shorter than the reference product used in the clinical trials and is therefore not a concern clinically.

Discussion

The sponsor seeks approval for a migraine indication. Currently, this Division requires that a new treatment for migraine demonstrate efficacy on headache (the primary analysis), and on the key migraine-associated symptoms of nausea, photophobia, and phonophobia. We have applied these standards consistently to all recent OTC products and recent triptan medications. Furthermore, when applied retrospectively to previously approved triptan, they hold up quite well.⁵ The body of evidence presented in this NDA fails to establish Bayer Migraine as an effective treatment for acute migraine because it appears to be ineffective against nausea. Nausea is a common symptom in migraine, occurring generally in half to two-thirds of migraines treated across various migraine trials.

At best, all one can say is that Bayer Migraine is effective for the headache associated with migraine. Since aspirin is already approved for the treatment of headache, granting a new indication for the headache of migraine would result in a pseudo-specific claim. This was the same objection I had to the approval of Motrin Migraine Pain, and it was the basis for my non-approval recommendation for that NDA. In the Motrin NDA, Motrin was shown to be effective against the pain of migraine, but it too failed on nausea.⁶ Therefore, the Agency ultimately did not grant a migraine claim for that drug, but instead approved it for the pain of migraine headache.

⁵ The only approved triptan product that fails this standard is Imitrex Nasal Spray 5mg, but we have ample and overwhelming evidence from other doses/formulations that sumatriptan itself is an effective anti-migraine agent.

⁶ I should add that it also failed in photophobia and phonophobia in one of the two pivotal trials.

Although the two NDA's may appear quite similar up to this point, I would like to point out a significant difference that raises even further doubt, in my mind, about the approvability of aspirin even for the pain of migraine headache.

The efficacy data, as presented by the sponsor and re-analyzed by Drs. Prohaska and Chen, show that the beneficial effect on headache is largely driven from the effect in the subgroup of patients who experienced a moderate headache at baseline. I once again show these results below (table 16 from the medical review).

Table 6: Percent Responders at Two Hours Post-Dose (by baseline pain intensity)

Study	Baseline Severity	ASA	PBO	p-value
S98-072	Moderate	69/123 (56.1%)	50/127 (39.4%)	0.008
	Severe	43/81 (53.1%)	22/75 (29.3)	0.003
S98-073	Moderate	78/125 (62.4)	55/116 (47.4)	0.020
	Severe	19/72 (26.4%)	21/65 (32.3%)	0.448
S98-074	Moderate	65/146 (44.5%)	44/161 (27.3%)	0.002
	Severe	11/45 (24.4%)	11/44 (25.0)	0.927

*CMH, stratified by Investigator

In only one study (study 072) was there a nominally significant effect on severe pain. In the other two studies, the effect was not nominally significantly different from placebo. In study 074, there was no numeric difference between the two groups, and, as it turned out, aspirin-treated patients with severe pain in study 073 numerically did worse than their placebo counterparts.

Now, I must point out that having an effect on severe pain has never been a requirement for the approval of a new migraine drug. Clearly, migraine studies are not designed or powered to detect such a treatment effect in this subgroup. In fact, the review of the Motrin NDA showed a questionable effect on severe pain, as shown in Table 7 below (taken from my Motrin NDA 19-012 review, table 26, page 33).

Table 7: Motrin NDA Studies 22 and 30 – 2-Hr Response, by Baseline Pain Intensity

Symptom	Study 22				Study 30			
	200 mg (n=169)	400 mg (n=177)	PBO (n=179)	p*	200 mg (n=176)	400 mg (n=177)	PBO (n=170)	p*
Response Rate, n (%)								
Baseline Mod Pain	53/113 (46.9%)	43/119 (36.1%)	39/117 (33.3%)	0.084	53/111 (47.8%)	53/125 (42.4%)	35/120 (29.2%)	0.011
Baseline Severe Pain	13/54 (24.1%)	21/58 (36.2%)	13/62 (21%)	0.144	15/65 (23.1%)	15/50 (30%)	6/47 (12.8%)	0.122

* chi-square

Although the overall comparison for severe pain failed to reach nominal significance in either Motrin study, I at least took comfort in the fact that numerically there was a dose-response relationship in favor of drug in both studies in the subset of patients with severe

pain at baseline.⁷ Such a relationship does not exist in the current application. Therefore, I do not have the same level of comfort that aspirin has a similar effect on severe pain.

