

EXCEDRIN MIGRAINE
(apap + aspirin + caffeine)

NDA 20-802

Index of Nonserious Initial and Follow-Up Reports

By Manufacturer File Number

Received 01/01/99 to 03/31/99

Initial Reports: Section IA; Follow-Up Reports: Section IB

MFR (CTU) FILE NO. -----	EXPANDED COSTART TERM -----	REPORTED TERM -----	REPORT TYPE -----
M094949	MALAISE	SICK	INITIAL
M094951	ABDOMINAL PAIN INSOMNIA	STOMACH ACHE UNABLE TO SLEEP	INITIAL
M094952	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M094955	TINNITUS	TINNITUS	INITIAL
M094956	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M094968	ABDOMINAL PAIN	STOMACH ACHE	INITIAL
M094972	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M094973	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M094974	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M094975	TREMOR NERVOUSNESS	SHAKES HYPER	INITIAL
M094996	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M095008	MALAISE	MALAISE	INITIAL
M095009	DIARRHEA LACK OF DRUG EFFECT	DIARRHEA LACK OF EFFECT	INITIAL
M095012	DYSPEPSIA	STOMACH PROBLEMS	INITIAL

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Received 01/01/99 to 03/31/99

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M095015	DYSPEPSIA TREMOR	UPSET STOMACH SHAKES	INITIAL
M095023	NERVOUSNESS	HYPER	INITIAL
M095024	NERVOUSNESS	JITTERY	INITIAL
M095025	TINNITUS	TINNITUS	INITIAL
M095037	TINNITUS	RINGING IN EARS	INITIAL
M095104	CIRCUMORAL PARESTHESIA	NUMBNESS FACE	INITIAL
M095105	NERVOUSNESS	JITTERY	INITIAL
M095106	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M095107	ABDOMINAL PAIN NAUSEA VOMITING SWEATING	STOMACH CRAMPS NAUSEA VOMITING SWEATING	INITIAL
M095108	NAUSEA SWEATING	NAUSEA SWEATY	INITIAL
M095109	TONGUE DISORDER	BURNING SENSATION TONGUE	INITIAL
M095110	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M095111	INSOMNIA	COULD NOT SLEEP	INITIAL

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-----	-----	-----	-----
M095112	TACHYCARDIA	FAST HEART RATE	INITIAL
M095113	PREGNANCY USE DURING	PREGNANCY USE DURING	INITIAL
M095114	ABDOMINAL PAIN	PAIN IN STOMACH	INITIAL
M095115	ASTHENIA	TIRED	INITIAL
M095116	MYASTHENIA PAROSMIA TASTE PERVERSION NERVOUSNESS	LEG WEAKNESS SMELL PERVERSION TASTE PERVERS SHAKY FEELING	INITIAL
M095117	DYSPEPSIA	UPSET STOMACH	INITIAL
M095118	RECTAL DISORDER	RECTAL TEAR	INITIAL
M095247	HYPERTENSION SOMNOLENCE	HIGH BLOOD PRESSURE DROWSY	INITIAL
M095248	DYSPEPSIA DEPERSONALIZATION	UPSET STOMACH FELT GOOFY	INITIAL
M095249	AGGRAVATION REACTION HEADACHE EDEMA URTICARIA TACHYCARDIA	HEADACHE EXACERBATED HEADACHE HEAD SWELLING HIVES INCREASED PULSE RATE	INITIAL
M095250	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL

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NDA 20-802

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MFR (CTU) FILE NO. -----	EXPANDED COSTART TERM -----	REPORTED TERM -----	REPORT TYPE -----
M095251	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL
M095252	MELENA	BLOOD IN STOOL	INITIAL
M095253	AGGRAVATION REACTION INTESTINAL ULCER	ULCER EXACERBATED COLON ULCERS	INITIAL
M095380	INSOMNIA	COULD NOT SLEEP	INITIAL
M095382	LACK OF DRUG EFFECT	LACK OF EFFECT	INITIAL

Attachment IV

to

Safety Review Update


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Excedrin® (acetaminophen / aspirin / caffeine) Migraine tablets, caplets, and gellabs

**FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
 BY MANUFACTURER CONTROL NUMBER**

RECEIVED FROM 01APR1999 THROUGH 30JUN1999

INITIAL REPORTS: SECTION IA; FOLLOW-UP REPORTS: SECTION IB

MANUFACTURER CONTROL NUMBER	FDA NUMBER	PREFERRED TERM	REPORTED TERM	REPORT TYPE
10002657-1		BURNING SENSATION NOS	BURNING SENSATION	INITIAL
10002780-1		DERMATITIS NOS	RASH	INITIAL
10002830-1		ABDOMINAL PAIN UPPER	STOMACHACHE	INITIAL
10002855-1		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
10002863-1		DIZZINESS (EXC VERTIGO) NAUSEA	DIZZINESS NAUSEA	INITIAL
10002947-1		VOMITING NOS	VOMIT	INITIAL
10003036-1		DIZZINESS (EXC VERTIGO) NAUSEA VOMITING NOS	LIGHTHEADED NAUSEA VOMITING	INITIAL
10003051-1		FEELING HOT FEELING JITTERY NERVOUSNESS SWEATING INCREASED	HOT JITTERY NERVOUS SWEATY	INITIAL
10003085-1		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
10003093-1		URTICARIA NOS	HIVES	INITIAL


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

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 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
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RECEIVED FROM 01APR1999 THROUGH 30JUN1999

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10003119-1		ABDOMINAL DISTENSION	BLOATING	INITIAL
10003127-1		VOMITING NOS	VOMITED	INITIAL
10003168-1		DRUG INEFFECTIVE NAUSEA	LACK OF EFFECT NAUSEA	INITIAL
10003218-1		DIZZINESS (EXC VERTIGO) HEART RATE INCREASED	DIZZINESS HEART RATE INCREASED	INITIAL
10003242-1		SEDATION	SLEEPY	INITIAL
10003408-1		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
10003416-1		FEELING JITTERY NAUSEA	JITTERY NAUSEA	INITIAL
10003424-1		ABDOMINAL PAIN UPPER	STOMACH PAIN	INITIAL
10003432-1		ABDOMINAL PAIN UPPER	STOMACH PAIN	INITIAL
10003705-1		ABDOMINAL PAIN UPPER EPISTAXIS	STOMACH PAIN NASAL BLEEDING	INITIAL
10003879-1		GASTRIC ULCER	STOMACH ULCER	INITIAL


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

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**FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
 BY MANUFACTURER CONTROL NUMBER**

RECEIVED FROM 01APR1999 THROUGH 30JUN1999

INITIAL REPORTS: SECTION IA; FOLLOW-UP REPORTS: SECTION IB

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10007144-1		GASTRIC ULCER	GASTRIC ULCER	INITIAL
10007201-1		NAUSEA	NAUSEA	INITIAL
10007235-1		THINKING ABNORMAL NEC	IRRATIONAL	INITIAL
10007268-1		DYSPEPSIA FEELING JITTERY	STOMACH PROBLEMS JITTERY	INITIAL
10007409-1		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
10008862-1		TINNITUS	RINGING IN EARS	INITIAL
10011708-1		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
10011716-1		NERVOUSNESS TASTE DISTURBANCE	NERVOUSNESS AFTER TASTE	INITIAL
10011740-1		VERTIGO NEC	VERTIGO	INITIAL
10011815-1		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
10011849-1		ABDOMINAL PAIN UPPER	STOMACH PAIN	INITIAL
10016210-1		DERMATITIS NOS	BUMPS	INITIAL


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

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**FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
 BY MANUFACTURER CONTROL NUMBER**

RECEIVED FROM 01APR1999 THROUGH 30JUN1999

INITIAL REPORTS: SECTION IA; FOLLOW-UP REPORTS: SECTION IB

MANUFACTURER CONTROL NUMBER	FDA NUMBER	PREFERRED TERM	REPORTED TERM	REPORT TYPE
		DYSPNOEA NOS	BREATHING DIFFICULT	
M076658		LIMB INJURY NOS	FINGER INJURY	INITIAL
M077508		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M095649		BREAST LUMP NOS	BREAST LUMP	INITIAL
M095651		HAEMORRHAGE NOS	BLEEDING INTERNALLY	INITIAL
M095653		NAUSEA	UPSET STOMACH	INITIAL
M095656		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M095658		NAUSEA NERVOUSNESS	NAUSEA NERVOUSNESS	INITIAL
M095678		BLOOD DYSCRASIA NOS	BLOOD THINNING	INITIAL
M095682		AMNESIA NEC	MEMORY LOSS	INITIAL
M095697		INSOMNIA NEC	SLEEPLESSNESS	INITIAL
M095700		ABDOMINAL PAIN NOS	STOMACH CRAMPS	INITIAL
M095707		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

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**FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
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RECEIVED FROM 01APR1999 THROUGH 30JUN1999

INITIAL REPORTS: SECTION IA; FOLLOW-UP REPORTS: SECTION IB

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M095708		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M095712		VOMITING NOS	VOMITING	INITIAL
M095721		ABNORMAL DREAMS DRUG INEFFECTIVE FEELING ABNORMAL	WEIRD DREAMS LACK OF EFFECT WEIRD FEELING	INITIAL
M095727		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M095732		ABDOMINAL PAIN UPPER NAUSEA	STOMACH ACHE STOMACH UPSET	INITIAL
M095743		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M095754		DEPERSONALISATION FEELING JITTERY THINKING ABNORMAL NEC	FEELING FUZZY SHAKINESS INABILITY TO THINK CLEARLY	INITIAL
M095793		DIARRHOEA NOS NAUSEA	DIARRHEA UPSET STOMACH	INITIAL
M095797		INSOMNIA NEC	SLEEPLESSNESS	INITIAL
M095801		TREMOR NEC	SHAKING	INITIAL


