CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-012/S-016

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA (Serial Number)	**19-012**
Sponsor:	**McNeil**
Drug:	**Motrin Migraine**
Proposed Indication:	**migraine**
Material Submitted:	**FAX**
Correspondence Date:	**12/9/99**
Date Received / Agency:	**12/10/99**
Date Review Completed	**12/29/99**
Reviewer:	**Armando Oliva, MD**

1. Introduction

On 12/3/99, members of our Division and the Division of OTC held a teleconference with the sponsor to discuss the pending sNDA for the treatment of migraine. During that conversation, we outlined the two major problems that preclude approval of the application at this time:

1. I could confirm that only 80% of the patients in the two efficacy studies treated a definite migraine. The headache diagnosis in the remaining 20% remain unclear. In the subgroup of "definite migraine", study 22 failed to demonstrate a nominally significant treatment effect on the 2-hour headache response rate.

2. Even if one assumes all patients treated a migraine, then both studies fail to show nominally significant treatment effects on all of the secondary outcome measures (nausea, photophobia, phonophobia). This further casts doubt on the claim that the drug is an effective treatment of migraine.

Following the conversation, we sent them a detailed account of the modified IHS criteria I used to diagnose a migraine, along with the appropriate datasets.

I received a fax from the sponsor on 12/10/99 which represents their response to our comments, which I review below.

2. FAX – 12/9/99

The original application was for treatment of the pain of migraine. Following the approval of the Excedrin Migraine sNDA for the treatment of migraine, the sponsor amended their application to request a similar indication for their product. In light of the 12/3/99 conversation (particularly issue #2 above), the sponsor states that they are prepared to withdraw the amendment in which they request approval for the treatment of migraine. That is to say, they wish that we consider and approve Motrin Migraine for the original intended indication: treatment of migraine pain.

In their fax, the sponsor reiterates their strong belief that the data presented in studies 22 and 30 continue to support a migraine pain indication. They recognize that we eliminated

20% of the patients from our analyses because of our inability to confirm their headache diagnosis. The state that they still believe that the intent-to-treat analysis, including all patients, is the appropriate analysis to use. Although I agree with this assertion, the interpretation of these positive findings is in question if the headaches treated cannot be verified as migraine.

3. Support for the Pain of Migraine Indication

The sponsor interprets the positive primary analyses of studies 22 and 30 to mean that Motrin Migraine is effective in the relief of migraine headache pain. Since the diagnosis of the headache treated remains, in my mind, in question for 20% of patients, my interpretation is that Motrin Migraine is effective in the treatment of headache in a population of migraine sufferers. In response, the sponsor has provided the following information to support the pain of migraine indication.

They performed subgroup analyses on three defined subgroups:

1. The 97% of patients who reported treating a headache which was typical of their usual migraine
2. The 82.4% of subjects that we identified as having a "definite migraine" PLUS an additional 31 subjects who treated a headache restricted to one temple.
3. The 80% of subjects that we identified as having a "definite migraine"

I discuss each subgroup analysis below.

3.1 "Typical Migraine"

Table 1 (sponsor tables 2 and 3, pages 8 and 9) shows the 2-hour and 4-hour headache response rates in the 97% of patients that reported treating a "typical migraine." Both 200mg and 400mg were nominally significantly superior to placebo in both studies.

Table 1: Two- and Four-Hour Headache Responses in Patients Reporting a "Typical Migraine" (97% of ITT Population)

Study	200mg	400mg	PBO	overall p-value
2-hr responses				
22	90/216 (41.7%) 0.004	91/223 (40.8%) 0.006	62/221 (28%)	0.006
30	86/216 (39.8%) 0.002	90/219 (41.1%) 0.002	57/214 (26.6%)	0.002
4-hr responses				
22	96/216 (44.4%) <0.001	101/223 (45.3%) <0.001	66/221 (29.9%)	<0.001
30	102/216 (47.2%) <0.001	98/219 (44.8%) <0.001	64/214 (29.9%)	<0.001

p-values are Cochran-Mantel-Haenszel test, stratified by initial level of pain intensity
individual p-values are comparison with placebo.