Since the treatment effect is largely driven by the effect seen on moderate pain⁸, then the only possible indication I can possibly envision granting at this time is the treatment of moderate pain associated with migraine headache. I don't believe this is a reasonable indication and I believe it would cause tremendous confusion for consumers. Already, we have three OTC products on the market that either treat the entire syndrome (Excedrin Migraine, Advil Migraine), or at least appears to reasonably treat the headache (Motrin Migraine Pain), regardless of severity. This product appears to fall short on both accounts (the appropriateness of an isolated pain of migraine headache claim notwithstanding). Therefore, I recommend a non-approval action.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

⁷ I also point out that the p-values given in Table 7 are for the overall comparison. I did not present p-values in my original review for the pairwise comparison between 400mg vs. placebo in severe pain. A simple pair-wise chi-square analysis of 400mg vs. placebo in study 22 in the Motrin NDA shows a p-value of 0.06, and for study 30, the p-value is 0.04.

⁸ I find it also interesting that study 073, although negative on its primary endpoint, was nominally positive in the subgroup of patients with moderate pain, further supporting this conclusion.

Barry N. Rosloff, Ph.D.
10/16/01

NDA 21-317 (Bayer aspirin for migraine)

I have been asked to comment on the sponsor's request to waive the requirements for animal studies "based on the Internal Analgesic Monograph that fully addresses this information. Aspirin is generally recognized as safe and effective by the Agency at the proposed dose in this application."

I believe that the waiver can be granted, primarily based on our usual practice of not requiring new animal studies if the clinical use of the drug will not be expanded in a significantly quantitative or qualitative manner. It is noted that we did not require additional animal studies in the analogous case of Excedrin for migraine (NDA 20-802).

Barry Rosloff

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Barry Rosloff
10/16/01 11:27:48 AM
PHARMACOLOGIST

**CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION**

FACSIMILE TRANSMISSION RECORD

DATE: May 18, 2001
FROM: Walter J. Ellenberg, Ph.D.
Division of OTC Drug Products, HFD 560
PHONE: 301-827-2247
TO: Judy Doyle
Bayer Consumer Care Division
36 Columbia Road
PO Box 1910
Morristown, NJ 07962
PHONE: 973-408-8181

No. of Pages (including cover) 2

This document is intended for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any view, disclosure, copying, or other action based on the content of this communication is not authorized.

Message:

Please refer to your submission regarding NDA 21-317 (Extra Strength Bayer Migraine). The following statistical problems have been identified and we request that you resolve and respond to each immediately:

1. Please clarify and define the variables "Time1, Time2, Time3, etc" located in Study98-072.

2. Please provide the formula used to determine the extrapolated results for Headache Severity at 2 hours (i.e. LSEV3).
3. It does not appear that the actual 2-hour efficacy results were used in the calculation. Please explain.

Example: Patient 18 (Study S98-072) had at "TIME3" (the 2 hour timepoint) a headache severity of 2 (SEV3), i.e. a non-responder. "TIME3" for this subject actually corresponded to 3 hours and 30 minutes (TIME3 minus BASETM). "TIME1" (the ½ hour timepoint) actually occurred 2 hours after "BASETM and had a severity of 1 (SEV1) which would have made this subject a responder.

4. Please re-analyze the statistical calculations for all three studies using those timepoints closest to the actual 2-hour assessment as opposed to "Time3". We request a LOCF algorithm for missing data. Those subjects with their first post-treatment efficacy assessment ≥ 3 hours should not be included in the 2-hour analyses.

Please contact Walt Ellenberg, Ph.D. (301) 827-2247 if you have any additional questions regarding this issue.