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

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**FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
 BY MANUFACTURER CONTROL NUMBER**

RECEIVED FROM 01APR1999 THROUGH 30JUN1999

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MANUFACTURER CONTROL NUMBER	FDA NUMBER	PREFERRED TERM	REPORTED TERM	REPORT TYPE
M095808		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M095819		INCREASED ACTIVITY INSOMNIA NEC	HYPER SLEEPLESSNESS	INITIAL
M095821		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M095824		NAUSEA	NAUSEA	INITIAL
M095828		NAUSEA	UPSET STOMACH	INITIAL
M095852		ABDOMINAL PAIN UPPER	STOMACH PAIN	INITIAL
M095857		DRUG INEFFECTIVE NAUSEA VOMITING NOS	LACK OF EFFECT NAUSEA VOMITING	INITIAL
M095859		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M095860		INSOMNIA NEC NERVOUSNESS TREMOR NEC	SLEEPLESSNESS NERVOUSNESS HANDS TREMBLING	INITIAL
M095861		INSOMNIA NEC	SLEEPLESSNESS	INITIAL

0150


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

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**FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
 BY MANUFACTURER CONTROL NUMBER**

RECEIVED FROM 01APR1999 THROUGH 30JUN1999

INITIAL REPORTS: SECTION IA; FOLLOW-UP REPORTS: SECTION IB

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M095878		TINNITUS	RINGING IN EARS	INITIAL
M096016		PAIN NOS STOMATITIS TONGUE DISORDER NOS	PAIN BURNING MOUTH WHITE SPOTS TONGUE	INITIAL
M096021		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096022		HEADACHE NOS	REBOUND HEADACHE	INITIAL
M096024		DIZZINESS (EXC VERTIGO) NAUSEA PYREXIA	DIZZY NAUSEA FELT FEVERISH	INITIAL
M096025		ABDOMINAL PAIN UPPER PYREXIA VOMITING NOS	STOMACH PAIN FELT FEVERISH VOMITING	INITIAL
M096028		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096029		DERMATITIS NOS	DERMATITIS NOS	INITIAL
M096030		CONDITION AGGRAVATED DYSPTNOEA NOS HEADACHE NOS NAUSEA	HEADACHE EXACERBATED DIFFICULTY BREATHING HEADACHE NAUSEA	INITIAL

0151

 **Bristol-Myers Squibb Company**

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

Excedrin® (acetaminophen / aspirin / caffeine) Migraine tablets, caplets, and gellabs

FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
BY MANUFACTURER CONTROL NUMBER

RECEIVED FROM 01APR1999 THROUGH 30JUN1999

INITIAL REPORTS: SECTION IA; FOLLOW-UP REPORTS: SECTION IB

MANUFACTURER CONTROL NUMBER	FDA NUMBER	PREFERRED TERM	REPORTED TERM	REPORT TYPE
		PALPITATIONS	PALPITATIONS	
M096031		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096032		ABDOMINAL PAIN UPPER	STOMACH PAIN	INITIAL
M096095		PRURITUS NOS RASH ERYTHEMATOUS SWELLING NOS	ITCHING REDNESS SWELLING	INITIAL
M096099		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096101		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096108		NERVOUSNESS	NERVOUSNESS	INITIAL
M096118		PRURITUS NOS	ITCHING OVER BODY	INITIAL
M096120		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096125		GASTRIC IRRITATION	GASTRIC IRRITATION	INITIAL
M096138		NAUSEA	NAUSEA	INITIAL
M096147		DYSPEPSIA OESOPHAGEAL REFLUX	DYSPEPSIA OESOPHAGEAL REFLUX	INITIAL

0152


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

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FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
 BY MANUFACTURER CONTROL NUMBER

RECEIVED FROM 01APR1999 THROUGH 30JUN1999

INITIAL REPORTS: SECTION IA; FOLLOW-UP REPORTS: SECTION IB

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M096149		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096154		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096156		DIZZINESS (EXC VERTIGO) NAUSEA	DIZZINESS NAUSEA	INITIAL
M096159		DIZZINESS (EXC VERTIGO) DRY MOUTH ERYTHEMA NEC HYPERSENSITIVITY NOS NAUSEA TACHYCARDIA NOS	DIZZINESS DRY MOUTH ERYTHEMA HYPERSENSITIVITY NAUSEA TACHYCARDIA	INITIAL
M096174		NAUSEA	NAUSEA	INITIAL
M096177		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096226		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096230		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096304		CONDITION AGGRAVATED TINNITUS	EAR RINGING EXACERBATED RINGING IN EARS	INITIAL

0153


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

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FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
 BY MANUFACTURER CONTROL NUMBER

RECEIVED FROM 01APR1999 THROUGH 30JUN1999

INITIAL REPORTS: SECTION IA; FOLLOW-UP REPORTS: SECTION IB

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M096314		ABDOMINAL PAIN UPPER NAUSEA	STOMACH PAIN NAUSEA	INITIAL
M096315		DIZZINESS (EXC VERTIGO) HOT FLUSHES NOS	DIZZINESS HOT FLUSHES	INITIAL
M096320		ABDOMINAL PAIN UPPER NAUSEA	ABDOMINAL PAIN UPPER NAUSEA	INITIAL
M096325		HEADACHE NOS	HEADACHE	INITIAL
M096382		ABDOMINAL PAIN UPPER NAUSEA	ABDOMINAL PAIN UPPER NAUSEA	INITIAL
M096386		PARAESTHESIA TONGUE	PARAESTHESIA TONGUE	INITIAL
M096391		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096396		NAUSEA	NAUSEA	INITIAL
M096421		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096480		HOT FLUSHES NOS HYPOAESTHESIA TINNITUS	HOT FLASHES HYPOAESTHESIA TINNITUS	INITIAL

0154


Bristol-Myers Squibb Company

Pharmaceutical Research Institute

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

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FDA: OVER THE COUNTER NEW DRUG APPLICATION 20-802
 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
 BY MANUFACTURER CONTROL NUMBER

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M096471		EYELID OEDEMA PERIORBITAL HAEMATOMA SPEECH DISORDER NEC TONGUE DISCOLOURATION NOS TONGUE OEDEMA	EYELID OEDEMA PERIORBITAL HAEMATOMA DIFFICULTY TALKING TONGUE DISCOLOURATION TONGUE OEDEMA	INITIAL
M096501		GASTROINTESTINAL UPSET	GASTROINTESTINAL UPSET	INITIAL
M096538		FEELING JITTERY	JITTERY	INITIAL
M096539		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096618		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096623		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096627		DRUG INEFFECTIVE SEDATION STUPOR SWEATING INCREASED TACHYCARDIA NOS	LACK OF EFFECT DROWSY RESPONSIVENESS DIMINISHED SWEATING HEART RACING	INITIAL
M096631		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096662		DUODENAL ULCER TINNITUS	DUODENAL ULCER TINNITUS	INITIAL


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Pharmaceutical Research Institute

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 INDEX OF NON-SERIOUS (NS) INITIAL AND FOLLOW-UP REPORTS
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M096685		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096689		INSOMNIA NEC TACHYCARDIA NOS THINKING ABNORMAL NEC	INSOMNIA NEC TACHYCARDIA NOS THINKING ABNORMAL NEC	INITIAL
M096697		DRY MOUTH LACRIMAL DISORDER NOS URTICARIA NOS	DRY MOUTH LACRIMAL DISORDER NOS URTICARIA	INITIAL
M096709		TASTE DISTURBANCE	TASTE DISTURBANCE	INITIAL
M096725		DIZZINESS (EXC VERTIGO) FEELING JITTERY	DIZZINESS FEELING JITTERY	INITIAL
M096739		DRUG INEFFECTIVE	DRUG INEFFECTIVE	INITIAL
M096745		CONFUSION FATIGUE STUPOR	CONFUSION FATIGUE STUPOR	INITIAL
M096751		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096752		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL


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Pharmaceutical Research Institute

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		NERVOUSNESS	NERVOUSNESS	
M096947		DRUG INEFFECTIVE	DRUG INEFFECTIVE	INITIAL
M096949		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096951		DERMATITIS NOS PRURITUS NOS	RED BLOTCHES PRURITUS NOS	INITIAL
M096952		DRUG INEFFECTIVE NAUSEA	DRUG INEFFECTIVE NAUSEA	INITIAL


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M096780		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096781		DRUG INEFFECTIVE	LACK OF EFFECT	INITIAL
M096790		DIZZINESS (EXC VERTIGO) FEELING JITTERY NERVOUSNESS SENSATION OF HEAVINESS	LIGHTHEADED JITTERY NERVOUSNESS SENSATION OF HEAVINESS	INITIAL
M096812		ABDOMINAL PAIN NOS	ABDOMINAL CRAMPING	INITIAL
M096815		DIZZINESS (EXC VERTIGO) NAUSEA	DIZZINESS NAUSEA	INITIAL
M096816		DIZZINESS (EXC VERTIGO)	DIZZINESS	INITIAL
M096819		ANXIETY NEC DYSPEPSIA FEELING JITTERY	ANXIETY DYSPEPSIA FEELING JITTERY	INITIAL
M096862		SKIN DISORDER NOS	SKIN DISORDER	INITIAL
M096936		DIZZINESS (EXC VERTIGO) NAUSEA	DIZZINESS NAUSEA	INITIAL
M096937		INSOMNIA NEC	INSOMNIA	INITIAL

