CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-802/S002

ADMINISTRATIVE DOCUMENTS

EXCEDRIN® MIGRAINE
DEBARMENT CERTIFICATION

16. Debarment Certification

Bristol-Myers Products hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

S Knapp 12/14/98

Steven J. Knapp, R.Ph.
Senior Director
Global Regulatory Affairs

LABELING REVIEW OF NDA SUPPLEMENT

NDA: 20-802
Supplement: SE1-002

Submission Date:	December 18, 1998
Received:	December 18, 1998
Review Date:	February 23, 1999
Amended:	July 28, 1999
Amended:	August 2, 1999
Amended:	August 4, 1999
Amended:	August 17, 1999

Applicant: Bristol-Myers Products
1350 Liberty Avenue
Hillside, New Jersey 07207-6050

Applicant's Representative: Steven J. Knapp R.Ph., Senior Director
Global Regulatory Affairs
(908-851-6119)

Drug: Excedrin® Migraine
(acetaminophen 250 mg, aspirin 250 mg,
and caffeine 65 mg) tablets/caplets geltabs

Pharmacologic Category: Pain reliever/pain reliever aid

Reviewer: Stephanie A. Mason

Submitted: Efficacy supplement - text version of the carton/bottle label, annotated text version, and mock-up of the carton and bottle label

Background: The sponsor conducted a label comprehension study (see September 28, 1998 letter) to assess consumer comprehension of the more detailed "***Use***" statement which includes symptoms versus a more general statement for the relief of migraine. The results of the study showed that comprehension of the more detailed "***Use***" statement was better than comprehension of the shorter statement. Thus, the sponsor proposes that the marketed product should include the more detailed "***Use***" statement described below.

An efficacy supplement was submitted to approved NDA 20-802 for Excedrin Migraine to modify the "***Use***" section of the labeling to read:

- for the relief of migraine (shorter statement)
- Excedrin Migraine relieves the symptoms of migraine including headache pain, nausea, sensitivity to light and sound, and difficulty in carrying out normal activities (detailed statement)

The "***Use***" statement would replace the currently approved "***Use***: for the temporary relief of mild-to-moderate pain associated with migraine headache." The sponsor also proposes to add new warning statements appropriate for the expanded use of the product.

The submitted labeling was developed using the approved labeling (NDA 20-802) for Excedrin Migraine as a template. The sponsor proposes that all package size bottle labels contain identical labeling, with full labeling on the carton and instructions on the bottle label directing consumer to the carton for full labeling.

In a new correspondence dated May 21, 1999, the sponsor sought confirmation of their interpretation of the OTC Labeling Requirements final rule dated March 17, 1999 (64 FR 13254), stating that the implementation date for this labeling would be May 16, 2001, as the product is marketed under an NDA that was approved prior to May 16, 1999. The sponsor was informed by the Agency that they would need to comply with the ***Drug Facts*** format for the submitted labeling. Thus, in a supplemental submission (N20-802/SEI-002/BL) dated July 16, 1999, the sponsor amended its application to include proposed labeling for 24-count carton in ***Drug Facts*** format utilizing the draft labeling submitted in S-002. **Note**: The sponsor changed the **Use** statement on the 24-count carton labeling.

A meeting was held on August 4, 1999, with HFD-560 and HFD-120 to discuss labeling concerns. This review reflects the conclusions made at that meeting.

1. **Reviewer's Comments**: We have the following comments on the **carton label**:

   a. Section 201.66(d)(2) in the OTC Labeling Requirements final rule requires that the letter height or type size for the title ***Drug Facts*** must appear in a type size greater than the largest type size used within the "***Drug Facts***" area. It must be no smaller than 8-point type.

   In order to accommodate full product labeling on its 24-count carton, the sponsor uses 7.1-point type for all its ***Drug Facts*** headers. This is not acceptable. The first ***Drug Facts*** header that comes before ***Active ingredients*** should be larger than the other ***Drug Facts*** headers located in the labeling. It is recommended that the sponsor use an 9-point type for this specific header.

   b. Under ***Purposes***, the letter "R" and "A" in "Reliever" and "Aid" should be lower case. This change should also be made on the immediate bottle label.

   c. New indications under the **Uses** section include nausea, sensitivity to light and sound, and difficulty in carrying out normal activities. The approved NDA 20-802 provided for the temporary relief of pain of migraine as the primary endpoint.

