

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20802**

**ADMINISTRATIVE DOCUMENTS**

EE

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee  
Attention: Dan Boring, Chair, (HFD-530) CRP2

FROM: Division of Anti-inflammatory, Analgesic and Ophthalmic Products, HFD-550  
Attention: Vispi P. Bhavnagri Phone: 827-2509

DATE: October 20, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Excedrin Migraine

Company Name: Bristol-Myers Products

Established name, including dosage form:

Aspirin (250 mg), acetaminophen (250 mg) and caffeine (65 mg) in tablets or caplets or geltabs.

Other trademarks by the same firm for companion products:

Excedrin® Extra Strength Tablets, Caplets and Geltabs.

Indications for Use (may be a summary if proposed statement is lengthy):

For the treatment of sign and symptoms of migraine.

Initial comments from the submitter (concerns, observations, etc.):

This is exactly the same formulation, manufacturing procedure etc., but for an additional indication of relieving the headaches associated with the onset of migraine

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month.  
Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct 96

Consult #881 (HFD-550)

EXCEDRIN MIGRAINE     aspirin (250), acetaminophen (250) and caffeine (250)

The trademark EXCEDRIN has a long marketing history and was not evaluated by the Committee. The product EXCEDRIN MIGRAINE is identical to a companion product called EXCEDRIN EXTRA STRENGTH. However, EXCEDRIN MIGRAINE was submitted via application, even though it is an OTC product. The application data was necessary to gain the additional labeling of Migraine.

Ordinarily, dual names for the same drug product is discouraged, however, since this product is OTC, where umbrella names are widely used and it was submitted pursuant to an application where a separate name was requested by the reviewing division and a tentative monograph will be written to include migraine in the OTC statement of identity, The Committee will not object to the proposed brand name.

The Committee has no reason to find the proposed proprietary name unacceptable.

*W. Young* 11/19/97, Chair  
CDER Labeling and Nomenclature Committee

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17-03-97  
JUN 21 1997

## JOINT DDMAC AND DODP REVIEW

**NDA #:** 20-802  
**Drug:** Excedrin Extra Strength (Migraine Label)  
**Sponsor:** Bristol Myers Products  
**Dated:** January 6, 1997  
**Protocol:** YB-02-96-08-D  
**Reviewers:** Karen Lechter, J.D., Ph.D.  
Rosemarie Neuner, M.D., M.P.H.  
**Reviewing Div.:** HFD-40  
**Review Completed:** June 10, 1997

The purposes of this label comprehension study were to determine whether consumers would understand when to consult a physician when using Extra Strength Excedrin, whether information about use for migraine headaches is sufficiently clear, and if the addition of the migraine information interferes with comprehension of the remainder of the label.

### **Communication Objectives**

- Consultation with a doctor before use is recommended if the headache is accompanied by vomiting.
- Consultation with a doctor before use is recommended if the headache is so severe as to require bed rest.
- Consultation with a doctor after use if recommended if
  - symptoms continue or worsen
  - any new or unexpected symptoms occur.

### **Methodology**

#### Participants

Nine hundred thirty-six (936) adults (at least age 18) participated. Thirty were eliminated because they did not meet the inclusion criteria. Of the remaining 906, 245 (27%) were high school non-graduates, 219 (24%) were age 50 or older, 74% were white, and 17% were black. All had used a non-prescription analgesic in the past six months to treat a headache and all had suffered from a migraine headache in the past five years. Of those, 41% had had their migraines diagnosed by a physician. All were English speaking.

Quotas were established for the following subgroups:

age 18-34 (33%)  
age 35-49 (33%)  
age 50+ (33%)  
males (40%)  
females (60%)

*Reviewers' comment: The proportion of doctor-diagnosed migraines increased with age in the population tested. Although they screened study candidates for a "history" of migraines, the protocol did not call for validation of this diagnosis, i.e., there were no direct questions to determine if candidates could discern between migraine headache and atypical headaches such as cluster, stress, and sinus headaches, nor was confirmatory medical information requested from the participants' physicians.*

### Materials

There were two versions of the labeling. Both were presented to participants in the form of empty packages. The front panels were identical. The back panels differed only with regard to the migraine indication and related safety warnings. The control version had no references to migraine.