0157

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
CONSULTATIVE EFFICACY REVIEW OF NDA SUPPLEMENT

Brand Name: Excedrin

Generic Name: aspirin, acetaminophen, caffeine

Sponsor: Bristol-Myers

Indication: migraine

NDA Number: 20-802

Original Receipt Date: 12/18/98

Review Author: Armando Oliva, MD

Review Completed: 5/12/99

Table of Contents

<i>1. Background</i>	<i>3</i>
<i>2. Proposed Labeling</i>	<i>4</i>
<i>3. Integrated Review of Efficacy</i>	<i>4</i>
3.1 The Development Program	4
3.2 Protocols	5
3.3 Efficacy Variables	8
3.4 Data Analysis Methods	9
3.5 Patient Population	11
3.6 Efficacy Results	16
<i>4. Safety Update</i>	<i>18</i>
<i>5. Consulting Neurologist's Report</i>	<i>19</i>
<i>6. Sponsor's Conclusions</i>	<i>19</i>
<i>7. Reviewer's Analyses</i>	<i>19</i>
7.1 Methods	19
7.2 Baseline Headache Characteristics	20
7.3 Nausea	21
7.4 Photophobia	22
7.5 Phonophobia	24
<i>8. Labeling Review</i>	<i>25</i>
8.1 Draft Product Labeling	25
8.2 Comments	27
<i>9. Conclusions</i>	<i>28</i>
<i>10. Recommendations</i>	<i>28</i>

1. Background

Excedrin Migraine is a combination analgesic product containing aspirin, acetaminophen, and caffeine. It is currently marketed for over the counter (OTC) use "for the temporary relief of mild to moderate pain associated with migraine headache."

The purpose of the supplement, as outlined in the cover letter, is to expand the "Use" section of the labeling to read:

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

The sponsor's request for a labeling change from "relief of migraine headache pain" to "relief of migraine," including the migraine-associated symptoms: headache pain, functional disability, nausea, photophobia, and phonophobia, is based on the following: [1] migraine headache pain is commonly associated with other symptoms: functional disability, nausea, photophobia, and phonophobia; [2] migraine headache sufferers understand that their migraine pain is often accompanied by these symptoms, and are able to recognize the symptoms; and [3] clinical data included in the original NDA demonstrate that Excedrin Migraine provides relief of migraine headache pain and the associated migraine symptoms.

Accordingly, the sponsor states that this labeling revision would provide useful information to consumers who suffer episodic migraine.

NDA 20-802 was submitted on 1/14/97. It contained the results of three randomized, double-blind, placebo-controlled studies. They each examined the effectiveness of Excedrin Migraine in the symptomatic relief of migraine, including headache pain, nausea, photophobia, phonophobia, and functional disability. Study endpoints were all prospectively defined and the NDA included analyses of all the data from these trials.

The original NDA, which focused on the relief of migraine headache pain, was approved on 1/14/98 "for the temporary relief of mild to moderate pain associated with migraine headache."

On 9/8/98, a pre-NDA meeting was held to discuss proposed labeling changes that would add information for consumers on the associated migraine symptoms. Participants included members of ODEV, the Division of OTC Products, the Division of Neuropharmacological Drug Products, and the Division of Analgesics, Anti-Inflammatory and Ophthalmic Drug Products. At this meeting, it was determined that the planned efficacy supplement should provide for the treatment of migraine. The Agency also agreed that the data contained in the original NDA was sufficient to support filing.

At the pre-NDA meeting, this Division (DNDP) expressed a desire NOT to incorporate each individual associated migraine symptom in labeling, but instead to grant a general "treatment for migraine" claim, similar to prescription labeling for the -triptans. In the current submission, the sponsor would still like to enumerate each symptom in labeling. They point out that this deviation from our recommendation is based on the results of a labeling comprehension study which reports better comprehension by patients when individual symptoms are enumerated in the labeling.

2. Proposed Labeling

The proposed labeling describes the product as Excedrin Migraine, containing:

- Acetaminophen 250mg
- Aspirin 250mg
- Caffeine 65mg

The dosing information is: 2 tablets, caplets, or geltabs every 6 hours as needed, not to exceed 8 in 24 hours, or as directed by a doctor. Do not take for more than 48 hours.

The Use section reads:

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

It also modifies the Warnings and other safety sections, which I describe fully in my labeling review (section 8, page 25).

3. Integrated Review of Efficacy

The application contains the results of the three randomized controlled trials which were included in the original NDA: GHBA-840, GHBA-841, and GHBA-842. I refer to them by their number only. Since efficacy for the treatment of migraine headache pain was established and subsequently led to approval of the NDA in January, 1998, I don't review those results here, but merely summarize them for completeness. I instead concentrate my review on the results of the secondary analyses, upon which the proposed changes to the Use section of labeling are based.

3.1 The Development Program

The development program was designed to evaluate a group of migraineurs for whom OTC therapy would be appropriate. Three strategies were employed to accomplish this:

1. The sponsor employed two complementing recruiting techniques, telephone interviews, and conventional recruiting methods (*i.e.*, private practice subjects, referrals, local advertising) to select a full spectrum of migraineurs representative of the entire migraine community, independent of physician consulting status.
2. The most severe segment of migraineurs (who may be less appropriate candidates for OTC therapy), such as those with migraines resulting in vomiting more than 20% of the time and those whose migraine usually required bed rest, were excluded from participation.

3. Subjects enrolled in the studies were diagnosed as migraineurs and the headache treated in the study was a migraine. These facts were documented.
 - Migraine diagnosis was confirmed using IHS criteria
 - Neurologists and headache specialists who participated in the studies confirmed that the treated headaches were migraines.
 - An independent neurologist reviewed a blinded random sample of 10% of the randomized subjects and confirmed that the treated headaches were in fact migraine.

3.2 Protocols

Three efficacy studies are described and referenced from the original NDA: 840, 841, and 842. Study 840 was a single center study and 841 and 842 were multi-center trials. The data in the efficacy supplement are exactly the same as those presented in the original NDA. However, the supplement contains new analyses on the secondary endpoints.

The three studies shared a similar design (see Table 1 below, taken from sponsor table 1.4.4.1, page 47 of their submission). Since Excedrin Migraine was intended for OTC use, the clinical studies were designed to assure that subjects recruited to participate were a representative sample of true migraine sufferers in the community who could self-recognize, self-treat, and self-rate their headaches and associated symptoms, whether or not they had been previously diagnosed with migraine.

The three studies all were double-blind, randomized, placebo-controlled, parallel group trials. Patients were randomized to either drug (2 tablets) or placebo. They were instructed to treat a single moderate or severe migraine headache. Rescue medication could be used at each subject's discretion. The studies each involved a screening phase, a selection phase, a treatment phase, and a follow-up visit. Each patient self-evaluated their migraines before and during treatment using a headache diary. The follow-up visit was scheduled to collect and review the diary.

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Table 1: Studies 840, 841, 842 – Trial Design

Table 1.4.4.1 Clinical Studies Included in the Integrated Summary of Effectiveness

Study No.	Title	Trial Design	Number of Subjects ^{ab}	Efficacy Evaluations ^c
GHBA-840	A Single-Center, Double-Blind, Randomized, Parallel-Group, Single-Dose, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Excedrin® Extra-Strength in Alleviating the Headache Pain of an Acute Migraine Attack	Single-Center, Double-Blind, Randomized, Parallel, Placebo-Controlled	390/378	Primary: PID,** RESPONDERS,** Secondary: PAR,** REMED**, TREMED, SPID, PTGLOB,** % PID, ONSET**, PRID, PAIN-FREE**, %SPID, TOTPAR, INVGLOB**, MAXPID, %MAXPID, MAXPAR, Functional Ability**, Nausea**, Vomiting, Photophobia**, Phonophobia**
GHBA-841	A Multi-center, Double-Blind, Randomized, Parallel-Group, Single-Dose, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Excedrin® Extra-Strength in Alleviating the Headache Pain of an Acute Migraine Attack	Multi-Center, Double-Blind, Randomized, Parallel, Placebo-Controlled	435/427	Same as above.
GHBA-842	A Multi-center, Double-Blind, Randomized, Parallel-Group, Single-Dose, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Excedrin® Extra-Strength in Alleviating the Headache Pain of an Acute Migraine Attack	Multi-Center, Double-Blind, Randomized, Parallel, Placebo-Controlled	422/415	Same as above.

Data Source: Individual clinical trial reports.

^{ab} Intent-to-treat/efficacy-evaluable subjects.

^c Variables presented in individual Clinical Trial Reports.

** Variables in this summary.

PID=Pain Intensity Difference; RESPONDERS=Subjects With Pain Intensity Reduced to Mild or None; PAR=Pain Relief; REMED=Subjects Who took Rescue Medication; TREMED=Time to Use of Rescue Medication; SPID=Sum of PID scores; PTGLOB=Subject Global Evaluation; ONSET=Time Until Pain Reduced to Mild or None; PRID=Pain Relief Intensity Difference; PAIN-FREE=Subjects Considered Pain-Free; TOTPAR=Sum of PAR scores; INVGLOB=Investigator Global Evaluation; MAXPID=Maximum PID Achieved; MAXPAR=Maximum PAR score.

