CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20802

MEDICAL REVIEW(S)

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MEDICAL OFFICER REVIEW

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Sponsor:	Bristol-Myers Products 1350 Liberty Avenue Hillside, NJ 07207-6050 Steven J. Knapp Senior Director, Global Regulatory Affairs TEL: 908-851-6119 — FAX: 908-851-6249
Drug Name:	Excedrin® Extra-Strength Tablets
Drug Class:	Analgesic Combination Drug (with caffeine)
Intended Use of Drug:	Pain associated with migraine headache
Consumer Safety Officer:	Sandra Cook
Medical Officer:	Rudolph M. Widmark, M.D., Ph.D.

Background®

Excedrin® Extra-Strength Tablets (Excedrin®ES) is a combination analgesic available OTC without prescription. Each tablet contains:

Acetaminophen	250 mg
Aspirin	250 mg
Caffeine	65 mg

The indications for Excedrin®ES are: For temporary relief of the pain of headache, sinusitis, colds, muscular aches, menstrual discomfort, toothaches and minor arthritis pain. Despite these various indications, Excedrin®ES is promoted primarily as "the headache medicine."

To round up the "headache medicine" image, the Sponsor has decided to investigate the efficacy of Excedrin®ES in the management of mild to moderate pain associated with migraine attacks.

Clinical Trials Reviewed

The Sponsor submitted the results of three identical clinical studies, each conducted by different investigators:

1. Study Protocol -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 [conducted 9/22/95 through 5/1/96]. One investigator participated in the study at 1 investigational site.

2. Study Protocol -841: 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 [conducted 8/17/95 through 6/22/96]. Ten investigators participated in the study at 10 investigational sites.

3. Study Protocol -842: 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 [conducted 8/30/95 through 5/3/96]. Ten investigators participated in the study at 9 investigational sites.

This Reviewer recognized the names of well-known headache specialists among the investigators listed as participants in the above trials (a listing of all investigators is given in Appendix 1). Since the study protocols are identical, as well as the drug formulations used in the three studies (-840, -841, and -842), the outcome of each trial should be expected to be comparable to the outcome of the others.

Study Objective: The objective of these studies was to assess the effectiveness of Excedrin® Extra-Strength in alleviating acute migraine headache pain.

Study Design: The studies were either single-center 840) or multi-center (-841 and -842), randomized, parallel-group, single-dose, placebo-controlled. Qualified patients were randomly assigned to receive Excedrin®ES or placebo as treatment for the headache pain of one acute migraine attack within 12 weeks after enrollment into the treatment phase. The studies involved a telephone screening phase, a selection phase, and a treatment phase. Using patient diary cards, patients were instructed to treat and evaluate, under double-blind conditions, the headache pain of one eligible migraine attack, together with functional ability, nausea, vomiting, photophobia, and phonophobia. The patients' experiences with their headache episodes were reviewed by the investigator during a follow-up visit to confirm and document whether the treated headache pain was due to a migraine.

Inclusion Criteria:

a) Males or females who had passed their 18th birthday.
b) Primary headache diagnosis was either migraine without aura or migraine with aura, as diagnosed according to the International Headache Society (IHS) criteria (Appendix 2), and headaches present for more than one year, beginning prior to age 50.
c) History, on average, of at least one migraine attack every two months, but no more than 6 migraine attacks monthly during the previous year. Typical migraine attack, left untreated, was to include headache pain of at least moderate pain intensity.
d) Ability to cooperate with the Investigator and be willing to give written informed consent, take assigned medication as per instructions, complete appropriate evaluation forms, and complete the full course of the study and keep assigned follow-up appointment.
e) Good general health.

Exclusion Criteria:

The following are selected exclusion criteria:

a) Migraine attacks were usually disabling or incapacitating (requiring bed rest).
b) History of vomiting ≥20% of the time during migraine attacks.
c) Current use of ergot alkaloids and/or ergotamine tartrate to treat migraine.

Treatment: Patients admitted to the study were randomly assigned to receive two tablets of either Excedrin®ES or placebo as treatment for the headache pain (of at least moderate intensity) of one acute migraine attack within 12 weeks enrollment.

Efficacy Variables Assessed: The following efficacy measures were collected at various observation points during the study: headache pain intensity (PI), pain relief (PAR), functional ability, nausea, vomiting, photo- and phonophobia. In addition, the time of rescue medication was to be recorded, and a global evaluation of treatment was made by the patient at the end of the treatment phase or at the time that rescue medication was administered (PTGLOB) and by the investigator at the follow-up visit (INVGLOB).