The proposed statements are not supported by the studies provided. The observed effects on the secondary symptoms of migraine were based upon analyses of secondary endpoints and conclusions drawn from such analyses only served to support an overall effect on migraine. Therefore, we have changed the indication for the use of the drug from one of symptomatic to the treatment of conditions and recommend that the indication for ***Uses*** be revised to read: ▪ treats migraine

Claims of functional disability (i.e., difficulty in carrying out normal activities) have not been allowed in prescription triptan labeling mainly because the Division (HFD-120) does not consider the scale use to be a validated measure of disability in migraineurs. Therefore, the identification of specific symptoms should not be included in the ***Uses*** section. (See medical review dated June 15, 1999.)

d. The recommended Allergy alert warning per the Agency's September 15, 1998 letter to sponsors who market products containing aspirin under an approved NDA was added. The required alcohol warning published in the OTC Drug Products Containing Analgesic/ Antipyretic Active Ingredients for Internal Use; Required Alcohol Warning final rule dated October 23, 1998 (63 FR 56789 at 56802) was also added. These changes are acceptable.

e. The word "**Reye**" should be revised to read "**Reye's**" syndrome. Also, the word "medicine" should be replaced with the word "drug" to read "Children and teenagers should not use this drug ...."

f. All colons following headers ***Uses, Warnings, Directions, Other information, and Inactive ingredients*** and subheaders **Do not use, Ask a doctor before use if you have, Ask a doctor or pharmacist before use if you are, Stop use and ask a doctor if** should be deleted.

g. In the statement **Do not use** ▪ if you have ever had an allergic reaction to any other pain reliever/fever reducer, the period should be deleted at the end of the sentence.

h. Under the heading **Ask a doctor before use if you have,** the new warning statement "a headache that is different from your usual migraines" was added to address potential issues related to consumers with headaches not due to migraine or secondary to serious underlying conditions. This is acceptable. The two other new warning statements "a migraine so severe as to require bed rest" and "vomiting with your migraine" were added to revise references to "migraine headache" to be consistent with the new ***Uses*** statement. While these two statements are consistent with prescription triptan labeling which instruct patients that the medication is not intended "to treat headaches that might be caused by other, more serious conditions," we recommend deleting the symptom "vomiting with your migraine" because this is a fairly common symptom associated with migraines.

Also, the description of conditions located under the above subheader have been rearranged to stratify conditions of concern from those of most concern to the least. A new statement was also included under the subheader: "▪ never had migraines diagnosed by a health professional" as the first bulleted statement.

i. The sponsor should revise the term "renal" disease to "kidney" disease, since this is a more consumer-friendly term.

j. The warning statement "your migraine is not relieved or worsens" was also added to address potential special issues related to consumers who experience headaches not caused by migraine or secondary serious underlying conditions. This is acceptable. However, we recommend that the sponsor revise the statement to read: "**Stop use and ask a doctor if** your migraine is not relieved or worsens after the first dose." In labeling for other prescription migraine drugs, we note that if the first dose is not effective, the diagnosis should be reconsidered prior to taking additional doses.

k. Addition of the **pregnancy/breast-feeding warning** is acceptable. However, the word "Prompt" should be changed to "Quick" to read: "Quick medical attention is critical for adults ...."

l. Under ***Directions***, the statement "do not take more than directed" has been moved from the first bulleted statement to the third bulleted statement.

m. Under ***Directions***, the phrase "every 6 hours" was deleted. Also, the bulleted statement "children under 12 years of age..." was deleted because the characteristics of migraines is different for children and adults. Before a claim for efficacy in treating migraines in children is made, the sponsor will need to provide evidence for efficacy in this population (i.e., children ages 12 to 17). This has been a requirement for all other prescription migraine products.

n. The statement "Do not take for more than 48 hours" was added under ***Directions***. We recommend that this statement be deleted.

o. On the side flap of the carton label, the term "tamper-evident" is added to replace "tamper-resistant" per the final rule for Tamper-Evident Packaging Requirements for OTC Drug Products, dated November 4, 1998 (63 FR 59463). The agency will continue to allow flexibility as to where the statement appears in the labeling and is not requiring that it be included within the ***Drug Facts*** area. However, if the statement is included in the ***Drug Facts*** area, it should be placed under the heading ***Other information***.

p. The location of the lot number should be designated on the carton.

The reviewer believes that the caffeine warning statement would be more visible from the other

warnings on the carton and bottle labels if a subsection heading was added. It would read as follows:

> **Caffeine Warning**: The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.

This change would also be consistent with the way the other warnings are presented. (This was suggested to the sponsor in their approval letter for NDA 20-802 on June 5, 1998.)

> q. The statement of identity should be presented in bold face type on the principal display panel in a size reasonably related to the most prominent printed matter on such panel.
>
> r. The Agency encourages manufacturers to include the required OTC drug labeling information essential for the safe and effective use of OTC drug products, on the immediate container (or pouch/blister card, if any) label. Thus, modifications as described above are suggested.

2. **Reviewer's Comments**: Concerning the **immediate bottle label**, we are recommending the following revisions although we are aware that the immediate bottle label is not subject to the OTC labeling requirements if the bottle container is in an outer carton that conforms to the standardized format of the final rule:

a. The headers **Do not use** and **Stop use and ask a doctor** should be bolded.

b. The headers ***Active ingredients***, ***Purposes***, ***Uses***, ***Warnings***, and ***Directions*** should be in italics.

c. The letter "**A**" in "**Alert**" should be lower case to be consistent with the carton label.

d. The second sentence after the pregnancy warning should be upper and lower case lettering and not all be capitalized.

e. The directions should be revised to read: adults: take 2 tablets with a full glass of water. If symptoms persist or worsen, ask your doctor.
   - under 18 years of age: ask a doctor before use

f. The storage statement should read: store at 20 - 25°C (68 - 77°F)

Conclusion: We recommend approval of this labeling supplement contingent upon agreement of the following:

1. All references to specific individual symptoms (i.e., nausea, sensitivity to light and sound, and difficulty carrying out normal activities) associated with migraine should be deleted.