3.2.1 Screening

Both a population based screening procedure, as well as conventional recruiting methods, were used to identify potential adult study participants. In order to be included in the studies, the typical pattern of headache symptoms had to resemble those of mildly to moderately disabling recurrent attacks of acute, episodic migraine that were not usually severely disabling or incapacitating (*i.e.*, requiring bed-rest) in terms of interference with ability to work or engage in usual daily activities.

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 sourcing eligible subjects from private practice patients, referrals, and local advertising.

All patients in study 840 and 20% of patients in 841 and 842 were screened using population based recruiting. Eighty percent (80%) of those enrolled in 841 and 842 were screened by conventional methods.

3.2.2 Selection Phase (Visit 1)

Those individuals who met the screening criteria attended visit 1. During this visit, the following were performed:

- Medical history
- Semi-structured diagnostic interview
- Complete physical examination
- Urine pregnancy test (female of child-bearing potential)

A headache specialist or neurologist performed the semi-structured diagnostic interview and neurological examination in order to identify those patients who met IHS diagnostic criteria for migraine (with or without aura) and fully met other inclusion/exclusion criteria. Patients were then asked to recall their last "migraine headache" and document it using the headache diary. These steps were taken to make sure that the subjects actually suffered from migraine.

Patients were enrolled on the basis of the following key inclusion criteria:

- Males or females ≥ 18 years
- Migraine headaches (IHS criteria) with or without aura, present for ≥ 1 year and beginning prior to age 50.
- ≥ 1 migraine attack every 2 months but no more than 6 migraine attacks monthly during the previous year

Patients were excluded if they had disabling or incapacitating migraine (requiring bed rest), or if they had a history of vomiting $\geq 20\%$ of the time during their migraine attacks, or if they concurrently were using ergot alkaloids including ergotamine tartrate.

3.2.3 Treatment Phase

Eligible subjects were randomized to drug or placebo. Medication was dispensed and they were instructed to take study medication at the onset of a moderate or severe migraine headache. Each had a checklist of migraine symptoms to assist them in correctly identifying a migraine attack. Efficacy measurement were entered in the diary at 0, 0.5, 1, 2, 3, 4, and 6 hours. Use of rescue medication and time to rescue was recorded. Any unusual symptoms were also recorded.

Subjects were to treat a migraine within 12 weeks of enrollment. They were to contact the investigator every 4 weeks (if they hadn't treated a headache) to review study procedures and re-establish the subject's continued eligibility. Those who failed to treat a migraine within 12 weeks of enrollment were dropped from the study.

3.2.4 Follow-up Phase (Visit 2)

Subjects returned for follow-up as soon as possible (but no later than 10 days) after having treated a migraine. The headache diary was reviewed in order to confirm and

document that the treated headache was a migraine. All unusual symptoms were evaluated.

3.3 Efficacy Variables

3.3.1 Recorded Values

The following efficacy variables were evaluated at defined observation times during each study:

Table 2: Studies 840, 841, 842 – Recorded Efficacy Variables

Description	Name	Values
Pain Intensity	PI	0 = none 1 = mild 2 = moderate 3 = severe
Pain Relief	PAR	0 = no relief 1 = a little relief 2 = some relief 3 = a lot of relief 4 = complete relief
Functional Disability		0 = none 1 = mild 2 = moderate 3 = severe 4 = incapacitating
Nausea		0 = none 1 = mild 2 = moderate 3 = severe
Vomiting		0 = no 1 = yes
Photophobia		0 = none 1 = mild 2 = moderate 3 = severe
Phonophobia		0 = none 1 = mild 2 = moderate 3 = severe
Time to Rescue	TREMED	[time]
Global Evaluation of Effectiveness	PTGLOB	1 = poor 2 = fair 3 = good 4 = very good 5 = excellent
Investigator Evaluation of Effectiveness	INVGLOB	1 = poor 2 = fair 3 = good 4 = very good 5 = excellent

Both the PTGLOB and INVGLOB were evaluated at the end of the treatment period (6 hours) or at the time when rescue was taken. All others variables were evaluated at 0, 0.5, 1, 2, 3, 4, 6 hours post-treatment.

The functional disability scale had the following descriptors for each score:

- 0 = none (able to perform all activities as usual)
- 1 = mild (usual activities require a little additional effort)
- 2 = moderate (usual activities require some additional effort)
- 3 = severe (usual activities require a great deal of additional effort)
- 4 = incapacitating (unable to perform usual activities)

3.3.2 Calculated Variables

The following efficacy variables were calculated from the recorded variables (Table 3).

Table 3: Studies 840, 841, 842 – Calculated Efficacy Variables

Description	Name	Derivation
Responders	RESPONDERS	1 if PI = mild or none
Pain-Free	PAIN-FREE	1 if PI = none
Time to Response	ONSET	Time until pain intensity was reduced to mild or none
Percent who took Rescue	REMED	Percent of subjects who took rescue medication
Pain Intensity Difference	PID	PI at a given time minus the PI at baseline
Sum of the Pain Intensity Difference	SPID	Weighted sums (by time interval) of all PID scores
Total Pain Relief	TOTPAR	Weighted sums (by time interval) of PAR scores
Percent PID	%PID	Percent of maximum possible PID using each subject's baseline PI score
Percent SPID	%SPID	Percents of maximum possible SPID using each subject's baseline PI score
Pain Relief Intensity Difference	PRID	Sum of PID and PAR
Maximum PID	MAXPID	Maximum observed PID
Maximum Percent PID	%MAXPID	Maximum observed %PID
Maximum PAR	MAXPAR	Maximum observed PAR

In addition, dichotomous variables for each associated migraine symptom were calculated at each post-baseline observation point. These variables identified subjects whose functional disability was reduced to mild or none, were without nausea, without photophobia, and without phonophobia.

3.4 Data Analysis Methods

The primary efficacy variables in the three studies were the pain intensity difference (PID) calculated at the 2 hour post-dosing observation time, and the percent of subject whose headache pain intensity had decreased to mild or none at 2 hours post-dosing. All other variables were secondary.

The sponsor's efficacy analyses were performed on the intent-to-treat population as well as on the efficacy-evaluable population. The intent-to-treat population was defined as all patients who took study medication and had both baseline and at least one post-baseline pain intensity measurement.

The efficacy evaluable population was the subset of the intent-to-treat population who had a diagnosis of migraine, who actually treated a migraine headache, and who recorded a pain intensity at 2 hours.

The primary efficacy analyses were performed on both the efficacy evaluable and intent-to-treat populations. The secondary analyses were performed on the intent-to-treat population. These secondary analyses were performed on only a subset of secondary variables.

Pain intensity, pain relief, functional disability, photophobia, phonophobia, vomiting, and nausea scores recorded after the use of rescue were assigned the more severe of either the baseline score or the last recorded value, and the post-rescue medication pain relief scores were assigned "no relief." Data for subjects who took rescue medication within 15 minutes of the nominal time point were not imputed. However, data for all subsequent time points were imputed as the most severe score of baseline or the last evaluation.

Missing data were imputed as the average between the adjacent observed values. If the last observation was missing, then the previous observation was carried forward. If two or more consecutive observations were missing, then no data were imputed for the purposes of analysis. These adjustments were made before derivation of calculated efficacy variables.

Comparisons between drug and placebo groups were made using an analysis of covariance (ANCOVA) model for PID and PRID at each time point, SPID at 2 and 6 hours postdose, MAXPID, and changes from baseline in functional disability, severity of nausea, photophobia, and phonophobia. Baseline scores were used as the covariates in the ANCOVA model. Preliminary tests for treatment-by-baseline score interactions were performed for the three individual controlled studies and treatment-by-investigator interactions were performed for 841 and 842. Since both interactions were rarely significant ($p < 0.10$), they were removed from the final analysis models. The final reduced ANCOVA model, including terms for treatment and investigator (841 and 842) as the main effects and baseline scores as a covariate, was used to test for treatment effects. The sponsor used SAS PROC GLM to perform these analyses.

An analysis of variance (ANOVA) model, including terms for treatment and investigator effect (841 and 842), was used to test for treatment differences with respect to %PID, %MAXPID, pain relief, maximum pain relief (MAXPAR), TOTPAR and %SPID at 2 and 6 hours postdose, and subject and investigator global evaluations.

The Cochran-Mantel-Haenszel (CMH) test, stratified by baseline pain intensity and investigator (841 and 842), was used to analyze the proportion of subjects who took

rescue medication (REMEDI), proportion of subjects considered RESPONDERS (pain intensity reduced to mild or none), and the proportion of subjects considered PAIN-FREE (pain intensity reduced to none) during the 6-hour postdose period. The general association form of the CMH test was used to carry out the treatment comparisons. For each treatment, the proportion of subjects who showed a shift in vomiting status compared to baseline was analyzed using the ~~CMH test~~. The proportion of subjects who vomited at each time point were analyzed using the CMH test (stratified by baseline vomiting status and investigator). The sponsor used SAS PROC FREQ to perform the analysis.

The treatment groups were compared with respect to time until pain was reduced to mild or none (ONSET) and time to the use of rescue medication (TREMEDI) using a Cox proportional hazards regression model. The model included treatment as the main effect and baseline pain intensity score as a covariate. If the specified event did not occur, the observation was censored at 6 hours postdose for subjects completing 6 hours of evaluation and at the last evaluation time point for subjects who discontinued prematurely (e.g., discontinued due to remedication or an adverse experience). In addition, the proportional hazards assumption was tested, and treatment-by-covariate interaction was assessed. The sponsor used SAS PROC PHREG to perform the analysis. The Kaplan-Meier procedure (SAS PROC LIFETEST) was used to obtain estimates for the time-to-event curves.