The primary efficacy variables were Pain Intensity Difference (PID) and the percent of patients with headache pain intensity reduced to mild or none (RESPONDERS) at 2 hours postdose. Secondary efficacy variables were Pain Relief, Percentage PID (%PID), Pain Relief Intensity Difference (PRID), percent of patients whose pain was reduced to none (PAIN-FREE), percent of patients who remedicated at or before each time point (REMED), time to remedication (TREMED), Sum of Pain Intensity Difference (SPID), Percent SPID (%SPID), and Total Pain Relief (TOTPAR) at 2 and 6 hours postdose, time until pain intensity was reduced to mild or none (ONSET), and the maximum observed values of PID, %PID, and PAR (MAXPID, %MAXPID, MAXPAR).

Safety Variables Assessed: Adverse experiences were recorded in the diary by the patients, or elicited at the final visit by the investigator. The intensity, duration, severity, and relation to study drug were recorded. No laboratory data were collected.

Safety variables were the percentage of patients who reported any adverse event during the study, both overall and by body system.

Statistical Methods: Since there were only two treatment groups, Excedrin®ES or placebo, the outcome variables were analyzed by using ANOVA and other non-parametric methods. Treatment success was the proportion of RESPONDERS (pain intensity reduced to mild or none) and the proportion of patients considered PAIN-FREE (pain intensity reduced to none).

Results

Results of efficacy and safety were obtained from "three" trial protocols involving 20 investigational sites. Since the protocols were identical, the results should be viewed together to show whether there were noticeable differences between different investigational sites implementing the same protocol.

Demographics

Patients were recruited and screened according to the provisions of the protocol. If found eligible, patients were randomized to one of the two treatment groups (Excedrin®ES or placebo). Of those randomized, not all actually took the study medication. The allocation of patients to treatment groups is shown Table 1. The number of patients given as "evaluable patients" constitutes the denominator of patients considered for efficacy. For safety, however, the denominator of patients is the total number of patients who "took study medication".

Table 1
Patient Allocation to Treatment Groups

Study Number	Number of Patients	Excedrin®ES	Placebo	Total
-840	Randomized	219	220	439
	Took Study Medication	192	198	390
	Evaluable Patients	187	191	378
-841	Randomized	235	235	470
	Took Study Medication	214	223	437
	Evaluable Patients	206	221	427

Table 1 (continued)
Patient Allocation to Treatment Groups

Study Number	Number of Patients	Excedrin®ES	Placebo	Total
-842	Randomized	223	225	448
	Took Study Medication	212	211	423
	Evaluable Patients	209	206	415

The demographic characteristics of the efficacy evaluable patients are shown in Table 2. As can be seen in this table, the patient population shows a predominance of female subjects. On the whole, the patient population at all three trial sites is quite similar in gender, race, and age distribution.

Table 2
Demographic Characteristics of the Study Population

Study Number		840			841			842		
		EXC N=187	PBO N=191	Σ *N=378*	EXC N=206	PBO N=221	Σ *N=427*	EXC N=209	PBO N=206	Σ *N=415*
Sex	Male	47	43	*90*	50	42	*92*	35	36	*71*
	Female	140	148	*288*	156	179	*335*	174	170	*344*
Race	White	146	163	*309*	173	195	*368*	189	184	*373*
	Black	39	28	*67*	22	12	*34*	8	14	*22*
	Hispanic	0	0	*0*	6	9	*15*	8	4	*12*
	Oriental	1	0	*1*	3	1	*4*	3	2	*5*
	Other	1	0	*1*	2	4	*6*	1	2	*3*
Age	Mean	35.3	35.8	*35.6*	37.8	35.9	*36.8*	37.8	37.6	*37.7*
	Median	36.0	36.0	*36.0*	36.5	34.0	*35.2*	37.0	36.0	*36.5*
	Std.dev.	9.6	10.2	*9.9*	11.2	12.0	*11.6*	10.7	10.7	*10.7*
	Range	18-65	18-66	*18-66*	18-81	17-87	*17-87*	18-67	18-68	*18-68*

Legend: EXC = Excedrin®ES
PBO = Placebo
Σ = Total

Tables 3 and 4 list the patients according to their symptom characteristics at baseline, i.e., before receiving the study medication.