2. The ***Uses*** section should be revised to read: "treats migraine."

3. The ***Directions*** section should be revised to read:

   - adults: take 2 tablets with a full glass of water
   - if symptoms persist or worsen, ask your doctor
   - do not take more than directed
   - under 18 years of age: ask a doctor before use

4. The additional warnings under **Ask a doctor before use if** : (1) you have a headache that is different from your usual migraines, (2) you have a migraine so severe as to require bed rest may be retained in the labeling.

5. The following warning should be revised to read: **Stop use and ask a doctor if** your migraine is not relieved or worsens after the first dose.

6. Under the **Ask a doctor before use if subheader,** add the bulleted statement ▪ you never had migraines diagnosed by a health professional.

Recommendation: The following other changes should also recommended to the sponsor:

1. The statement of identity should be presented in bold face type on the principal display panel in a size reasonably related to the most prominent printed matter (i.e., Excedrin) on such panel.

2. The word "Reye" should be revised to read "Reye's" syndrome. Also, the word "medicine" should be replaced with the word "drug" to read "Children and teenagers should not use this drug ...."

3. Under the subheading **Ask a doctor before use if you have,** the word "renal" should be replaced with the word "kidney."

4. The location of the lot number should be designated on the carton label.

5. On the carton and bottle label, the storage statement should read: ▪ store at 20 - 25°C (68 - 77°F).

6. On the bottle label, the headers **Do not use** and **Stop use and ask a doctor** should be bolded.

7. On the bottle label, the headers ***Active ingredients***, ***Purposes***, ***Uses***, ***Warnings***, and ***Directions*** should be in italics.

8. The letter "**A**" in "**Alert**" should be lower case to be consistent with the carton label.

9. On the bottle label, the second sentence after the pregnancy warning should changed to upper and lower case letters.

10. Final printed labeling should be submitted for all representative packaging that the sponsor intends to market.

/S/
Stephanie A. Mason, IDS

/S/
Debbie L. Lumpkins, Microbiologist
Team Leader 3

Rosemarie Neuner, M.D., M.P.H.
/S/

cc:
NDA 20-802
HFD-560/Div File
HFD-120/Div File
HFD-560/K. Rothschild
HFD-560/S. Mason
HFD-560/D. Lumpkins:8/2/99
HFD-560/Dr. Neuner:8/13/99
HFD-560/Dr. Katz:8/3/99:8/18/99
HFD-560/Dr.Ganley
R/D:2/23/99:Rev:7/22/99
F/T:SMason:8/ /99
20-802se.wpd

/S/
8/24/99

SEP 21 1999

LABELING REVIEW OF NDA SUPPLEMENT--ADDENDUM

NDA: 20-802
Supplement: SE1-002

Submission Date: December 18, 1998
Received: December 18, 1998
Review Date: September 15, 1999

Applicant:

Bristol-Myers Products
1350 Liberty Avenue
Hillside, New Jersey 07207-6050

Applicant's Representative:

Steven J. Knapp, R.Ph., Senior Director
Global Regulatory Affairs
(908-851-6119)

Drug:

Excedrin® Migraine
(acetaminophen 250 mg, aspirin 250 mg,
caffeine 65 mg) tablets/caplets/geltabs

Pharmacologic Category:

Pain reliever/pain reliever aid

Reviewer:

Stephanie A. Mason

Submitted:

Revised labeling, 50 count coated tablets

On September 1, 1999, the Agency faxed its comments to the sponsor concerning its draft labeling submitted in an efficacy supplement for Excedrin Migraine. On September 15, 1999, via facsimile, the sponsor provided a copy of its revised labeling for Excedrin Migraine that was amended to reflect the Division's comments. The labeling changes were made to accommodate required information on its outer carton using the modified small packaging format.

The following has been re-arranged to read:

Warnings

Ask a doctor before use if you have ▪ never had migraines diagnosed by a health professional
▪ a headache that is different from your usual migraines
▪ the worst headache of your life ▪ fever and stiff neck
▪ headaches beginning after or caused by head injury, exertion, coughing or bending
▪ experienced your first headache after the age of 50 ▪ daily headaches
▪ a migraine so severe as to require bed rest ▪ bleeding problems
▪ asthma ▪ ulcers ▪ liver disease ▪ kidney disease
▪ stomach problems such as heartburn, upset stomach, or stomach pain that do not go away or recur

Stop use and ask a doctor if ▪ an allergic reaction occurs. Seek medical help right away.
▪ your migraine is not relieved or worsens after first dose
▪ new or unexpected symptoms occur ▪ ringing in the ears or loss of hearing occurs

Directions ▪ do not take more than directed
▪ adults: take 2 tablets with a full glass of water ▪ if symptoms persist or worsen, ask your doctor
▪ under 18 years of age: ask a doctor before use

Other information ▪ store at 20 - 25°C (68 - 77°F)
▪ read all product information before using. Keep this box for important information.