All p-values were rounded to 3 decimal places, and statistical significance was declared if the rounded p-value was less than or equal to 0.05 for between-treatment comparisons and less than or equal to 0.10 for tests of treatment-by-baseline score and treatment-by-investigator interactions. In describing the results, the sponsor used the word "significance" to refer to statistical significance and not to clinical importance.

Similar analyses were performed on the pooled efficacy data from all three studies.

3.5 Patient Population

3.5.1 Disposition

A total of 1357 subjects were randomized in the three studies. Disposition for these patients are shown in Table 4 (sponsor table 2.1.1, page 55). I use the abbreviations "EM" for Excedrin Migraine and "PBO" for placebo.

Table 4: Studies 840, 841, 842 – Disposition of Patients

Number of Subjects	Total	EM	PBO
<i>Randomized</i>	1357	677	680
840	439	219	220
841	470	235	235
842	448	223	225
<i>Took Study Medication</i>	1250	618	632
840	390	192	198
841	437	214	223
842	423	212	211

Number of Subjects	Total	EM	PBO
<i>Intent to Treat Analysis</i>	1247	616	631
840	390	192	198
841	435	212	223
842	422	212	210
<i>Efficacy-Evaluable Analysis</i>	1220	602	618
840	378	187	191
841	427	206	221
842	415	209	206

3.5.2 Demographics

The sponsor focused on the efficacy-evaluable population for their primary analysis and the demographic and baseline characteristics are shown for this population. There were no statistically significant differences with regard to age, gender, and race (Table 5, sponsor table 2.2.1.1, page 56). The subjects in the three studies ranged in age from 17-87 years, with a mean age of 36.7. The majority were female (79%) and white (86%). They do not present demographic data by individual study, but they reference the data in the individual study reports in the original NDA.

Table 5: Pooled Studies – Demographic of Efficacy Evaluable Population

	Total (N= 1220)	EM (N= 602)	PBO (N= 618)	p-value
<i>Age (yrs)</i>				0.369
Mean	36.7	37.0	36.4	
S. D.	10.82	10.62	11.01	
Median	36.0	37.0	35.0	
Range	17- 87	18- 81	17- 87	
<65	1205 (98.8%)	595 (98.8%)	610 (98.7%)	
>65	15 (1.2%)	7 (1.2%)	8 (1.3%)	
<i>Gender</i>				0.298
Male	253 (20.7%)	132 (21.9%)	121 (19.6%)	
Female	967 (79.3%)	470 (78.1%)	497 (80.4%)	
<i>Race</i>				0.297
White	1050 (86.1%)	508 (84.4%)	542 (87.7%)	
Black	123 (10.1%)	69 (11.5%)	54 (8.7%)	
Hispanic	27 (2.2%)	14 (2.3%)	13 (2.1%)	
Oriental	10 (0.8%)	7 (1.2%)	3 (0.5%)	
Other	10 (0.8%)	4 (0.7%)	6 (1.0%)	

For the pooled studies, there were no statistically significant differences in the two treatment groups with respect to migraine history parameters. The majority (EM 81%, PBO 80%) had a diagnosis of migraine without aura. Sixty-seven percent (67%) of the Excedrin Migraine population and 60% of the placebo population used only OTC medications for their migraines. Treatment with OTC medication had been generally effective in 73% of the Excedrin Migraine treated patients and in 74% of the placebo treated patients. The migraine history for the pooled efficacy evaluable population is shown in Table 6 (sponsor table 2.2.2.1, page 59). I remind the reader that those patients reporting vomiting in greater than 20% of their attacks were excluded from the studies; however several managed to enter the study.

Table 6: Pooled Studies – Migraine History

	Total (N= 1220)	EM (N= 602)	PBO (N= 618)	p- value
<i>Primary Headache Diagnosis</i>				
Migraine Without Aura	985 (80.7)	489 (81.2)	496 (80.3)	0.578
Migraine With Aura	235 (19.3)	113 (18.8)	122 (19.7)	
<i>Usual Degree of Disability With Treatment</i>				
None	157 (12.9)	80 (13.3)	77 (12.5)	0.747
Mild	477 (39.1)	237 (39.4)	240 (38.8)	
Moderate	463 (38.0)	220 (36.5)	243 (39.3)	
Severe	120 (9.8)	63 (10.5)	57 (9.2)	
Incapacitating	0 (0.0)	0 (0.0)	0 (0.0)	
Unknown	3 (0.2)	2 (0.3)	1 (0.2)	
<i>Usual Degree of Disability Without Treatment</i>				
None	16 (1.3)	7 (1.2)	9 (1.5)	0.559
Mild	99 (8.1)	48 (8.0)	51 (8.3)	
Moderate	477 (39.1)	246 (40.9)	231 (37.4)	
Severe	593 (48.6)	288 (47.8)	305 (49.4)	
Incapacitating	5 (0.4)	1 (0.2)	4 (0.6)	
Unknown	30 (2.5)	12 (2.0)	18 (2.9)	
<i>Usual Intensity of Headache Pain With Treatment</i>				
None	94 (7.7)	49 (8.1)	45 (7.3)	0.485
Mild	406 (33.3)	189 (31.4)	217 (35.1)	
Moderate	559 (45.8)	278 (46.2)	281 (45.5)	
Severe	158 (13.0)	84 (14.0)	74 (12.0)	
Incapacitating	0 (0.0)	0 (0.0)	0 (0.0)	
Unknown	3 (0.2)	2 (0.3)	1 (0.2)	
<i>Usual Intensity of Headache Pain Without Treatment</i>				
None	0 (0.0)	0 (0.0)	0 (0.0)	0.554
Mild	0 (0.0)	0 (0.0)	0 (0.0)	
Moderate	337 (27.6)	170 (28.2)	167 (27.0)	
Severe	851 (69.8)	419 (69.6)	432 (69.9)	
Incapacitating	4 (0.3)	1 (0.2)	3 (0.5)	
Unknown	28 (2.3)	12 (2.0)	16 (2.6)	
<i>Usual Duration of Attacks With Treatment (hours)</i>				
N	1205	596	609	0.627
Mean	11.48	11.32	11.64	
S. D.	17.66	17.22	18.09	
Median	4.00	4.00	4.00	
Range				
<i>Usual Duration of Attacks Without Treatment (hours)</i>				
N	1054	531	523	0.915
Mean	27.39	27.20	27.59	
S. D.	25.39	25.61	25.19	
Median	24.00	20.00	24.00	
Range				
<i>Average Frequency of Attacks (per month)</i>				
Mean	2.35	2.41	2.28	0.099
S. D.	1.50	1.50	1.50	
Median	2.00	2.00	2.00	
Range				
<i>Nausea With Migraine Attacks</i>				
Migraine With Aura				0.662
Always	64 (5.2)	30 (5.0)	34 (5.5)	

	Total (N= 1220)	EM (N= 602)	PBO (N= 618)	p- value
Frequently	105 (8.6)	49 (8.1)	56 (9.1)	
Rarely	41 (3.4)	23 (3.8)	18 (2.9)	
Never	25 (2.0)	11 (1.8)	14 (2.3)	
<i>Migraine Without Aura</i>				0.858
Always	160 (13.1)	85 (14.1)	75 (12.1)	
Frequently	436 (35.7)	215 (35.7)	221 (35.8)	
Rarely	229 (18.8)	112 (18.6)	117 (18.9)	
Never	160 (13.1)	77 (12.8)	83 (13.4)	
<i>Vomiting During Migraine Attacks</i>				0.770
<i>Migraine With Aura</i>				
Always	0 (0.0)	0 (0.0)	0 (0.0)	
> 20% of the time	0 (0.0)	0 (0.0)	0 (0.0)	
< 20% of the time	107 (8.8)	50 (8.3)	57 (9.2)	
Never	128 (10.5)	63 (10.5)	65 (10.5)	
<i>Migraine Without Aura</i>				0.493
Always	1 (0.1)	0 (0.0)	1 (0.2)	
> 20% of the time	3 (0.2)	1 (0.2)	2 (0.3)	
< 20% of the time	367 (30.1)	176 (29.2)	191 (30.9)	
Never	614 (50.3)	312 (51.8)	302 (48.9)	
<i>Age at First Onset of Migraine (years)</i>				0.439
N	1217	601	616	
Mean	20.6	20.8	20.5	
S. D.	9.0	9.0	9.0	
Median	19.0	20.0	18.0	
Range	3-54	3-48	4-54	
<i>Usual Pharmacological Treatment for Migraine</i>				0.457
None	18 (1.5)	7 (1.2)	11 (1.8)	
Nonprescription med only	793 (65.0)	402 (66.8)	391 (63.3)	
Prescription med only	152 (12.5)	72 (12.0)	80 (12.9)	
Both prescription and nonprescription med	257 (21.1)	121 (20.1)	136 (22.0)	
<i>Were Treatments Effective?</i>				
<i>Nonprescription med only</i>				0.720
N	793	402	391	
Yes	583 (73.5)	295 (73.4)	288 (73.7)	
No	210 (26.5)	107 (26.6)	103 (26.3)	
<i>Prescription med only</i>				0.848
N	152	72	80	
Yes	129 (84.9)	61 (84.7)	68 (85.0)	
No	23 (15.1)	11 (15.3)	12 (15.0)	
<i>Both prescription and nonprescription med</i>				0.193
N	257	121	136	
Yes	196 (76.3)	96 (79.3)	100 (73.5)	
No	61 (23.7)	25 (20.7)	36 (26.5)	
<i>Family History of Migraine</i>				0.927
Yes	658 (53.9)	321 (53.3)	337 (54.5)	
No	432 (35.4)	209 (34.7)	223 (36.1)	
Unknown	130 (10.7)	72 (12.0)	58 (9.4)	

3.5.3 Baseline Headache Characteristics

Of the 1220 efficacy evaluable patients, 1014 (83%) treated a migraine without aura and the remaining 206 patients (17%) treated a migraine with aura. There was no difference

between treatment groups with respect to the presence of an aura (EM 17.1%, PBO 16.7%, $p=0.865$). Baseline headache characteristics are shown in Table 7 (adapted from sponsor table 2.2.3.2, page 61) and . There were no statistically significant differences between the two treatment groups in any of the baseline headache characteristics.