Table 3
Symptom Characteristics of Efficacy-Evaluable Study Subjects

Study Number		840			841			842		
		EXC N=187	PBO N=191	Σ *N=378*	EXC N=206	PBO N=221	Σ *N=427*	EXC N=209	PBO N=206	Σ *N=415*
Aura	Yes	27	29	*56*	48	56	*104*	38	37	*75*
	No	160	162	*322*	158	165	*323*	171	169	*340*
One-sided Pain	Yes	126	123	*249*	160	155	*315*	151	151	*302*
	No	61	68	*129*	46	66	*112*	58	55	*113*
Pulsating Pain	Yes	166	171	*337*	175	193	*368*	176	180	*356*
	No	21	20	*41*	31	28	*59*	33	26	*59*
Pain Aggrav. by Routine Phys. Activ.	Yes	160	170	*330*	169	184	*353*	178	179	*357*
	No	27	21	*48*	37	37	*74*	31	26	*57*
	N/R	0	0	*0*	0	0	*0*	0	1	*1*
Menstrual Pain at Time of Migraine	Yes	29	23	*52*	23	43	*66*	34	34	*68*
	No	100	106	*206*	114	120	*234*	108	117	*225*
	N/A	56	60	*116*	69	56	*125*	65	55	*120*
	N/R	2	2	*4*	0	2	*2*	2	0	*2*

Legend: EXC = Excedrin®ES N/R = not recorded
PBO = Placebo N/A = not applicable
Σ = Total

In Table 3 it can be seen that the patient population, though similar between studies, has also some slight differences in baseline symptomatology, such as, e.g., the ratio between patients with aura and those without is 1 to 6 in -840, 1 to 3 in -841, and 1 to 5 in 842. Otherwise, the patient distributions are amazingly similar.

This similarity continues in data presented in Table 4, with some slight deviations. For instance, study -840 had marginally more patients with severe headache pain at baseline than the other two studies.

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Table 4
Baseline Characteristics of Efficacy-Evaluable Study Subjects

Study Number		840			841			842		
		EXC N=187	PBO N=191	Σ *N=378*	EXC N=206	PBO N=221	Σ *N=427*	EXC N=209	PBO N=206	Σ *N=415*
Pain Intensity	mod.	117	113	*230*	139	156	*295*	144	144	*288*
	sev.	70	78	*148*	67	65	*132*	65	62	*127*
Functional Disability	none	6	2	*8*	8	4	*12*	7	6	*13*
	mild	17	23	*40*	29	36	*65*	37	32	*69*
	mod.	91	89	*180*	100	106	*206*	94	97	*191*
	sev.	65	68	*133*	61	62	*123*	58	55	*113*
	incap.	8	9	*17*	8	13	*21*	12	15	*27*
	N/R	0	0	*0*	0	0	*0*	1	1	*2*
Have Nausea	none	86	91	*177*	78	93	*171*	77	66	*143*
	mild	73	73	*146*	92	96	*188*	88	90	*178*
	mod.	25	26	*51*	30	29	*59*	40	48	*88*
	sev.	3	1	*4*	6	3	*9*	4	2	*6*
Have Vomiting	No	182	190	*372*	201	221	*422*	206	202	*408*
	Yes	5	1	*6*	5	0	*5*	3	4	*7*
Have Photophobia	none	3	6	*9*	16	12	*28*	9	16	*25*
	mild	56	44	*100*	68	62	*130*	73	67	*140*
	mod.	104	109	*213*	98	116	*214*	99	97	*196*
	sev.	24	32	*56*	24	31	*55*	28	26	*54*
Have Phonophobia	none	14	6	*20*	28	14	*42*	22	20	*42*
	mild	42	56	*98*	58	84	*142*	74	76	*150*
	mod.	97	109	*206*	96	102	*198*	88	89	*177*
	sev.	34	20	*54*	24	20	*44*	24	21	*45*
	N/R	0	0	*0*	0	1	*1*	1	0	*1*

Legend: EXC = Excedrin®ES; PBO = Placebo; Σ = Total; mod. = moderate; sev. = severe; incap. = incapacitating; N/R = not recorded

Efficacy

Migraine diagnosis of patients included in trials -840, 841 and 842: Since these studies were designed to investigate the effectiveness of Excedrin®ES in the management of pain associated with a migraine attack, it was important to make sure that the diagnosis of patients enrolled in the trials was indeed migraine and not another form of headache. The correctness of the diagnosis was checked by Dr. Richard Stein, assigned statistician to this NDA, on the basis of the diagnostic criteria for migraine of the IHS (International Headache Society) (see Appendix 2). A few patients were identified who did not fulfill the diagnostic criteria for having migraine headache, as defined in the trial protocols. By eliminating these "misdiagnosed" patients from the statistical analysis, however, did not change the p-values of the outcome variables (see Statistical Review of NDA 20-802). The dose-effect curves are also in this statistical review.