/S/
Stephanie A. Mason, IDS

/S/
Debbie L. Lumpkins, B.S., Microbiologist

cc:
NDA 20-802
HFD-560/Div File
HFD-560/K.Rothschild
HFD-120/R.Levin
HFD-120/A.Oliva
HFD-120/R.Chen
F/T:SMason:9/17/99
HFD-560/S.Mason
HFD-560/C.Ganley
HFD-560/L.Katz
HFD-560/Lumpkins
HFD-560/R.Neuner
HFD-560/L.Roberts

/S/ 9/21/99

APPROVED
OCT 7 ...

CARTON LABEL COPY- MODIFIED SMALL PACKAGE LABELING FORMAT

Principal display panels (PDP)

NEW Pain Reliever/Pain Reliever Aid

EXCEDRIN®
MIGRAINE
Acetaminophen, Aspirin and Caffeine Tablets

Logo # (of Dosage Units) COATED (*Insert Dosage Form)

BACK PANEL

Drug Facts

Active ingredients (in each tablet)		***Purposes***
Acetaminophen	250 mg	Pain reliever
Aspirin	250 mg	Pain reliever
Caffeine	65 mg	Pain reliever aid

Uses ▪ treats migraine

Warnings

Reye's syndrome: Children and teenagers should not use this drug for chicken pox, or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.

Allergy alert: aspirin may cause a severe allergic reaction which may include:
▪ hives ▪ facial swelling ▪ asthma (wheezing) ▪ shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen and aspirin or other pain relievers/fever reducers. Acetaminophen and aspirin may cause liver damage and stomach bleeding.

Caffeine warning: The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.

Do not use ▪ if you have ever had an allergic reaction to any other pain reliever/fever reducer

Ask a doctor before use if you have ▪ never had migraines diagnosed by a health professional
- a headache that is different from your usual migraines
- the worst headache of your life ▪ fever and stiff neck
- headaches beginning after or caused by head injury, exertion, coughing or bending
- experienced your first headache after the age of 50 ▪ daily headaches
- a migraine so severe as to require bed rest ▪ bleeding problems
- asthma ▪ ulcers ▪ liver disease ▪ kidney disease
- stomach problems such as heartburn, upset stomach, or stomach pain that do not go away or recur

Ask a doctor or pharmacist before use if you are taking a prescription drug for:
- anticoagulation (thinning of the blood)
- diabetes
- gout
- arthritis

Stop use and ask a doctor if
- an allergic reaction occurs. Seek medical help right away.
- your migraine is not relieved or worsens after first dose
- new or unexpected symptoms occur
- ringing in the ears or loss of hearing occurs

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

Directions
- do not take more than directed
- adults: take 2 tablets with a full glass of water
- if symptoms persist or worsen, ask your doctor
- under 18 years of age: ask a doctor before use

Other information
- store at 20 - 25°C (68 - 77°F)
- read all product information before using. Keep this box for important information.

Inactive ingredients benzoic acid, carnauba wax, hydroxpropylcellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, mineral oil, polysorbate 20, povidone, propylene glycol, simethicone emulsion, sorbitan monolaurate, stearic acid, may also contain: FD&C blue no. 1, titanium dioxide

Questions or comments? Call 1-800-468-7746

DISTR. BY: **BRISTOL-MYERS PRODUCTS**
A BRISTOL-MYERS SQUIBB CO.

MINUTES OF A MEETING
February 1, 1999
9201 Corporate Blvd.
Rockville, MD
Conference Rm. S200B

Fileability Meeting for NDA 20-802/SE1-002, Excedrin Migraine

CDER Participants:

Division of OTC Drug Products, HFD-560
Linda Katz, Deputy Director
Rosemary Cook, Supervisory Project Manager
Kerry Rothschild, Project Manager
Debbie Lumpkins, Team Leader
Rosemarie Neuner, Medical Officer
Stephanie Mason, IDS

Division of Neuropharmaceutical Drug Products, HFD-120
Lana Chen, Project Manager
Kun Jin, Supervisory Statistician

Meeting Objective: To determine the fileability of the efficacy supplement to NDA 20-802, and establish timelines for its review

Bristol-Myers Products submitted supplemental NDA 20-802/SE1-002 as an efficacy supplement for Excedrin Migraine. The supplement provides for the new indication as follows:

For relief of migraine; for relief of migraine symptoms including headache pain, sensitivity to light and sound, and difficulty in carrying out normal activities.