In the test version, the "Uses" section contained "Headache, including Migraine Headache." The reference to migraine did not appear in the control label. The section "Ask a Doctor Before Use If" contained the following statements. The underlined portion does not appear in the control version.

- Your headache (including migraine headache) is accompanied by vomiting
- Your headache (including migraine headache) is so severe you require bed rest

A screening questionnaire and a main questionnaire were used. The main questionnaire contained 5 open-ended questions. For most open-ended questions, there was at least one corresponding closed-ended question. There were 7 closed-ended questions dealing with the communication objectives and an additional question asking which products had been used in the past 5 years to treat various types of headaches.

## Procedure

Mall intercepts were conducted in 32 geographically dispersed locations across the country. There were 8 malls in each of four geographic quadrants of the country. To attain a total of 245 high school non-graduates, 158 additional persons were recruited to add to the 87 in the original sample.

Participants who qualified for the study and who were willing to participate were assigned to view either the test label or the control label. Five-hundred seventy-six (576) were exposed to the test label and 330 to the control label, in a two to one randomization (test package:control).

Participants were told the following:

Bristol-Myers Squibb is planning to make some changes on the label of its Excedrin product. As part of their effort, we would like you to answer some questions based on the new labeling. Here is the new labeling. Please read the label as though you were deciding whether or not to purchase the product. Take as much time as you need. When you are done, I will ask you some questions about what you have read.

The interviewer then asked the questionnaire questions. For the multiple choice questions, a card containing the choices was handed to the participants. The interviewer recorded all responses. During the response period, the labeled package was available for reference.

## Results

(Note: Results reported as different are at the  $p \leq 0.05$  level unless otherwise noted.)

**1. Based on the label instructions, what symptoms or conditions does this Excedrin product treat? Please be as specific and complete as you can in your answer.**

Eighty-nine percent (89%) of test label participants and 95% of control label participants mentioned headache. Most of these responses were non-migraine. Only those who saw the test label mentioned migraine. The major categories of responses are listed below. There were no differences by education level or by age group (18-34, 35-49, and 50+).

	<u>Test Label</u>	<u>Control Label</u>
	(503)	(245)
	%	%
Headache	89	95
Non-Migraine	86	95
Migraine	23	-
Other pains	80	83

*Reviewer's Comment: When asked this open-ended question, only 23% of the study participants from the test label group were able to recall a migraine indication. This may have been because respondents included migraine as part of the general headache indication. Another reason for this low percentage may have been related to the type of question asked. For example, if a multiple choice type question been asked, the percentage of patients who identified a migraine indication may have been higher.*

**2. Based on the label instructions, if the symptoms you are treating with Excedrin continue or worsen after you take the product, what, if anything, does it suggest you do? Please be as specific and complete as you can in your answer. If this information is not provided on the label, you may say you don't know.**

For this question 88% of persons seeing the test label and 89% of those seeing the control label provided correct responses to consult a doctor. Significantly more of the high school graduates (91%) provided correct responses than non-graduates (80%). However, this difference was not found in the corresponding closed ended question, Q.6. (See Q. 6 below.) There were no differences among the age groups.

**3. Based on the label instructions, if you are treating symptoms with Excedrin and new or unexpected symptoms occur, what, if anything, does it suggest you do? Please be as specific and complete as you can in your answer. If this information is not provided on the label, you may say you don't know.**

Eighty-nine percent (89%) of those who saw the test label and 87% of those who saw the control correctly mentioned consulting with a doctor. For the test label, the more educated participants scored better (90%) than the less educated (83%), and the youngest education group scored worse (79%) than the middle aged group (93%). Although these differences were statistically significant, they were not confirmed in the corresponding closed-ended question, Q.7. (See Q.7 below.)

**4. Based on the label instructions, if you have a headache or migraine that is accompanied by vomiting, what, if anything, does it suggest you do first? Please be as specific and complete as you can in your answer. If this information is not provided on the label, you may say you don't know.**

For the test and control labels, 86% and 87%, respectively, gave the correct responses to this question to consult a doctor. Fourteen percent (14%) and 13%, respectively, did not provide a correct response. The report did not indicate what incorrect responses were given.