The results of the 2-hour and 6-hour efficacy assessments are given in Tables 5 through 8. For the purpose of easier comparison, Tables 7 and 8 are a rearrangement of Tables 5 and 6: First, the tables are showing the three trial sites next to each other; then the tables are arranged by treatment groups from the three study sites. It should not be forgotten that study -840 was a single-center trial with a single investigator; study -841 had 10 investigational sites with 10 investigators, and study -842 had 9 investigational sites with 10 investigators. Since the demographics showed similar patient populations for the three studies, it was of great interest to see to what degree, if any, the results differed between the studies.

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Table 5
Efficacy Results from Studies -840, -841, and -842

	840		841		842	
Treatment	EXC[3]	PBO[4]	EXC	PBO	EXC	PBO
Results Obtained	N=187	N=191	N=206	N=221	N=209	N=206
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)
• RESPONDERS	64%*	37%	59%*	31%	56%*	31%
• Mean PAR (s.d.[1])	2.0 (1.40)*	1.0 (1.16)	1.6.(1.34)*	0.9 (1.20)	1.7 (1.45)*	0.8 (1.10)
• Patients with no pain	26%*	7%	17*	9%	21%*	5%
• Patients without nausea	73%*	66%	57%*	57%	59%*	46%
• Patients without photophobia	40%*	14%	29%*	19%	35%*	17%
• Patients without phonophobia	42%*	17%	32%*	20%	36%*	20%
• Patients with little or no f.d.[2]	66%*	34%	59%*	35%	53%*	33%

Legend: [1] s.d. = standard deviation
[2] f.d. = functional disability
[3] EXC = Excedrin®ES
[4] PBO = Placebo
* significantly different from placebo ($p<0.05$)

Table 6
Efficacy Results from Studies -840, -841, and -842

	840		841		842	
Treatment	EXC[3]	PBO[4]	EXC	PBO	EXC	PBO
Results Obtained	N=187	N=191	N=206	N=221	N=209	N=206
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)
• RESPONDERS	82%*	55%	78%*	48%	76%*	53%
• Mean PAR (s.d.[1])	2.7 (1.64))*	1.4 (1.69)	2.2 (1.67)*	1.2 (1.57)	2.2 (1.70)*	1.3 (1.59)
• Patients with no pain	61%*	28%	47*	21%	45%*	21%
• Patients without nausea	80%*	68%	72*	57%	72%**	56%
• Patients without photophobia	66%*	35%	58*	27%	52%*	33%
• Patients without phonophobia	66%*	35%	57*	31%	54%*	34%
• Patients with little or no f.d.[2]	75%*	45%	69*	39%	63%*	38%

Legend:
[1] s.d. = standard deviation
[2] f.d. = functional disability
[3] EXC = Excedrin®ES
[4] PBO = Placebo
* significantly different from placebo ($p<0.05$)
** significantly different from placebo ($p<0.01$)

Considering the statistical significances of the outcome variables in the "three" trials, there was no noticeable difference between the efficacy results. The rearrangement of the data in Tables 7 and 8 will make a comparison of the data even easier.

Table 7
Efficacy Results from Studies -840, -841, and -842

	Excedrin® ES			Placebo		
	840	841	842	840	841	842
Results Obtained	N=187	N=206	N=209	N=191	N=221	N=206
at 2 hours:						
• Mean PID (s.d.)	1.2 (0.95)*	0.9 (0.85)*	0.9 (0.93)*	0.5 (0.96)	0.4 (0.89)	0.4 (0.83)
• RESPONDERS	64%*	59%*	56%*	37%	31%	31%
• Mean PAR (s.d.[1])	2.0 (1.40)*	1.6.(1.34)*	1.7 (1.45)*	1.0 (1.16)	0.9 (1.20)	0.8 (1.10)
• Patients with no pain	26%*	17*	21%*	7%	9%	5%
• Patients without nausea	73%*	57%*	59%*	66%	57%	46%
• Patients without photophobia	40%*	29%*	35%*	14%	19%	17%
• Patients without phonophobia	42%*	32%*	36%*	17%	20%	20%
• Patients with little or no f.d.[2]	66%*	59%*	53%*	34%	35%	33%