The supplement was received on December 18, 1998, the user fee goal date is October 18, 1999, and, if fileable, the filing date will be February 16, 1999.

Fileability issues are as follows:
1. Project mgmt. - Kerry Rothschild. The submission was missing (1) a statement that all clinical trials were conducted in accordance with the IRB/Declaration of Helsinki provisions of the CFR; (2) copies of package inserts from countries in which the product has previously been approved for marketing; (3) a statement that the integrated summary of safety includes all safety data from all sources; and (4) a statement that all information in the CANDA submission and Archival submission are identical.

Project management, nevertheless, considers the application fileable. Sponsor will be asked to submit the above.

2. Biostatistics - Kun Jin. Application Fileable. Statistical review to be completed by June 15,

1999.

3. Clinical HFD-560 - R.Neuner. Application Fileable. Review to be completed by June 25, 1999.

4. Clinical HFD-120 - (L. Chen, PM, for) A. Oliva. Application Fileable. Review to be completed by June 1, 1999.

5. IDS HFD-560 - S. Mason. Application Fileable. Review to be completed by June 1, 1999.

6. Filing Decision - L.Katz. Application fileable.

Agreements:

Application to be filed. K. Rothschild to contact sponsor regarding information to be requested. Monthly team meetings and labeling day to be scheduled as well.

Minutes Preparer: /S/

Kerry Rothschild,
Project Manager

cc: NDA 20-802
HFD-560/Div Files
HFD-560/Rothschild/Katz/Cook/Lumpkins/Neuner/Mason
HFD-120/L.Chen/Jin/R.Chen/Oliva

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: June 15, 1999
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-802 Excedrin
To: file

Background:

NDA 20-802 was submitted 1/14/97 to support the use of Excedrin as a treatment for migraine. Following evaluation of the application, the drug was approved on 1/14/98 for the treatment of the pain associated with migraine. This indication is different from other migraine therapies that are approved for the acute treatment of migraines. The reason for this difference stems from whether or not the treatment of migraine is an indication that qualifies for over the counter (OTC) marketing. Initially, the treatment of migraine was not thought to be an OTC indication but the treatment of the pain of migraine was an OTC indication.

With this supplement, submitted 12/18/98, the sponsor wants to make two changes to the labeling. One, is to broaden the use claim to: "Relief of migraine" and "Excedrin Migraine relieves the symptoms of migraine including headache pain, nausea, sensitivity to light and sound, and difficulty in carrying out normal activities." The second is to provide additional warning statements.

Our division was ask to consult on this supplement to address the efficacy issues related to migraine treatments. Dr. Oliva has reviewed the efficacy portion of the supplement. Dr. Richard Chen provided statistical consultation.

Comments:

In our division, we recently approved five different drug for the acute treatment of migraine. In regards to efficacy, we approved the drugs based on two or more adequate and well controlled studies that demonstrated a statistically significant difference in the frequency of headache response between patients with moderate to severe migraine headache pain treated with drug and those treated with placebo. Headache response was defined as a change of headache pain from moderate or severe to mild or no pain 2 or 4 hours following treatment. We have also told many other sponsors that a migraine claim can be achieved using these criteria.

Evidence for efficacy

The studies provided in this application demonstrate a statistically significant difference in headache response at 2 hours in the Excedrin group compared to the placebo group in all three studies. I have summarized the results from this analysis in the following table. More details on the analysis of these results can be found in Dr. Oliva's review and the reviews with the original NDA.

Results at 2 Hours (sponsor's results)

Study	Study 840		Study 841		Study 842		Pooled	
Treatment	EM	PBO	EM	PBO	EM	PBO	EM	PBO
Number of patients	N=187	N=191	N=206	N=221	N=209	N=206	N=602	N=618
Headache Response	64%	37%	59%	31%	56%	31%	59%	33%
p value	<0.001		<0.001		<0.001		<0.001	

When evaluating drugs for the acute treatment of migraine, we want to be assured that the patients treated migraine headaches rather than "tension" headaches resulting from muscular or skeletal problems. Dr. Oliva reviewed the baseline characteristics of the migraines treated by patients in the Excedrin trials and concluded that there was a question on whether or not the headache was a migraine in only 5% or 50 of the 1249 patients enrolled in the studies.

We also evaluate other symptoms frequently associated with migraines such as nausea, vomiting, photophobia and phonophobia. For every drug for the acute treatment of migraine, there is a lower percentage of these symptoms 2 hours after treatment in patients given drug compared to those given placebo. Because these studies are not designed to specifically assess the role of the drug in the treatment of each of these symptoms, we do not use these findings to establish the efficacy of the drug in the treatment of migraines and do not specifically describe these findings in labeling. An increase in any of these symptoms in the drug treated patients would raise questions as to the benefit of the drug as an acute treatment for migraines. Dr. Oliva reviewed the findings of these other migraine symptoms. The results are summarized in the following table.