Table 7: Pooled Studies – Baseline Migraine Characteristics

	EM (N= 602)	PBO (N= 618)
<i>Migraine Without Aura</i>	499	515
Moderate	336 (67%)	349 (68%)
Severe	163 (33%)	166 (32%)
Pain on one side of head	366 (73%)	353 (68%)
Headache pulsating	424 (85%)	456 (89%)
Aggravated by walking stairs/routine physical activity	421 (84%)	445 (86%)
<i>Migraine With Aura</i>	103	103
Moderate	64 (62%)	64 (62%)
Severe	39 (38%)	39 (38%)
Pain on one side of head	71 (69%)	76 (74%)
Headache pulsating	93 (90%)	88 (85%)
Aggravated by walking stairs/routine physical activity	86 (83%)	88 (85%)

Table 8: Pooled Studies – Additional Baseline Migraine Characteristics

	EM (N= 602)	PBO (N= 618)	p-value
<i>Baseline Pain</i>			0.892
Moderate	400 (66.4%)	413 (66.8%)	
Severe	202 (33.6%)	205 (33.2%)	
<i>Functional Disability</i>			0.391
None	21 (3.5%)	12 (1.9%)	
Mild	83 (13.8%)	91 (14.7%)	
Moderate	285 (47.3%)	292 (47.2%)	
Severe	184 (30.6%)	185 (29.9%)	
Incapacitating	28 (4.7%)	37 (6.0%)	
Unknown	1 (0.2%)	1 (0.2%)	
<i>Nausea</i>			0.682
None (0)	241 (40.0%)	250 (40.5%)	
Mild (1)	253 (42.0%)	259 (41.9%)	
Moderate (2)	95 (15.8%)	103 (16.7%)	
Severe (3)	13 (2.2%)	6 (1.0%)	
Mean	0.8	0.8	
S. D.	0.78	0.75	
<i>Vomiting</i>			0.053
No	589 (97.8%)	613 (99.2%)	
Yes	13 (2.2%)	5 (0.8%)	
<i>Number of Subjects With</i>			
Photophobia & Phonophobia	522 (86.7%)	558 (90.3%)	
Photophobia only	51 (8.5%)	25 (4.0%)	
Phonophobia only	15 (2.5%)	19 (3.1%)	
Neither	13 (2.2%)	15 (2.4%)	
Unknown	1 (0.2%)	1 (0.2%)	

	EM (N= 602)	PBO (N= 618)	p-value
<i>Photophobia</i>			
None (0)	28 (4.7%)	34 (5.5%)	
Mild (1)	197 (32.7%)	173 (28.0%)	
Moderate (2)	301 (50.0%)	322 (52.1%)	
Severe (3)	76 (12.6%)	89 (14.4%)	
Mean	1.7	1.8	0.256
S. D.	0.74	0.76	
<i>Phonophobia</i>			
None (0)	64 (10.6%)	40 (6.5%)	
Mild (1)	174 (28.9%)	216 (35.0%)	
Moderate (2)	281 (46.7%)	300 (48.5%)	
Severe (3)	82 (13.6%)	61 (9.9%)	
Unknown	1 (0.2%)	1 (0.2%)	
Mean	1.6	1.6	0.754
S. D.	0.86	0.76	

3.6 Efficacy Results

Since all three efficacy studies (840, 841, and 842) had almost identical designs (840 was single center, the other two were multicenter studies), I discuss the results of all three together.

The primary efficacy variables were the PID and percent responders at two hours. Secondary variables included mild or no functional disability, no nausea, no photophobia, and no phonophobia, as well as the primary variables at other time points. Other supportive variables were pain-relief, percent pain-free, time to response, percent using rescue, and subject's and investigator's global evaluation.

The efficacy evaluable population was used for the primary efficacy analysis and it included all variables described above. The sponsor presented data for each of the three individual studies and the pooled data. In addition, data for subgroups defined by demographic and baseline migraine characteristics were analyzed for the efficacy evaluable subject population for the two primary variables and the associated migraine symptoms.

An intent-to-treat analysis was conducted on PID, percent responders, and percent pain-free to confirm the results of the efficacy evaluable analysis. These results were similar to the efficacy evaluable analysis. I don't include this analysis here because the product has already been approved for the relief of migraine headache pain.

Table 9 summarizes the results for the important efficacy variables for the three studies (adapted from sponsor table 4.3.1, page 18, and tables 3.2.1.1-3.5.4.1, pages 66-96 of their submission). The shaded cells represent those analyses which reached statistical or nominal significance.

Table 9: Studies 840, 841, 842 – Efficacy Results (Efficacy Evaluable Subjects)

	840		841		842		Pooled	
	EM N=187	PBO N=191	EM N=206	PBO N=221	EM N=209	PBO N=206	EM N=602	PBO N=618
Results at 2 Hours								
Mean PID (S. D.)	1.2 (0.95)	0.5 (0.96)	0.9 (0.85)	0.4 (0.89)	0.9 (0.93)	0.4 (0.83)	1.0 (0.91)	0.4 (0.89)
p value	<0.001		<0.001		<0.001		<0.001	
Headache Response	64%	37%	59%	31%	56%	31%	59%	33%
p value	<0.001		<0.001		<0.001		<0.001	
Mean PAR (S. D.)	2.0 (1.40)	1.0 (1.16)	1.6 (1.34)	0.9 (1.20)	1.7 (1.45)	0.8 (1.10)	1.8 (1.41)	0.9 (1.16)
p value	<0.001		<0.001		<0.001		<0.001	
No Pain	26%	7%	17%	9%	21%	5%	21%	7%
p value	<0.001		0.008		<0.001		<0.001	
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	
No Functional Disability	63%	30%	51%	29%	47%	25%	54%	28%
p value	<0.001		<0.001		<0.001		<0.001	
Results at 6 Hours								
Mean PID (S. D.)	1.6 (1.07)	0.8 (1.25)	1.3 (1.09)	0.6 (1.10)	1.2 (1.14)	0.6 (1.17)	1.4 (1.11)	0.6 (1.17)
p value	<0.001		<0.001		<0.001		<0.001	
Headache Response	82%	55%	78%	48%	76%	53%	79%	52%
p value	<0.001		<0.001		<0.001		<0.001	
Mean PAR (S. D.)	2.7 (1.64)	1.4 (1.69)	2.2 (1.67)	1.2 (1.57)	2.2 (1.70)	1.3 (1.59)	2.4 (1.69)	1.3 (1.62)
p value	<0.001		<0.001		<0.001		<0.001	
No Pain	61%	28%	47%	21%	45%	21%	51%	23%
p value	<0.001		<0.001		<0.001		<0.001	
No Nausea	63%	43%	61%	32%	64%	41%	63%	39%
p value	0.004		<0.001		<0.001		<0.001	
No Photophobia	66%	33%	54%	23%	51%	28%	57%	28%
p value	<0.001		<0.001		<0.001		<0.001	
No Phonophobia	64%	34%	51%	27%	50%	28%	55%	29%
p value	<0.001		<0.001		<0.001		<0.001	
No Functional Disability	72%	43%	64%	34%	60%	32%	65%	36%
p value	<0.001		<0.001		<0.001		<0.001	

Shaded cells indicate significant difference from placebo (p<0.05)
 EM= Excedrin Migraine, PBO = Placebo; PID = Pain Intensity Difference; PAR = Pain Relief

All analyses showed statistically or nominally significant improvements in efficacy variables with treatment compared with placebo, with the exception of nausea at 2 hours in studies 840 and 841, and phonophobia for study 841 at 2 hours, but all were positive at 6 hours for all three studies, as were the pooled analyses.

Of the 1220 subjects in all three studies, only 15 (1.2%) were over the age of 65. The small numbers in this subgroup prevents drawing any meaningful conclusions regarding the primary and secondary efficacy variables and age using 65 years as the cutoff.

Nine-hundred sixty-seven (967) or 79% of the subjects in the three studies were female. There were no gender differences with regard to PID, percent responders, nausea, photophobia, phonophobia, or functional disability.

Most of the subjects were white (1050/1220 or 82%). There were no race differences with regard to PID, percent responders, nausea, photophobia, phonophobia, or functional disability.

4. Safety Update

The application contains a safety update for the original NDA. I did not review the safety information in the original NDA as this was reviewed prior to approval. Excedrin Migraine has been approved since 1/98. The same formulation, under the name of Excedrin Extra Strength (ES) has been available for over 20 years (_____). Since the safety of the product is really not an issue in this application, I only briefly summarize the safety update here. Excedrin Migraine was added to the sponsor's existing adverse event collection process in accordance with federal regulations following its approval on 1/14/98. This safety update summarizes the spontaneous AE recording since approval. It covers the period 1/1/98 through 9/30/98. It also includes spontaneous AE reporting for Excedrin ES.