There were no statistically significant differences between the high school graduates and the high school non-graduates. Thirteen percent (13%) of the graduates and 15% of the non-graduates did not produce a correct response. For the test label, fewer in the youngest age group (81%) provided a correct answer than those in the middle-aged group (90%). This difference was found to be statistically significant.

**5. Based on the label instructions, if you have a headache or migraine that is so severe that you require bed rest, what, if anything does it suggest you do first? If this information is not provided on the label, you may say you don't know.**

Eighty-five percent (85%) of participants correctly stated they should consult a doctor. There was a significant difference between responses from the test label group and the control label group on this question. Eighty-five percent (85%) of the test group and 52% of the control group indicated a doctor should be consulted. This was a significant difference. For the control label, fewer high school graduates (49%) than non-graduates (61%) stated they should consult a doctor. This was a significant difference.

For the test label, there were no differences among the three age groups. However, within each age group, the differences between the test and control label were significant. In addition, for the control label, the youngest group said to consult a doctor less frequently (40%) than the middle aged group (59%) or the oldest group (60%). The differences between age groups are not supported by differences in responses to the corresponding closed-ended question, Q.9. (See Q.9 below.)

*Reviewer's comment: Differences were to be expected between the label groups, as the control label did not make reference to what to do in this situation.*

**6. If the symptoms for which you are taking Excedrin continue or worsen after you take the product, which one action on the card, if any does the label suggest that you do?**

The responses for the two label groups appear below. There were no differences based on education level or age group.

	<u>Test Label</u>	<u>Control Label</u>
	(503)	(245)
	%	%
Take another regular dose of Excedrin	4	6
Take another, smaller, dose of Excedrin	2	0
Take another, larger, dose of Excedrin	2	0
Ask a doctor	88	85
Take another brand of pain reliever	1	2
None of the above	4	6

7. If you are treating symptoms with Excedrin and new or unexpected symptoms occur which one of the actions on the card, if any, does the label suggest that you do?

There were no differences on this question between the two label groups, as demonstrated below. There were no differences based on education level. For the youngest age group (18-34), significantly more who saw the test label (92%) gave correct responses, compared with 81% in the control group, and more who saw the control label said "none of the above" (12%), as compared with the test label (4%).

	<u>Test Label</u>	<u>Control Label</u>
	(503)	(245)
	%	%
Take another regular dose of Excedrin	2	2
Take another, smaller, dose of Excedrin	1	1
Take another, larger, dose of Excedrin	1	1
Ask a doctor	91	87
Take another brand of pain reliever	-	1
None of the above	4	9

8. If you have a headache or migraine that is accompanied by vomiting, which one of the actions on the card, if any, does the label suggest that you do first?

Ninety-one percent (91%) of the test label participants and 87% of the control label participants correctly chose the "ask a doctor" response. There were no differences between the two education groups. There were no differences among the three age groups.

The responses to the multiple choice question are as follows:

	<u>Test Label</u>	<u>Control Label</u>
	(503) %	(245) %
Take the regular dose of Excedrin	2	2
Take a smaller dose of Excedrin	1	-
Take a larger dose of Excedrin	-	-
Ask a doctor	91	89
Take another brand of pain reliever	1	1
None of the above	5	8

*Reviewers' comment: It is interesting to note that all age groups understood the importance of seeking medical intervention if vomiting occurred. This implies that participants understood the point that the label was conveying to seek medical intervention if the severity of illness increased.*

**9. If you have a headache or migraine that is so severe that you require bed rest, which one of the actions on the card, if any, does the label suggest that you do first?**

Again, persons who saw the test label did significantly better on this question than those who saw the control label, which made no reference to symptoms severe enough to require bed rest. Responses to each of the multiple choice items are shown below. On the test label, the two education groups both answered correctly about 90% of the time. For the control label, 63% of the high school graduates said they should consult a doctor, and 73% of the non-graduates answered this way. There were no differences among the age groups on this question. However, within each age group, the test label group gave the response to ask a doctor significantly more often than the control label group.

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	<u>Test Label</u>	<u>Control Label</u>
	(503)	(245)
	%	%
Take the regular dose of Excedrin	4	4
Take a smaller dose of Excedrin	-	-
Take a larger dose of Excedrin	2	-
Ask a doctor	88*	65
Take another brand of pain reliever	1	1
None of the above	5	28#

\*Significantly different than other label at  $p \leq 0.05$  level, with 95% confidence interval (16.1%, 29.2%).