Results at 2 Hours (sponsor's results)

Study	Study 840		Study 841		Study 842		Pooled	
Treatment	EM	PBO	EM	PBO	EM	PBO	EM	PBO
Number of patients	N=187	N=191	N=206	N=221	N=209	N=206	N=602	N=618
No Nausea	54%	41%	37%	34%	45%	28%	45%	33%
p value	0.057		0.0483		0.002		<0.001	
No Photophobia	39%	11%	23%	15%	33%	13%	32%	13%
p value	<0.001		0.034		<0.001		<0.001	
No Phonophobia	38%	15%	22%	16%	29%	13%	30%	14%
p value	<0.001		0.073		<0.001		<0.001	

Dr. Chen also took all patients with symptoms at baseline and compared the proportion without symptoms. The results at 2 hours are summarized in the following table.

Results at 2 Hours in patients with the specific associated symptoms at baseline

Study	Study 840		Study 841		Study 842		Pooled	
Treatment	EM	PBO	EM	PBO	EM	PBO	EM	PBO
% without nausea at 2 hours	54%	41%	52%	38%	45%	28%	45%	33%
P value	0.056		0.601		0.004		0.004	
% without photophobia at 2 hrs	38%	11%	23%	15%	33%	13%	32%	13%
P value	<0.001		0.028		<0.001		<0.001	
% without phonophobia at 2 hrs	38%	15%	22%	16%	29%	13%	30%	14%
P value	<0.001		0.082		<0.001		<0.001	

Not all of the differences were associated with a nominal p value less than 0.05. For patients with nausea, only 1 of the 3 studies had differences associated with a nominal p value < 0.05. 2 of the 3 studies had a nominal p value < 0.05 for photophobia. Dr. Chen "corrected" the p value for multiple comparisons resulting in only one of three studies being " positive". Numerically, the results for nausea, photophobia and phonophobia were in favor of the drug. The number of patients with vomiting was very small and not included in the results.

We also questioned how the patients enrolled in these studies compare to the those enrolled in other migraine trials. In the Excedrin trials unlike the trials for the other migraine drugs, patients were excluded if they had disabling or incapacitating migraine (requiring bed rest), if they had a history of vomiting ≥20% of the time during their migraine attacks, or if they concurrently were using ergot alkaloids. In the trials, 5 to 6% of the patients rated their headaches as incapacitating.

Another difference was that a population based screening procedure was used in addition to conventional recruiting methods to identify potential adult study participants. In the population based screening, subjects were called using random digit dialing. Telephone interviews were conducted and those with suspected migraine headaches were brought in for screening evaluation and diagnosis (visit 1). Conventional recruiting methods

included identifying eligible subjects from private practice patients, referrals, and local advertising. The population based screening was used in only one of the three studies and did not affect the efficacy conclusions.

To get an idea of how the patients studied in the Excedrin trials differed to those in other migraine trials, I compared the baseline characteristics and demographics of the patient population with those in other migraine therapies databases.

For the Excedrin population the mean age was around 36 which compares with a mean age of 41 in recent migraine applications. Approximately 80% of the patients were female which is similar to other migraine trials. When asked about their past history of migraines, patients in the Excedrin trials noted that most of their headaches (around 80%) did not have an aura, were severe (around 70%) and occurred at a frequency of a little over 2 times per month on average. Headaches lasted on average of 27 hours without treatment. I looked at information on the past history of migraine for patients studied in previous migraine trials and found similar findings. There was variation from study to study with headache frequency ranging from 2 to 4 per month and headache lasting up to 44 hours.

In the Excedrin trial, 65% treated headaches with non prescription drugs which were effective about 75% of the time. In a recent application for another migraine treatment, 50% used a triptan to treat their migraines with a 76% success rate.

In the Excedrin trials, 83% of the headaches treated did not have an aura, 33% of the headaches were rated as severe, 60% had nausea, and 95% had photophobia, and 90% had phonophobia. I compared this to a recent triptan database where 65% of the headaches treated did not have an aura, 25% were rated as severe, 50% had nausea, 82% had photophobia and 73% had phonophobia.

From the evidence provided in the application, it appears that the study populations in the studies were adequate for the evaluation of the treatment of migraine. The study design of the studies were also adequate to provide the evidence for efficacy. The sponsor has demonstrated in the three studies that Excedrin use is associated with an increase in headache response rate at 2 hours compared to placebo and therefore, is effective for the acute treatment of migraine.

Labeling changes

The sponsor wants to change the use statement from:
"Use:

- For the temporary relief of mild to moderate pain associated with migraine headache."

To:

Use:

- For the relief of migraine
- Excedrin relieves the symptoms of migraine including headache pain, nausea, sensitivity to light and sound, and difficulty in carrying out normal activity.

The proposed statements are not supported by the studies provided. The first statement says the use is for relief of migraine. First, it is not clear what is meant by "relief". Does relief mean that the migraines are cured? Only a minority of patients had no pain 2 hours after treatment. The percentage of patients without pain is summarized in the following table. Most patients still had at least mild pain and many still had associated symptoms. Second, since the studies only evaluated 6 hours following treatment and migraines can last more than 24 hours, we have no idea if the pain returned and possibly worsened after treatment. The use statement "for the temporary treatment of migraine" is supported by the studies.