During the 10 month safety update reporting window, a total of 1868 events were reported, of which 935 were associated with Excedrin Migraine, and 933 were associated with Excedrin ES.

The most frequently reported AE's, defined as >5% of all AE's reported, for Excedrin Migraine were: no drug effect, nervousness, and nausea. For Excedrin ES, they were: no drug effect, abdominal pain, nervousness, dizziness, nausea, and dyspepsia. This suggests that the two products have similar AE profiles, even though they are labeled for different indications (migraine headache vs. headache, sinusitis, colds, muscular aches, menstrual discomfort, toothache, and minor arthritis pain).

There were 41 serious reports for both formulations, 9 of which were for Excedrin Migraine, and the remaining 32 were for Excedrin ES. The largest three groups included the majority of the cases and involved the nervous systems (27), body as a whole (22) and digestive (7) and were similar to those events received prior to approval.

There was one death, that of a 7 year old girl whose parent administered Excedrin ES for the child's headache chronically for about one year (off-label use due to age). The child was subsequently found to have a cerebral aneurysm and she died after surgery.

The sponsor concludes that the safety data collected thus far on Excedrin Migraine demonstrates an excellent safety profile which has not changed relative to Excedrin ES since its launch.

5. Consulting Neurologist's Report

Dr. John Edmeads, neurologist and Professor of Medicine at the University of Toronto, was asked to review about 10% of the headache treatment records of patients in studies 840 (n=38), 841 (n=43), 842 (n=42), in a blinded manner, to determine whether the headaches treated were migraine and whether the investigator's diagnosis was correct, using IHS diagnostic criteria for migraine with or without aura.

In all three studies, all the cases reviewed were "clearly migraine" and the investigator's diagnoses were correct. He found no instance of an incorrect diagnosis, and no instance of a headache treated by a patient that was not migraine.

6. Sponsor's Conclusions

Based on the results of study 840, 841, and 842, the sponsor concludes that Excedrin Migraine is an effective anti-migraine medication based on the following:

- Excedrin Migraine is effective in relieving migraine headache pain.
- Excedrin Migraine is effective in relieving the associated symptoms of migraine including functional disability, nausea, photophobia, and phonophobia.
- Excedrin Migraine has an effective safety profile and is well tolerated.
- Excedrin Migraine is an appropriate OTC migraine medication.

7. Reviewer's Analyses

7.1 Methods

I used the electronic case report tabulations, submitted as SAS transport files, to perform my own efficacy analysis of the data. I used JMP version 3.2.2 to perform the following descriptive analyses. I decided to look at three of the four endpoints on which the change in labeling is proposed: nausea, photophobia, and phonophobia. I chose not to analyze clinical disability since our Division does not consider this a validated measure of migraine disability and we have not permitted such claims in labeling of other migraine drugs.

Since the efficacy measures under review in this submission are all secondary endpoints, the nature of these analyses are, by their nature, only descriptive. Any p values that I report do not carry any statistical inferential power. Since all three studies share very similar designs, I decided to pool them in the analyses described below. I decided, somewhat arbitrarily, to focus on the results at 2 and 4 hours. I chose 2 hours since this is the traditional time when migraine efficacy is measured. I also chose 4 hours since a drug which is not effective at this time point will likely result in re-medication or use of rescue (if it hasn't occurred already).

The sponsor submitted an efficacy dataset for each study, which I combined to form one large pooled dataset. This contained 8,746 records for 1,249 patients. I grouped the

patients by study and treatment as shown in Table 10. These numbers coincide very closely with the intent to treat population numbers in the sponsor generated table (Table 4, on page 11; there are 2 more Excedrin-treated patients from study 841 on my list).

Throughout this section, I used the abbreviation (RA) for a table generated from my own "reviewer's analysis."

Table 10: (RA) – Efficacy Dataset of Treated Patients

Study	N	Excedrin	PBO
840	390	192	198
841	437	214	223
842	422	212	210

As described in the protocols, patients were instructed to record efficacy measurements at baseline (0), 0.5, 1, 2, 3, 4, and 6 hours after taking study medication. Thus each patient had 7 records, one for each time point. In reality, there were 3 patients in study 842 who had eight records each. For some reason, the record for the 6 hour time point was repeated twice for each patient, with the exact same efficacy data recorded in both. Since these were duplicate records, I deleted them. There were 8 patients that took rescue prior to 2 hours. Six occurred on placebo and 2 on Excedrin Migraine. I reviewed those records individually and verified that their worst pre-rescue nausea, photophobia, phonophobia scores were recorded after rescue was taken. I kept them in my "intent to treat" analysis.

7.2 Baseline Headache Characteristics

My first analysis was to assess whether patients in the database actually treated a migraine headache. The sponsor provided baseline characteristics for the treated headache in the following variables:

BASE-SEV baseline headache severity (0=none, 1=mild, 2=mod, 3=severe)
NAUSEA (at time 0) degree of nausea (0=none, 1=mild, 2=mod, 3=severe)
VOMITING (at time 0) vomiting present, yes or no
SENLIGHT (at time 0) photophobia (0=none, 1=mild, 2=mod, 3=severe)
SENSOUND (at time 0) phonophobia (0=none, 1=mild, 2=mod, 3=severe)
HAVEAURA aura present, yes or no
ONESIDE unilateral headache, yes or no
HAPULSAT pulsating headache, yes or no
PAINAGGR pain aggravated by activity, yes or no

I used the following IHS criteria for diagnosis of a migraine attack:

- A. 4-72 hours duration
- B. At least 2 of the following:
 - Unilateral
 - Pulsating
 - Moderate or severe (interferes with daily activity)
 - Aggravation by physical activity (e.g., walking stairs)
- C. At least one of the following:

- Nausea and/or vomiting
- Photophobia and phonophobia

Since the headache was being treated with study medication and could have resolved in under 4 hours with therapy, I did not apply criterion A to the headache in question.

Of the 1,249 patients in the efficacy dataset, only one patient had a missing baseline severity score (patient 841-4-2134). This 21 y/o female patient failed to meet either criterion A nor B so I decided she did not treat a migraine (Her headache was aggravated by physical activity and she had mild photophobia. All other baseline measures for migraine were negative). All remaining subjects recorded either moderate or severe pain at baseline, which fulfills half of criterion B above. I then identified all records for each patient that recorded either pulsating pain, unilateral pain, or pain that was aggravated by physical activity. All of these patients met criterion B above. Next, I identified all patients who had either nausea or vomiting OR photophobia and phonophobia at baseline (criterion C). I considered all those who met both IHS criterion B and C to have treated a migraine.

Based on my analysis of the 1249 patients in the three studies, the vast majority (1199 or 96%) treated a migraine headache. The breakdown by study and treatment assignment is shown in Table 11. Although there were more “non-migraine” headaches treated in the Excedrin Migraine group compared to placebo, the difference did not reach nominal significance (p=0.15, Fisher’s exact test).

Table 11: (RA) – Distribution of Migraine Diagnosis among Treated Headaches

Study	Headache Diagnosis	Total	Excedrin Migraine	Placebo
840	Not Migraine	7	4	3
	Migraine	383	188	195
841	Not Migraine	21	14	7
	Migraine	416	200	216
842	Not Migraine	22	12	10
	Migraine	400	200	200
Total	Not Migraine	50	30	20
	Migraine	1199	588	611

My conclusion is that the vast majority (96%) in the three studies did treat a migraine headache, and that the few non-migraine headaches were reasonably balanced between the two groups.

7.3 Nausea

Nausea was measured at each time point using a four point scale (0=none, 1=mild, 2=mod, 3=severe). I created a derived binary variable to designate whether nausea was present or absent.

Of the 8,743 records for the 1,249 patients, there were 18 missing nausea measurements. I reviewed each one individually. No baseline measurements were missing. The 18 missing measurements occurred in 5 patients. I used a last post-treatment observation

carried forward approach to impute missing data. Using this approach, I was able to impute 10 of the missing 18 measures. One patient had no post-treatment nausea measurements (841-11-2037). These resulted in six missing records. I removed her from the analysis. The remaining 2 missing records occurred at 0.5 and 1 hours in patient 841-3-2464.

Table 12 shows the distribution of nausea at baseline. There was no difference in the incidence of baseline nausea between the two groups. ($p=1.00$, Fisher's exact test). Nausea was present in about 59% of all patients at baseline.

Table 12: (RA) – Pooled Studies, Nausea at Baseline

	Excedrin Migraine	PBO	Total
Nausea Absent	252	257	509
%	40.78	40.73	
Nausea Present	366	374	740
%	59.22	59.27	
Total	618	631	1249

Table 13 and Table 14 show the distribution of nausea at 2 and 4 hours. At both time points, the incidence of nausea was lower in the Excedrin Migraine treated group ($p=0.004$ and $p<0.001$ for 2 and 4 hours, respectively, Fisher's exact test).

Table 13: (RA) – Pooled Studies, Nausea at 2 hours

	Excedrin Migraine	PBO	Total
Nausea Absent	392	350	742
%	63.53	55.47	
Nausea Present	225	281	506
%	36.47	44.53	
Total	617	631	1248

Table 14: (RA) – Pooled Studies, Nausea at 4 Hours

	Excedrin Migraine	PBO	Total
Nausea Absent	448	374	822
%	72.61	59.27	
Nausea Present	169	257	426
%	27.39	40.73	
Total	617	631	1248

I conclude that treatment with Excedrin Migraine was associated with decreased nausea of migraine.