Legend: [1] s.d. = standard deviation
[2] f.d. = functional disability
* significantly different from placebo ($p<0.05$)

Table 8
Efficacy Results from Studies 840, -841, and 842

	Excedrin®ES			Placebo		
	840	841	842	840	841	842
Results Obtained	N=187	N=206	N=209	N=191	N=221	N=206
at 6 hours:						
• Mean PID (s.d.)	1.6 (1.07)*	1.3 (1.09)*	1.2(1.14)*	0.8 (1.25)	0.6 (1.10)	0.6 (1.17)
• RESPONDERS	82%*	78%*	76%*	55%	48%	53%
• Mean PAR (s.d.[1])	2.7 (1.64))*	2.2 (1.67)*	2.2 (1.70)*	1.4 (1.69)	1.2 (1.57)	1.3 (1.59)
• Patients with no pain	61%*	47*	45%*	28%	21%	21%
• Patients without nausea	80%*	72*	72%**	68%	57%	56%
• Patients without photophobia	66%*	58*	52%*	35%	27%	33%
• Patients without phonophobia	66%*	57*	54%*	35%	31%	34%
• Patients with little or no f.d.[2]	75%*	69*	63%*	45%	39%	38%

Legend: [1] s.d. = standard deviation
[2] f.d. = functional disability
* significantly different from placebo ($p<0.05$)
** significantly different from placebo ($p<0.01$)

If Tables 5 and 6 showed statistical consistency between the "three" studies, Tables 7 and 8 showed numerical consistency as well. Since the patient population was similar in the study centers, this outcome consistency is reassuring that the efficacy findings are supporting the claim that two tablets of Excedrin®ES are beneficial in managing the pain associated with a migraine attack. For the results presented as dose-effect and time-effect curves, see statistical review.

Safety

For assessment of safety, the reports of adverse events collected from all patients who took drug (Excedrin*ES or placebo) in the "three" studies were pooled, resulting in 618 subjects who took Excedrin*ES and 632 individuals who took placebo. A total of 111 Excedrin®ES -

treated patients (18.0%) and 68 placebo-treated patients (10.8%) had one or more adverse experiences. The investigators assessed that of these 84 Excedrin®ES -treated patients (13.6%) and 44 placebo-treated patients (7.0%) were possibly or probably related to study medication. Although no patient had an adverse experience that could be defined as serious, one placebo-treated patient did not complete the 6-hour evaluation period because of adverse experiences. Table 9 summarizes these data.

Table 9
Summary of Adverse Experiences Reported in Studies 840, 841 and 842

Number (%) of Patients With:	Excedrin*ES (N=618)	Placebo (N=632)	p-value
One or more Adverse Experiences	111 (18.0)	68 (10.8)	<0.001
Possibly or Probably Drug-Related Adverse Events	84 (13.6)	44 (7.0)	<0.001
Serious Adverse Experiences	0	0	1.000
Adverse Experiences Causing Withdrawal	0	1 (0.2)	1.000

Among the body systems, CNS, GI and "body as a whole" had the highest incidence of adverse events.

Fifty-five Excedrin®ES -treated patients (7.4%) and 21 placebo-treated patients (3.3%) had adverse experiences of the nervous system; the difference between the two treatment groups was statistically significant ($p<0.001$). The most frequently occurring adverse experiences ($\geq$0.5%) in Excedrin®ES -treated were nervousness (4.4%), dizziness (2.8%), somnolence (0.8%), insomnia (0.5%), paresthesia (0.5%), and tremor (0.5%).

Forty-six Excedrin®ES -treated patients (7.4%) and 28 placebo-treated patients (4.4%) had adverse experiences of the digestive system; the difference between the two treatment groups was statistically significant ($p<0.03$). The most frequently occurring adverse experiences ($\geq$0.5%) in Excedrin®ES -treated were nausea (4.9%), dyspepsia (1.8%), and diarrhea (0.6%).

Twenty-two Excedrin®ES -treated patients (3.6%) and 17 placebo-treated patients (2.7%) had adverse experiences of the "body as a whole". The most frequently occurring adverse experiences ($\geq$0.5%) in Excedrin®ES -treated were abdominal pain (1.1%), back pain (0.6%), and asthenia (0.5%).