Results at 2 Hours (sponsor's results)

Study	Study 840		Study 841		Study 842		Pooled	
Treatment	EM	PBO	EM	PBO	EM	PBO	EM	PBO
Number of patients	N=187	N=191	N=206	N=221	N=209	N=206	N=602	N=618
Headache Response	64%	37%	59%	31%	56%	31%	59%	33%
No Pain	26%	7%	17%	9%	21%	5%	21%	7%

The sponsor wants to include in labeling "Excedrin Migraine relieves the symptoms of migraine including headache pain, nausea, sensitivity to light and sound, and difficulty in carrying out normal activities". Before I go on to discuss the issue of associated symptoms, I should note the measure used by the sponsor to assess the ability to carry out normal activities, asking the patient if they can carry out normal activities, is not a valid assessment of functioning. Migraines can interfere with functioning in subtle but significant ways such as interfering with the ability to concentrate and just asking someone if they can perform "normal" activities is not sufficient for assessing this outcome. The statement that the drug relieves difficulties in carry out normal activities as a result of a migraine is misleading. Most, if not all, migraine trials include this type of assessment of returning to normal activities, and we have not included this claim in any recent labeling for migraine drugs. Other sponsors are conducting studies evaluating the effects of migraine treatments on functioning with more valid measures.

The issue of including in labeling that a drug relieves the symptoms of nausea, vomiting, photophonia and phonophobia has been debated with all recent drugs approved for the treatment of migraine. There are many problems with making this claim in labeling. The treatment of the pain associated with migraine does not appear to be independent from the treatment of the associated symptoms. For example, in these trials, over 80% of the patients who had a reduction of their headache pain also had a reduction of the associated symptoms. Around 70% of patients who did not have pain response did not have relief of their other associated symptoms. This may be why an analgesic without any specific mechanism of action against the underlying cause of migraine is an effective treatment for migraine. The same may not be true for treatment of other migraine symptoms.

Recently, we saw results from treating migraines with an anti emetic. The incidence of nausea was decreased but the other associated symptoms including pain were not changed.

The typical migraine studies, including the studies provided with this submission, are not designed to answer the question as to the efficacy of the drug to specifically treat any one migraine symptom except pain. Patients are enrolled based on their pain, not on their associated symptoms. For example, in these studies, only a small percentage of patients had moderate to severe nausea at the time of treatment. When comparing the rate of nausea response, defined as going from moderate to severe nausea to mild or no nausea, for the drug and placebo treated patients, the numbers were in favor of drug but the difference did not reach a nominal p value of < 0.05 in two of the three studies. Approximately 60 to 65% of patients had either photophobia or phonophobia at baseline. Comparisons of response rates for photophobia and phonophobia were associated with a nominal p value of < 0.05 in favor of the drug in 2 of 3 studies (see Dr. Chen's analysis presented earlier in the review).

I have summarized the results for patients who had the associated symptoms at baseline in the following table. The definition of a responder is the same as with pain.

Results at 2 Hours in patients with the specific associated symptoms at baseline (* p value < 0.05)

Study	Study 840		Study 841		Study 842		Pooled	
Treatment	EM	PBO	EM	PBO	EM	PBO	EM	PBO
Number of patients	N=187	N=191	N=206	N=221	N=209	N=206	N=602	N=618
Moderate to severe nausea at baseline	16%	15%	18%	14%	21%	25%	18%	18%
Nausea responder at 2 hours (mild to no nausea)	68%	54%	52%	34%	68%*	41%	63%*	42%
% of headache responders with nausea response at 2 hours							87%	83%
% of headache non responders with nausea response at 2 hours							35%	34%
Moderate to severe photophobia at baseline	68%	72%	58%	66%	60%	60%	62%	66%
Photophobia responder at 2 hours	63%*	41%	50%*	29%	51%*	27%	55%	33%
% of headache responders with photophobia response at 2 hours							90%	85%
% of headache non responders with photophobia response at 2 hours							38%	32%
Phonophobia at baseline	69%	66%	57%	55%	53%	53%	59%	58%
Phonophobia responder at 2 hours	68%*	47%	58%*	35%	60%*	33%	62%	39%
% of headache responders with phonophobia response at 2 hours							86%	81%
% of headache non responders with phonophobia response at 2 hours							32%	20%

If the associated symptoms of a migraine are going to be included, which ones are described? Only the ones with positive results? Should the associated symptoms not evaluated also be included? How about the ones that do not seem to improve with treatment? By stating that "Excedrin relieves the symptoms of migraine including ..." this specifically notes that all symptoms are relieved by Excedrin which is not supported by the studies. Because of the problems with assessing the associated symptoms, we have not included the individual symptoms in the indications section for any migraine drug label. Even the statement "Excedrin relieves migraines" implies that all symptoms are relieved. For all recent migraine drug labeling the indication is simply for the acute treatment of migraines.