#Significantly different than other label at  $p \leq 0.05$  level, with 95% confidence interval (-29.2%, -16.8%).

*Reviewers' comment: Technically speaking, the correct response for the control label is "none of the above," as the label was silent on this issue. More graduates than non-graduates seeing the control label answered this way.*

**10. Based on the label instructions, which one of the statements on the card correctly describes when, if ever, you should not use Excedrin?**

There were no differences between labels on this question, between education levels, or among age groups. Approximately 80% in both label groups gave correct responses.

	<u>Test Label</u>	<u>Control Label</u>
	(503)	(245)
	%	%
If you are allergic to Aspirin or have Asthma	12	7
If you have ulcers or bleeding problems	4	7
Both of the above (Correct Response)	80	78
None of the above	5	7

*Reviewers' comment: This question is assessing participants' comprehension of the aspirin monograph warning. It is notable that approximately 80% from both groups understood that the product should not be used by individuals who are allergic or have a history of peptic ulcer disease. The comprehension increases to above 90% when adding up respondents who captured at least one of the warnings.*

*However, the high proportion of correct responses may be due in part to a “yea-saying” bias induced by the fact that the first three choices were partially or totally correct. Addition of incorrect choices to the question may have tempered this effect.*

**11. Based on the label instructions, which one of the statements on the card correctly describes when, if ever, you should ask a doctor before taking Excedrin?**

Responses to both labels were similar. A high percentage gave correct responses. There were no differences by education level. The significance of differences, if any, among age groups for each label was not reported.

	<u>Test Label</u>	<u>Control Label</u>
	(503)	(245)
	%	%
If the painful area is red or swollen	7	6
If you are under a doctor’s care for any continuing medical condition such as diabetes	10	7
Both of the above (Correct Response)	79	81
None of the above	4	6

*Reviewers’ Comments: This question assesses the participants’ comprehension of the product specific warnings. Approximately 80% of the participants answered correctly. The comprehension increases to above 94% when adding up respondents who captured at least one of the warnings.*

*Again the “yea-saying” bias may have been a factor in the results from this question.*

**12. Based on the label instructions, which one of the statements on the card correctly describes when, if ever, you should ask a doctor after you have been using Excedrin?**

Equal proportions in both label groups answered this question correctly (approximately 80%). There were no differences by education level. The significance of differences among age groups for each label was not tested.

	<u>Test Label</u>	<u>Control Label</u>
	(503)	(245)
	%	%
<b>If your symptoms continue or worsen If ringing in the ears or loss of hearing occurs</b>	13	11
<b>Both of the above (Correct Response)</b>	3	2
<b>None of the above</b>	80	82
	3	4

*Reviewers' Comment: See Reviewers' Comment to Q.11 above.*

**13. You mentioned that you suffer (X type headache). Which brands or products on the card, if any, have you used in the past 5 years to treat (X type headache)? [repeated for all headaches mentioned]**

*Reviewers' comment: The sponsor listed almost 30 products currently approved for the OTC market. This question was asked for every type of headache from which the participants indicated they suffered. This was a marketing question unrelated to the label.*

### **Comments**

It is possible the screener sensitized participants to migraine concerns, making it more likely that those seeing the migraine label would respond correctly to the questions that involve migraine issues. However, the relatively high scores on all the questions by both label groups suggests this was probably not a biasing influence.

The closed-ended questions contained three in a row that offered a choice of "none of the above" and "both of the above." All required the response "both of the above." It would have been better to intersperse these with other questions that required a different response.

None of the questions asked the participants who may have had contraindications whether or not they would use the product or whether they would consult a physician before use. It would have been useful to have this information to determine the effectiveness of the warning section of the class labeling for aspirin-containing products.

The study did not determine whether participants who said they had migraines truly had

migraines. The result is that the study population may not have been entirely migraine sufferers. This possibility probably did not influence the study outcomes since this product is already approved for a general headache indication.

Differences that were significant among subgroups for the open-ended questions generally were not found for the corresponding closed-ended questions. It is possible that the open-ended differences were due to variations caused by the somewhat subjective scoring system. For this reason, it is not the usual practice in marketing studies to test the significance of differences for open-ended questions. They have been presented here to provide a more complete record.