Ten Excedrin®ES -treated patients (1.6%) had adverse experiences of the cardiovascular system, compared to 3 placebo-treated patients (0.5%); this difference was not statistically significant but approached statistical significance ($p=0.054$). The most frequently occurring adverse experiences ($\geq$0.5%) in Excedrin®ES -treated was tachycardia (0.8%).

Tinnitus occurred in 0.5% of the Excedrin®ES -treated patients, compared with 0.3% of placebo-treated patients.

Twelve Excedrin®ES -treated patients (1.9%) and 11 placebo-treated patients (1.7%) had severe (not serious) adverse experiences. The most frequently occurring severe adverse experiences were nausea (Excedrin®ES , 0.6%; placebo, 0.8%) and nervousness (Excedrin®ES , 0.5%; placebo, 0%).

Table 10
Number (%) of Patients With Adverse Experiences by Body System

Adverse Experience		Excedrin*ES (N=618)	Placebo (N=632)	p-value
Body As a Whole		**22 (3.6)**	**17 (2.7)**	**0.418**
Most frequent (≥0.5%):	Abdominal pain	7 (1.1%)	3 (0.5%)	0.220
	Back pain	4 (0.6%)	0	0.059
	Asthenia	3 (0.5%)	3 (0.5%)	1.000
Cardiovascular System		10 (1.6)	3 (0.5)	0.054
Digestive System		**46 (7.4)**	**28 (4.4)**	**0.030**
Most frequent (≥0.5%):	Nausea	30 (4.9%)	11 (1.7%)	0.002
	Dyspepsia	11 (1.8%)	4 (0.6%)	0.072
	Diarrhea	4 (0.6%)	0	0.059
Musculoskeletal System		2 (0.3%)	2 (0.3)	—
Nervous System		**55 (8.9)**	**21 (3.3)**	**<0.001**
Most frequent (≥0.5%):	Nervousness	27 (4.4%)	5 (0.8%)	<0.001
	Dizziness	17 (2.8%)	7 (1.1%)	0.039
	Somnolence	5 (0.8%)	3 (0.5%)	0.502
	Insomnia	3 (0.5%)	3 (0.5%)	1.000
	Paresthesia	3 (0.5%)	1 (0.2%)	0.369
	Tremor	3 (0.5%)	0	0.121
Respiratory System		3 (0.5)	6 (0.9)	—
Skin and Appendages		0	1 (0.2)	—
Special Senses		7 (1.1)	5 (0.8%)	—
Urogenital System		2 (0.3)	0	—
Patients with No Adverse Experience		**507 (82.0)**	**564 (89.2)**	
Patients with ≥1 Adverse Experiences		**111 (18.0)**	**68 (10.8)**	

— = Statistical testing was not performed

Comments

The results of the clinical studies submitted in support speak for themselves: The OTC-drug Excedrin* Extra-Strength Tablets can be used by laymen patients to alleviate the pain associated with their migraine headache. Those patients who are not helped by Excedrin®ES will eventually have to have their migraine diagnosis confirmed by a physician and will end up by receiving a prescription drug for controlling their migraine headaches, such as an ergot preparation or the serotonin (5-HT) receptor agonist Imitrex® (sumatriptan).

Before concluding this review, however, I would like to address several issues that have been brought up since the submission of this NDA. Some of these subject-matters have been discussed in the past with the Sponsor at meetings I was unable to attend. It is for this reason that I express below my opinion regarding the issues below.

Issues Related to This Submission — A personal view

Importance of migraine diagnosis for consumers: If "purity" of migraine diagnosis was essential in the clinical efficacy trials (the only way to investigate whether Excedrin®ES is useful in the management of pain associated with migraine attacks), for the consumer who has recurrent, bothersome headaches and goes to buy an OTC analgesic product, the correct classifying diagnosis of the headache becomes unnecessary: This is the first step of self-treatment all headache sufferers take, whether their headache is migraine or not. Only when the OTC medication ceases to provide any benefit, people seek medical advice (after "helpful hints" from family and friends have failed), the headache specialist always being the last in the chain of advice givers.