The sponsor states that their proposal for the inclusion of the associated symptoms is based on a labeling comprehension study. They say that patients understood the labeling better if the associated symptoms were included in labeling.

The labeling comprehension study was inadequate to assess comprehension of labeling to assure the safe use of the drug. The difference between the groups found in this study could simply be related to a misunderstanding of what can occur with a migraine. People who have migraines with pain, nausea and phonophobia may not know that photophobia is a symptoms of migraine and therefore, will not know that a treatment for migraine could treat photophobia. To use the drug safely, people should not have to know all of the symptoms that may occur with migraines. To understand the use statement "Use: For temporary treatment of migraines", patients will have to understand what is meant by migraine. They will have to know if they have a migraine and understand that they can take this drug as a treatment for their migraine. If people don't understand the term migraine, do not know the symptoms that they have with a migraine and do not understand that a drug indicated for the treatment of migraines can treat their migraines, then we should reconsider having a treatment for migraine as an OTC drug.

There is two additional problems with the proposed labeling. The directions in labeling includes children. The characteristics of migraines is different for children and adults. Prior to making a claim for efficacy in treating migraines in children, the sponsor must provide evidence for efficacy in this population, children ages 12 to 17. We have required this for all other migraine drugs.

Finally, the directions call for the drug to be given every 6 hours if pain persists. In labeling for other migraine drugs, we note that if the first dose is not effective, the diagnosis should be reconsidered prior to taking additional doses. Therefore, the directions should be changed and the statement "stop using this product and see your Doctor if your migraine is not relieved or worsens" should be clarified to read "stop using this product and see your Doctor if your migraine is not relieved or worsens after the initial dose". This is a safety concern since we do not want people to treat more serious conditions that may present with symptoms similar to those seen with migraines.

Recommendations:

I recommend approval of the supplement with the following labeling changes from the sponsor's proposed labeling:

> Use: For the temporary treatment of migraines.
>
> Directions: Adults: 2 tablets with a full glass of water. If symptoms persist or worsen, consult your Doctor. Children: Do not give to children under age 18 unless directed by a doctor.
>
> Stop using this product and see a doctor if:
> Your migraine is not relieved or worsens after the initial dose.

These recommendations will make the labeling consistent with the labeling for other migraine treatments.

/S/
Randy Levin, M.D.
Neurology Team Leader

COOK

45 DAY MEETING CHECKLIST

ABILITY:

initial overview of the NDA application: YES NO

ROJECT MANAGEMENT:

(1) Do any of the following apply to this application (*i.e.*, if YES, the application MUST BE REFUSED TO FILE under 314.100(e) and there is no filing over protest):

(a) Is the drug product already covered by an approved application? Efficacy Supplement — NO

(b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)? — NO

(c) Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR? — NO

(2) Do any of the following apply to this application (*i.e.*, if NO, the application MAY BE REFUSED TO FILE under 314.100(d) and there is the potential for filing over protest):

(a) Does the application contain a completed application form as required under 314.50 or 314.55? — Yes

(b) On its face, does the application contain the sections of an application required by regulation and Center guidelines? — Yes

(c) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under 25.24 of the CFR? — NA

(d) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries? Yes

(e) Is the NDA indexed and paginated? Yes

(f) On its face, is the NDA legible? Yes

(g) Has the applicant submitted all required copies of the submission and various sections of the submission? Yes

(h) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? NA

(i) Does the application contain a statement that all nonclinical laboratory studies was conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements? NA

(j) If required, has the applicant submitted carcinogenicity studies? NA

(k) On its face, does the application contain at least two adequate and well-controlled clinical trials? Yes

(l) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR? NO

(m) Have all articles/study reports been submitted either in English or translated into English? Yes

(n) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR? Yes

(o) Has the applicant submitted the required FRAUD POLICY notice? Yes

(p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated? NO

(q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS? NO

(r) If this is a CANDA submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDA and the archival hardcopy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions? NO

(3) From a project management perspective, is this NDA fileable? If "no", please state on reverse why it is not. yes

/S/
oject Manager

/S/
pervisory Project Manager

Request Items # (2) [redacted]
From Sponsor (L)
(P)
(Q)
(R)

45 DAY MEETING CHECKLIST

LEABILITY:

initial overview of the NDA application:	YES	NO

CLINICAL:

(1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	✓	
(2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	✓	
(3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	✓	
(4) If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?		✓
(5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	✓	
(6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	✓	
(6) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	✓	
(7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✓	
(8) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	✓ (datasets)	

(9) Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? NA

(10) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? yes

(11) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? yes.

(12) Has the applicant presented a safety assessment based on <u>all</u> current world-wide knowledge regarding this product? No

(13) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package? yes.

(14) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? yes

(15) From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. yes.

If certain claims are not filable, please state which claims they are and why they are not filable.

/S/

Reviewing Medical Officer

/S/

Supervisory Medical Officer