Sincerely,



Linda M. Katz, M.D. M.P.H.
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

MINUTES OF A TELECONFERENCE
October 5, 2001

NDA: 21-317

DRAFT

Meeting Type: Teleconference

Sponsor: Bayer Corporation, Consumer Care Division

Subject: A teleconference was held to discuss several issues which were raised during the review of the NDA application submitted by Bayer on December 18, 2001 regarding Extra Strength Bayer Migraine. These issues were submitted to Bayer via facsimile on October 2, 2001 (see attached).

Project Manager: Walter J. Ellenberg, Ph.D.

FDA Participants

Division of OTC Drug Products

Jonca Bull, M.D. Director ODE V
Charles Ganley, M.D., Division Director
Linda Katz, M.D., M.P.H., Deputy Division Director
Rosemarie Neuner, M.D., Medical Officer
Debbie Lumpkins, IDS Team Leader
Walter J. Ellenberg, Ph.D., Regulatory Project

Division of Neuropharmacological Drug Products

Russell Katz, M.D., Division Director
Armando Oliva, M.D., Medical Officer Team Leader
LanaChen, R.Ph., Regulatory Project Manager

Sponsor Participants:

Judy Doyle, Associate Director, Regulatory Affairs
Joanne Robinette, Director Regulatory Affairs
Dr. Randy Koslo, Director Medical and Clinical Affairs
Dr. Laureen MacEachern, Senior Associate Director Clinical Affairs
Diana Plaza, Manager Clinical Affairs

- 1. The data submitted do not support effectiveness for all of the symptoms of migraine, and do not support an indication for the treatment of the full migraine syndrome. Statements printed in the package insert and elsewhere in labeling concerning the effectiveness of the product for migraine symptoms other than pain are, therefore, not acceptable. Statements reflective of the demonstrated efficacy of the product, such as "Clinically proven to treat mild to moderate migraine pain", would be acceptable.**

The sponsor wanted our opinion on the possibility of allowing them to claim they won on photophobia, phonophobia, and functional ability. They were informed that it is expected that the three endpoints (nausea, photophobia, and phonophobia) are lumped together as

associated symptoms and it was expected for the win to be with all three in order to obtain the claim of a migraine product. Dividing the associated symptoms is not permitted. Interestingly, the sponsor did not raise any concern about the indication statement of mild to moderate pain of migraine.

- 2. The principle display panel (PDP) of the Bayer Migraine product lacks an appropriate statement of identity. Labeling regulations (21 CFR 201.61) require that the PDP bear a statement of identity as one of its principal features, and that the statement include the established name of the drug, followed by the pharmacological category or intended action. The statement needs to be in direct conjunction with the most prominent display of the proprietary name. The regulations also require that the statement be in bold face type in a size reasonably related to most prominent printed matter. The letter accompanying the submission states that the application is for Extra Strength Bayer Migraine (500 mg buffered aspirin). Thus, the statement of identity should include the name "buffered aspirin tablets 500 mg" followed by "Pain reliever" and should appear prominently with the trade name. The PDP in the labeling submitted does not meet these requirements and needs to be revised.**

The sponsor offers no comments.

- 3. The trade name "Bayer Genuine Extra Strength Migraine" as used on the PDP, the side panel, the end panel, and in the package insert is misleading. It implies that the product is an extra strength migraine product. There is no data to show that the proposed product is better than other approved migraine products, and, therefore, the name is not acceptable.**

The sponsor requested additional comments about our concern for the trade name. We informed them that the Agency's objection focused on their placement of the descriptor, "extra strength", as it suggests that the product is an extra strength medication to treat migraines. It was recommended they review the Motrin label for a suggested method of naming. The descriptor "extra strength" should only modify aspirin.

- 4. The submission failed to provide data which justifies the statement "Plus Helps Protect Against Stomach Upset." In the tentative final monograph (TFM) for OTC internal analgesic drug products, published in the FEDERAL REGISTER of November 16, 1988 (53 FR 46204), the Agency concluded that there was not sufficient evidence to clearly demonstrate that buffered aspirin may help those individuals subject to stomach upset associated with aspirin ingestion. Therefore, the TFM did not provide for a statement of decreased gastric irritation for buffered aspirin products. The TFM, however, provided the optional statement "contains buffering ingredients" for those products that meet United States Pharmacopeial Convention (U.S.P.) standards for buffered aspirin. The statement "Plus Helps Protect Against Stomach Upset," should be removed from labeling until such time that the statement can be supported by data.**

The sponsor offers no comments.