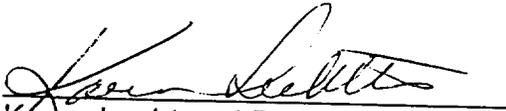
A warning statement on the label, consistent with that specified by the Code of Federal Regulations for OTC stimulant products, should appear on the label. The comprehension of this warning and the alcohol warning were not assessed by this labeling comprehension study.

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ON ORIGINAL**

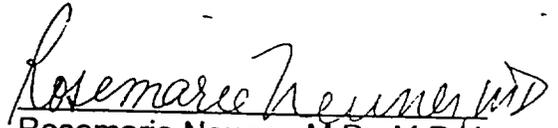
**APPEARS THIS WAY  
ON ORIGINAL**

**Conclusion:**

This study adequately demonstrates that the tested sponsor's proposed labeling is understood by potential users who are probable migraine sufferers. Although they understood the migraine-specific elements of the label as well as the more general elements, a surprisingly small percentage of participants who saw the test label reported that the product was indicated for migraines. The inclusion of migraine-specific information did not affect comprehension of other elements of the labeling. Among the three age groups and two education levels, there were few differences, and most of those appeared only in the open-ended responses, which may involve more variability and error than the closed-ended responses. None of the subgroup differences appear to be systematic, and therefore, it can be concluded that comprehension among all of the groups was comparable.



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Products, HFD-560

cc:

HFD-40/Morris/Lechter/Sherman/Reading  
NDA 20-802

HFD-560/Bowen/Katz/Lumpkins/Neuner/Mason/Division File DB 06/12/97

HFD-550/Chambers/Widmark/Cook/Division File

WAC 6/21/97

## DEPUTY DIRECTOR REVIEW

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG  
PRODUCTS DIVISION -- HFD-550

NDA #: **20-802**  
SUBMISSION DATE: June 13, 1997.  
TYPE: Safety Update.  
REVIEW DATE: Dec. 18, 1997.  
REVIEWER: John Hyde, Ph.D., M.D.

NAME: **Excedrin Migraine Tablets, Caplets  
and Geltabs**  
(acetaminophen, aspirin, and  
caffeine tablets).

SPONSOR: Bristol-Myers Products  
1350 Liberty Avenue  
Hillside, NJ 07027

PHARMACOLOGIC CATEGORY: Combination analgesic.  
PROPOSED INDICATIONS: Pain of Migraine Headache.  
DOSAGE FORM & ROUTE: Tablets: acetaminophen 250 mg,  
aspirin 250 mg, caffeine 65 mg; Oral.  
CSO: S. Cook.

**RESUME:**

The safety update covered 12/1/96 - 4/30/97. In that period about units were sold and 391 adverse events were reported. The common events were lack of effect, dyspepsia and nausea. One was serious: a 72 year old woman was hospitalized for syncope and required treatment with iron.

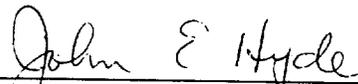
**CONCLUSIONS:**

Details about the one serious event are lacking, but a plausible explanation is anemia from GI bleeding caused by the aspirin component of Excedrin. There is nothing in this update that changes the impression of the safety profile of the product.

**RECOMMENDATIONS:**

None. This safety update does not point to any need to modify the product labeling recently proposed by the Agency for this NDA.

Orig-NDA # 20-802  
HFD-550/Div File  
HFD-340  
HFD-550/CSO/Cook  
HFD-550/MO/JHyde

 12-18-97  
John E. Hyde, Ph.D., M.D.