The issue of the amount of caffeine in Excedrin®ES : Excedrin®ES contains 65 mg of caffeine per tablet, along with 250 mg each of aspirin and acetaminophen. Two tablet will double the amounts of a single tablet: There is concern that 130 mg of caffeine represents an unsafe amount of caffeine. Patients usually know whether they tolerate caffeine or not. Those who have a caffeine-intolerance cannot tolerate 130 mg, 65 mg, 32.5 mg or an even lesser amount of caffeine: These patients cannot tolerate caffeine, whatever the amount. The other argument against the 130 mg of caffeine is that it will induce abuse. If someone wants caffeine, I seriously doubt that they will ingest Excedrin®ES instead of one or more cups of coffee. Caffeine in the Excedrin®ES formulation may have a dual role in its pharmacodynamic action: It may facilitate the absorption of aspirin and acetaminophen, thus providing drug levels faster than without it. It plays the role of a cranial vasoconstrictor with a favorable effect on the symptoms of a migraine attack (Cafergot®, containing 2 mg of ergotamine tartrate and 100 mg of caffeine, is the best example for these caffeine effects).

Does the combination drug policy apply to Excedrin®ES : When a combination drug, i.e., a drug that has more than one pharmacologically active ingredient, the Applicant must

prove that each component contributes to the claimed action. Excedrin®ES is such a combination drug. The question is whether the combination policy would apply to a drug that is available OTC for many years and is known by the consumers as the "headache medication." Based on pure pharmacological considerations, the drug combination in Excedrin®ES makes sense: Caffeine is promoting the absorption of the other two components and has by itself a beneficial effect (cerebral vasoconstriction). Aspirin is an analgesic and has an effect on platelets which is seemingly also beneficial. Acetaminophen is an analgesic that complements the effect of aspirin. The caffeine and acetaminophen components made it possible to keep the dosage of aspirin to a minimum, which increases the safety margin of aspirin. It is the opinion of this Reviewer that Excedrin®ES should be excepted from the combination policy for the reasons mentioned above.

Conclusions

The Sponsor has substantiated in well-designed, placebo-controlled, multi-center studies that:

- Two tablets of Excedrin* Extra-Strength is a dosage effective in the management of moderate or severe pain associated with migraine headache, as demonstrated by clinically meaningful and statistically significant reductions in pain intensity scores and significantly higher pain relief scores, compared with placebo (see Statistical Review).
- The dosage of two Excedrin* Extra-Strength Tablets provides superior relief of migraine headache pain, compared to placebo, as demonstrated by a significantly higher percentage of patients whose baseline headache pain was reduced to mild or NONE at 2 hours post-dosing and at all other time-points.
- Two Excedrin* Extra-Strength Tablets provide a significantly earlier onset of, and a greater, pain relief from migraine headache pain, compared with placebo.
- Two Excedrin* Extra-Strength Tablets were associated with clinically meaningful and statistically significant relief of the symptoms associated with an attack of migraine headache, such as nausea, photophobia, phonophobia, and impaired functional ability.
- The adverse events of two Excedrin* Extra-Strength Tablets reported in the studies submitted were not different from the adverse experiences known to be associated with aspirin, acetaminophen, or caffeine.
- The label of Excedrin* Extra-Strength Tablets must conform with the "OTC label" format, but in addition should have, visibly imprinted across the label of the container and the box, the words: CONTAINS CAFFEINE.

Recommendation

Because of the evidence from clinical trials that two tablets of Excedrin® Extra-Strength are effective and relatively safe in the management of pain associated with migraine headache, when taken OTC by laymen, this Reviewer recommends approval of the claim.

RM. Widmark 6-2-97

Rudolph M. Widmark, MO Date

JEH 6-2-97

MAC 6/21/97

CC: Orig. NDA
HFD-550
HFD-340
HFD-550/CSO/SCook
HFD-550/CHEM/VBhavnagri
HFD-550/PHARM/AMukherjee
HFD-725/STAT/RStein
HFD-550/MO/RWidmark
HFD-550/SMO/JHyde
HFD-550/DIR/WChambers

Appendix 1

List (per Protocol) of Investigators Participating in Excedrin®ES Migraine Headache Pain

Protocol -840

1. Richard B. Lipton, MD

Protocol -841

1. Harvey Blumenthal, MD
2. David Smith, MD
3. Jack Klapper, MD
4. Robert Kunkel, MD
5. Ninian Mathew, MD
6. Stephen Silberstein, MD
7. Donald Mehlisch, MD
8. Arthur H. Elkind, MD
9. Jerome Goldstein, MD
10. David Cook, MD