- 5. The statement "Ask Your Doctor About Other Benefits of Bayer Aspirin", located on the side panel, is not acceptable. Consumers would likely associate the statement with cardiovascular use. The 500 mg dosage unit is not appropriate for most cardiovascular uses. Further, the statement mentions benefits without a corresponding statement**

alerting consumers that serious side effects can occur with self treatment. Moreover, the statement specifically refers to other benefits of "Bayer Aspirin" even though other aspirin products have the same benefits. Therefore, the statement needs to be removed from labeling.

The sponsor offers no comments.

6. Compliance with the labeling specifications described 21 CFR 201.66 must be established by providing the following: 1) labeling specifications for type size, etc. in the "Drug Facts", 2) verification that all of the print in the "Drug Facts" is the same, and 3) verification of the bolding of the "Drug Facts" headings and subheadings.

The sponsor offers no comments.

7. Please refer to the attached Drug Facts prototype and make the changes to the content and format accordingly.

The sponsor offers no comments.

[Redacted content]

Prepared by: _____
Walter Ellenberg, Ph.D.

Lana Chen, R.Ph.

Approved by: _____
Charles Ganley, M.D.,
Director OTC Drug Products

10 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.



NDA 21-317

INFORMATION REQUEST LETTER

Bayer Corporation Consumer Care Division
Attention: Ms. Judy Doyle
Associate Director, Regulatory Affairs
36 Columbia Road
Morristown, New Jersey 07962

Dear Ms. Doyle:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Extra Strength Bayer Migraine (aspirin) 500 mg capsule-shaped tablet.

We also refer to your submission dated February 7, 2001 regarding the discrepancies noted between the paper and electronic version of the NDA.

We are reviewing the general content and format, as well as the Clinical, Biopharmaceutic, and Statistical sections of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Project Management

1. Please submit copies of all labeling from all countries in which the product was previously approved for marketing for the treatment of migraine pain and symptoms.

Clinical/Statistical

1. Please provide the case report tabulations/data sets in electronic format (SAS Transport). We requested these items at the pre-NDA meeting. You should submit them as quickly as possible and in accordance with the guidance document on electronic NDAs (<http://www.fda.gov/cder/guidance/2353fnl.pdf>).
2. The All-ITT analysis is not consistent with the type of ITT analysis requested. Typically for migraine studies, we define ITT as all subjects that took study medication and have at least one valid post-dosing observation. You have included 1191 subjects in the All-ITT analyses. Using our definition, there would only be 1180 subjects since 11 were thought to have taken study medication but never followed up or returned the diary. These 11 subjects made follow-up appointments but failed to keep them and it was assumed that they took study medication and were labeled treatment failures. Please provide new analyses for each individual study that would be consistent with the ITT analyses originally requested using the 1180 subjects described above. The analyses should include a comparison of headache response at 2 hours, and the proportion of patients with secondary migraine symptoms at 2 hours (nausea, photophobia, and phonophobia).

/s/

Charles Ganley
3/15/01 07:57:21 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-317

Bayer Corporation Consumer Care Division
Attention: Judy Doyle
Associate Director, Regulatory Affairs
36 Columbia Road
P. O. Box 1910
Morristown, NJ 07962-1910

Dear Ms. Doyle:

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

Name of Drug Product: Extra Strength Bayer Migraine (acetylsalicylic acid) 500 mg

Review Priority Classification: Standard (S)

Date of Application: December 15, 2000

Date of Receipt: December 18, 2000

Our Reference Number: NDA 21-317

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 February 16, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 18, 2001 and the secondary user fee goal date will be December 18, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days

from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products,
HFD-560
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products,
HFD-560
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Walter J. Ellenberg, Ph.D., Regulatory Project Manager, at 301-827-2247.

Sincerely,

Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

/s/

Rosemary Cook

1/4/01 06:34:00 PM