7.4 Photophobia

Photophobia was also measured at each time point using a four point scale (0=none, 1=mild, 2=mod, 3=severe). I created a derived binary variable to designate whether photophobia was present or absent.

Of the 8,743 records for the 1,249 patients, there were 20 missing photophobia measurements. I reviewed each one individually. No baseline measurements were missing. The 20 missing measurements occurred in 6 patients. I used a last post-treatment observation carried forward approach to impute missing data. I was able to impute 12 of the missing 20 measures. One patient had no post-treatment photophobia measurements (841-11-2037, the same one with missing nausea measurements described in the previous section). These totaled six missing records. I removed her from the analysis. The remaining 2 missing records occurred at 0.5 and 1 hours in patient 841-3-2464 (also the same patient with missing 0.5 and 1 hour nausea measurements described in the previous section).

Table 15 shows the distribution of photophobia at baseline. There was no difference in the incidence of baseline photophobia between the two groups. ($p=0.28$, Fisher's exact test). Photophobia was present in about 94% of all patients at baseline.

Table 15: (RA) – Pooled Studies, Photophobia at Baseline

	Excedrin Migraine	PBO	Total
Photophobia Absent	32	42	74
%	5.18	6.66	
Photophobia Present	586	589	1175
%	94.82	93.34	
Total	618	631	1249

Table 16 and Table 17 show the distribution of photophobia at 2 and 4 hours. At both time points, the incidence of photophobia was lower in the Excedrin Migraine treated group ($p<0.001$ at both 2 and 4 hours, respectively, Fisher's exact test).

Table 16: (RA) – Pooled Studies, Photophobia at 2 hours

	Excedrin Migraine	PBO	Total
Photophobia Absent	214	109	323
%	34.68	17.27	
Photophobia Present	403	522	1175
%	65.32	82.73	
Total	617	631	1248

Table 17: (RA) – Pooled Studies, Photophobia at 4 Hours

	Excedrin Migraine	PBO	Total
Photophobia Absent	327	176	503
%	53.00	27.89	
Photophobia Present	290	455	745
%	47.00	72.11	
Total	617	631	1248

I conclude that treatment with Excedrin Migraine was associated with decreased photophobia of migraine.

7.5 Phonophobia

Phonophobia was also measured at each time point using a four point scale (0=none, 1=mild, 2=mod, 3=severe). I created a binary variable to designate whether photophobia was present or absent.

Of the 8,743 records for the 1,249 patients, there were 23 missing photophobia measurements. I reviewed each one individually. Two baseline measurements were missing. The 23 missing measurements occurred in 7 patients. I used a last post-treatment observation carried forward approach to impute missing data. Using this approach, I was able to impute 10 of the missing 23 measures. One patient had no post-treatment photophobia measurements (841-11-2037, the same one with missing nausea and photophobia measurements described in the previous sections). These totaled six missing records. I removed her from the analyses. The remaining 7 missing records included 1 missing baseline for 841-21-285, the 0.5 and 1 hour measurements in patient 841-3-2464 (also the same patient with missing 0.5 and 1 hour nausea and photophobia measurements described in the previous section), and 4 missing records for 842-14-3210, including the baseline measure and the two hour measure. This last patient was not included in the 2 hour analysis.

Table 18 shows the distribution of phonophobia at baseline. There was a baseline imbalance showing a higher incidence of phonophobia in the placebo group (93% vs. 89%, $p=0.01$, Fisher's exact test).

Table 18: (RA) – Pooled Studies, Phonophobia at Baseline

	Excedrin Migraine	PBO	Total
Phonophobia Absent	68	44	112
%	11.02	6.98	
Phonophobia Present	549	586	1135
%	88.98	93.02	
Total	617	630	1247

Table 19 and Table 20 show the distribution of phonophobia at 2 and 4 hours. At both time points, the incidence of phonophobia was lower in the Excedrin Migraine treated group ($p<0.001$ at both 2 and 4 hours, respectively, Fisher's exact test). Because of the baseline imbalance shown in the previous table, I performed a Cochran-Mantel-Haenszel test, grouping by baseline phonophobia as a binary variable (present or absent). The p values remained $p<0.001$ for both time points. Numerically a 4% percent point advantage to the drug group at baseline became a roughly 17% advantage over placebo at 2 and 4 hours.

Table 19: (RA) – Pooled Studies, Phonophobia at 2 hours

	Excedrin Migraine	PBO	Total
Phonophobia Absent	229	122	351
%	37.18	19.33	
Phonophobia Present	387	509	896
%	62.82	80.67	
Total	616	631	1247

Table 20: (RA) – Pooled Studies, Phonophobia at 4 Hours

	Excedrin Migraine	PBO	Total
Phonophobia Absent	348	190	538
%	56.40	30.11	
Phonophobia Present	269	441	710
%	43.60	69.89	
Total	617	631	1248

I conclude that treatment with Excedrin Migraine was associated with decreased phonophobia of migraine.

8. Labeling Review

My labeling review below includes a copy of the sponsor’s draft product labeling. I limit my review of the labeling to only those issues pertaining to the diagnosis and treatment of migraine. These are located in two sections:

- Use section
- Warnings section

8.1 Draft Product Labeling

The underlined text indicates text that is new or different compared to the currently approved product labeling for Excedrin Migraine.

EXCEDRIN MIGRAINE
ACETAMINOPHEN, ASPIRIN AND CAFFEINE TABLETS

Important: Read all product information before using. Keep this box for important information.

Active Ingredients	(per [* Insert Dosage Form])	Purposes
Acetaminophen	250 mg	Pain Reliever
Aspirin	250 mg	Pain Reliever
Caffeine	65 mg	Pain Reliever Aid

Use:

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

WARNING: Children and teenagers should not use this medicine for chicken pox, or flu symptoms, before a doctor is consulted about Reye 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

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

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. 5

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.

Ask a Doctor Before Use If You Have:

- a headache that is different from your usual migraines
- the worst headache of your life
- fever and stiff neck
- bleeding problems
- ulcers
- asthma
- liver disease
- renal disease
- stomach problems such as heartburn, upset stomach, or stomach pain that do not go away or recur
- daily headaches
- headaches beginning after or caused by head injury, exertion, coughing or bending

Ask a Doctor Before Use If You Have: (Continued)

- experienced your first headache after the age of 50
- a migraine so severe as to require bed rest
- vomiting with your migraine

Ask a Doctor Before Use If You Are:

- taking a prescription drug for anticoagulation (thinning of the blood), diabetes, gout or arthritis

Stop Using This Product and See a Doctor If:

- an allergic reaction occurs. Seek medical help right away
- your migraine is not relieved or worsens
- 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 SPECIFICALLY 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. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

Directions: Adults and children over 12 years: 2 (* insert dosage form) with a full glass of water every 6 hours while symptoms persist, not to exceed 8 (* insert dosage form) in 24 hours, or as directed by a doctor. Do not take for more than 48 hours. Children: Do not give to children under 12 unless directed by a doctor.

8.2 Comments

8.2.1 "Use" Section

The first bullet states that Excedrin Migraine is for the relief of migraine. The second bullet describes the individual symptoms that are relieved: headache pain, nausea, sensitivity to light and sound, and difficulty carrying out normal activities.

In the pre-NDA meeting between the sponsor and the various review divisions held on 9/8/98, our Division stated the position that medications that relieve the pain of migraine as well as the associated symptoms of migraine should be indicated for the treatment of migraine—the entire syndrome. We have avoided in labeling the enumeration of the individual migraine-associated symptoms in the indication section.

The observed effect on the secondary symptoms of migraine were all based upon analyses of secondary endpoints and conclusions drawn from such analyses only serve to support an overall claim of an anti-migraine effect. Since these were not primary endpoints in the studies, claims of efficacy for each individual symptom may be misleading. Whether they are misleading in this particular instance is open for discussion, since the nominal p values from the secondary analyses were quite low. Nonetheless, I believe it sets an undesirable precedence to emphasize results of secondary analyses so prominently in labeling.

The sponsor argues that the results of a labeling comprehension study (not reviewed here) indicate that patients have a better understanding of the potential therapeutic benefits of the medication when the individual migraine symptoms are enumerated. Although this may be true, it doesn't eliminate the concern I described.

Regarding claims of functional disability, we have not allowed similar claims in –triptan labeling largely because the Division doesn't consider the scale use to be a validated measure of disability in migraineurs.

8.2.2 "Warnings" Section

The warnings section contains three new warnings:

- *Ask a doctor before use if you have a headache that is different from your usual migraines.*
- *Ask a doctor before use if you have a migraine so severe as to require bed rest, or vomiting with your migraine*

These two statements are consistent with –triptan labeling (Maxalt) which instruct patients that the medication is not intended "to treat headaches that might be caused by other, more serious conditions."

- *Stop using this product and see a doctor if your migraine is not relieved or worsens.*

This is similar to the patient information section of the -triptan labeling. The Maxalt labeling states "If your condition worsens, seek medical attention."

9. Conclusions

I conclude that, based on the results of three adequate and well controlled clinical trials, treatment with Excedrin Migraine is associated with improvement in the migraine related symptoms of nausea, photophobia, and phonophobia.

10. Recommendations

I recommend approval of the efficacy supplement with changes in the proposed labeling as I have described.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. */S/* (see NY memo)

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cc:
HFD-120
NDA 20-802
electronic copy-Levin