Protocol -841

1. James Couch, Jr., MD, PhD
2. Robert Nett, MD
3. Joel Saper, MD
4. Fred Sheftell, MD
5. Steward Tepper, MD
6. Robert Ryan, Jr., MD
7. Sheila Jacobson, MD
8. Frederick Schaerf, MD, PhD

9.a. Henry Frazer, PharmD
9.b. Reuben Richardson, MD

Alphabetical List of Investigators Participating in Excedrin®ES Migraine Headache Pain, with Their Affiliation

Investigator		Affiliation
Blumenthal, Harvey, MD	841	Neurological Associates of Tulsa 6565 S. Yale Ave., Suite 312 Tulsa, OK 74136
Cook, David, MD	841	4207 Lake Boone Trail Raleigh, NC 27607
Couch, James, Jr, MD, PhD	842	Univ. Hospital Neurological Center 800 NE 13th, Rm. 6E-238 Oklahoma City, OK 73126
Elkind, Arthur, H, MD	841	Elkind Headache Center 20 Archer Avenue Mount Vernon, NY 10550
Frazer, Henry, A, PharmD	842	Drug Research and Analysis Corp. 303 South Ribley, Suite 1100 Montgomery, AL 36104
Goldstein, Jerome, MD	841	The San Francisco Headache Clinic 909 Hyde Street, Suite 230 San Francisco, CA 94109
Jacobson, Sheila, MD	842	Research for Health 902 Frostwood, Suite 315 Houston, TX 77024
Klapper, Jack, MD	841	Colorado Neurology and Headache Center 1155 E. 18th Avenue Denver, CO 80218
Kunkel, Robert, MD	841	Cleveland Headache Foundation 9500 Euclid Avenue, A50 Cleveland, OH 44195

Investigator		Affiliation
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Mathew, Ninan, T, MD	841	Houston Headache Clinic 1213 Herman, Suite 350 Houston, TX 77004
Mehlisch, Donald, R, MD	841	BioMedical Research Group 3200 Red River, Suite 300 Austin, TX 78705
Nett, Robert, MD	842	Texas Headache Institute 1804 NE Loop 410, Suite 100 San Antonio, TX 78217
Richardson, Reuben, MD	842	Drug Research and Analysis Corp. 303 South Ribley, Suite 1100 Montgomery, AL 36104
Ryan, Robert, E, Jr, MD	842	Ryan Headache Center 621 S. New Ballas Rd, Suite 537A St. Louis, MO 63141
Saper, Joel, MD	842	Michigan Headache Pain and Neurological Institute 3120 Professional Drive Ann Arbor, MI 48104
Schaerf, Frederick, MD, PhD	842	Medical Studies 12645 New Brittany Blvd. Building 15 Fort Myers, FL 33907
Scheftell, Fred, MD	842	NE Center for Headache 778 Long Ridge Road Stamford, CT 06902
Silberstein, Stephen, MD	841	Comprehensive Headache Center 1 Penn Boulevard Philadelphia, PA 19144

Investigator		Affiliation
Smith, David, MD	841	Innovative Medical Research, Inc. 1950 Century Blvd., Suite 23 Atlanta, GA 30345
Tepper, Steward, MD	842	1145 Broadway Seattle, WA 98122

APPEARS THIS WAY
ON ORIGINAL

Migraine Diagnostic Criteria (abbreviated)
International Headache Society (IHS)

1.1 *Migraine Without Aura* (Common Migraine)

A. At least 5 attacks fulfilling criteria B to D
B. Headache attacks lasting 4 to 72 hours (untreated or treated unsuccessfully)
C. Headache has at least two of the following 4 characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe intensity (inhibits or prohibits daily activities)
    4. Aggravation by walking stairs or similar routine activities
D. During headache, at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. At least one of the following:
    1. History, physical and neurological examinations do not suggest organic disorder
    2. History, physical and neurological examinations do not suggest organic disorder, but such disorder is ruled out by appropriate investigations
    3. Organic order is present, but migraine attacks do not occur *de novo* in close temporal relation to the disorder

1.2 *Migraine With Aura* (Classical Migraine)

A. At least 2 attacks fulfilling criteria B
B. At least three of the following four characteristics:
    1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
    2. At least one aura symptom develops gradually over more than 4 minutes, or two or more symptoms occur in succession
    3. No aura symptom lasts more than 60 minutes. If more than one symptom is present, accepted duration is proportionally erased
    4. Headache follows aura with a free interval of less than 60 minutes, but may begin before the aura
C. At least one from 1.1.E (above)