EXCLUSIVITY SUMMARY for NDA # 20-802 SUPPL # \_\_\_\_\_

Trade Name Excedrin Migraine Generic Name (Acetaminophen, aspirin, and Caffeine) Tablets, Caplets, and Gelscaps 250mg, 250mg, and 65mg

Applicant Name Bristol-Myers Products HFD- 550

Approval Date, if known \_\_\_\_\_

**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? (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 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# \_\_\_\_\_  
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# 17-552 Tylenol Extra-Strength Tablets  
NDA# 17-534 Fiorinal  
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:

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YES /\_\_\_/ NO /\_\_\_/

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

YES /\_\_\_/ NO /X/

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

If yes, explain: \_\_\_\_\_

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

-        - 840        - 841        - 842

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

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

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

Investigation #1                      YES /\_\_\_/                      NO /X/  
Investigation #2                      YES /\_\_\_/                      NO /X/

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

\_\_\_\_\_  
\_\_\_\_\_

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

Investigation #1                      YES /\_\_\_/                      NO /X/  
Investigation #2                      YES /\_\_\_/                      NO /X/

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

\_\_\_\_\_  
\_\_\_\_\_

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

-840                      -842  
841                      \_\_\_\_\_

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 / <u>X</u> /	NO / ___ / Explain: _____
	:	_____
Investigation #2	:	:
IND #	YES / <u>X</u> /	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? N/A

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: \_\_\_\_\_

Sandra N. Cook  
Signature  
Title: Consumer Safety Officer

12/10/97  
Date

John E Hyde

1-14-98

Signature of Division Director

Debra Bonum, DDDP-520

Date  
12/18/97

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

## **15. Claimed Exclusivity**

As required by 21 C.F.R. § 314.50 (j), the following information is provided in support to the request for exclusivity:

- (1) Pursuant to the provisions of Section 505(c)(3)(D)(iii) and 505(j)(4)(iii) of the Food, Drug and Cosmetic Act Bristol-Myers Products is requesting three years marketing exclusivity for the migraine headache pain indication for Excedrin® Extra Strength Tablets under 21 C.F.R. § 314.108(b)(4).
- (2) Bristol-Myers Products certifies that to the best of its knowledge, each of the clinical investigations included in this New Drug Application meets the definition of "new clinical investigation" set forth in 21 C.F.R. §314.108(a).
- (3) Bristol-Myers Products certifies that a thorough search of the scientific literature was conducted, and to the best of the applicant's knowledge, no published studies were available which provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigations in this application.
- (4) Bristol-Myers Products certifies that it was the sponsor named in the Form FDA 1571 for IND under which the new clinical investigations that were essential to approval were conducted.

**APPEARS THIS WAY  
ON ORIGINAL**

**BRISTOL-MYERS PRODUCTS  
Hillside, New Jersey 07207**

### **13. Patent Information**

There are no U.S. patents pertaining to the drug product Excedrin® Extra Strength Tablets.

There is one U.S. patent pertaining to the composition of the formulation of Excedrin® Extra Strength Tablets (Patent Number 4,943,565 "Analgesic Tablet of Aspirin and Caffeine containing Low-Substitute Hydroxypropyl Cellulose" issued to Bristol-Myers Squibb Company on July 24, 1990.)

The person signing this application on behalf of the applicant declares that he is aware of no other U.S. patent which claims the drug Excedrin® Extra Strength Tablets, and with respect to which U.S. patents a claim of patent infringement could reasonable be asserted against a person, not licensed thereunder by the owner, who engages in the manufacture, use or sale of Excedrin® Extra Strength Tablets.

**APPEARS THIS WAY  
ON ORIGINAL**

**BRISTOL-MYERS PRODUCTS  
Hillside, New Jersey 07207**

## 14. Patent Certification

This section is not applicable

APPEARS THIS WAY  
ON ORIGINAL

BRISTOL-MYERS PRODUCTS  
Hillside, New Jersey 07207

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-802

Supplement # \_\_\_\_\_

Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550 Trade (generic) name/dosage form: Excedrin Migraine (Acetaminophen, aspirin and caffeine) Tablets, Caplets, and Gellets, 250mg, 250mg, and 65mg. Action:  AP AE NA

Applicant Bristol-Myers Products

Therapeutic Class \_\_\_\_\_

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate  Adequate  Inadequate

Indication in this application The temporary relief of mild to moderate pain associated with migraine headache.  
(For supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE.** 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 subgroups. Further information is not required.
2. **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. 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, explain the status of discussions on the back of this form.
  - c. 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.
3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.
4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Samaha D. Cook  
Signature of Preparer and Title (PM, CSO, MO, other):

12/9/97  
Date

cc: Orig NDA/PLA # 20-802  
HFD-550 /Div. File  
NDA/PLA Action Package  
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

JSH 12-17-97  
JUB 12-17-97

E: 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.