The sponsor also points out that each patient was requested to answer a series of questions listed in front of their headache diary in order to be sure that the headache treated was a migraine. These question were, in fact, the same modified IHS criteria-

based algorithm that I applied to identify "definite migraines" in my original review. Unfortunately, the results of these questions were not captured in the diary or case report form, so all that I have for review is the final global assessment whether the headache was typical of their usual migraines.

3.2 Sponsor's Modification of "Definite Migraine" Subgroup

In my original review, I described the modified IHS criteria used to identify a definite migraine. I included patients that recorded having a unilateral headache in the algorithm. Using this criteria, 80% of patients met this modified definition. The sponsor points out that there were an additional 31 patients that recorded have a headache isolated to one temple. I agree that these patients should also be included for consideration in the "definite migraine" category because of the unilateral nature of their pain. Table 2 shows the 2-hr and 4-hr headache response rates for this subgroup (sponsor tables 8 and 9, pages 21 and 22).

Table 2: Two- and Four-Hour Headache Responses in Patients Reporting an FDA defined "Definite Migraine" plus Those with Pain Limited to One Temple (82.4% of ITT Population)

Study	200mg	400mg	PBO	overall p-value
2-hr responses				
22	70/176 (39.8%) 0.036	68/182 (37.4%) 0.094	53/183 (29%)	0.088
30	70/180 (38.9%) 0.004	71/181 (39.2%) 0.007	45/177 (25.4%)	0.004
4-hr responses				
22	78/176 (44.3%) 0.016	75/182 (41.2%) 0.062	58/183 (31.7%)	0.041
30	84/180 (46.7%) 0.001	80/181 (44.2%) 0.004	52/177 (29.4%)	0.001

p-values are Cochran-Mantel-Haenszel test, stratified by initial level of pain intensity
individual p-values are for comparison with placebo.

In this analysis, study 22 remains negative at 2 hours, whereas study 30 continues to show nominally significant treatment effects in favor of either dose of drug at 2 hours.

3.3 FDA Defined "Definite Migraine" Subgroup

The sponsor provides their analysis of my defined subgroup of definite migraine. I have already acknowledged that this number likely represents an "underestimate" of the true definite migraine subgroup. The sponsors numbers differ slightly from mine, because of slightly different definitions of a responder (I used pain intensity of 0 or 1, the sponsor used pain intensity <1.5 because there were some patients with decimal values due to interpolation). However, the conclusions are the same using either the FDA or sponsor analyses: study 22 was negative, and study 30 was positive at 2 hours.

Table 3: Two- and Four-Hour Headache Responses in Patients Reporting an FDA defined "Definite Migraine" (80% of ITT Population)

Study	200mg	400mg	PBO	overall p-value
2-hr responses				
22	67/169 (39.6%) 0.040	64/177 (36.2%) 0.160	52/179 (29%)	0.112
30	68/176 (38.6%) 0.003	69/177 (39%) 0.007	43/170 (25.3%)	0.006
4-hr responses				
22	75/169 (44.4%) 0.009	72/177 (40.7%) 0.052	55/179 (30.7%)	0.026
30	81/176 (46%) 0.001	79/177 (44.6%) 0.002	49/170 (28.8%)	0.001

p-values are Cochran-Mantel-Haenszel test, stratified by initial level of pain intensity
individual p-values are for comparison with placebo.

4. Reviewer's Analyses

The sponsor now requests approval for the original indication: relief of migraine pain. I believe the sponsor has already shown that Motrin Migraine is effective for the treatment of headache in a population of migraine sufferers since both studies 22 and 30 are positive in this regard. The question, in my mind, remains whether we can conclude that the drug is effective in the treatment of migraine pain specifically.

This revolves around the ability to verify that the patients did, in fact, treat a migraine. The sponsor correctly points out that, inherent in any study which relies on subjective patient data, there will always be reason to question the diagnosis in some cases. The sponsor argues that patients were instructed to answer a series of questions (on page 1 of the headache diary) to make sure that the treated headache was a migraine, and that 97% of patients reported treating a headache which was typical of their usual migraines. Is this sufficient evidence to convince us that 97% of the headaches treated were migraine?

The answer to this question is not clear to me. Certainly, it would be more convincing had they collected the answers to the patient questionnaire on page one of the headache diary, which are, in fact, an application of the modified IHS criteria which I used in my review. My opinion is that we should apply the same, or at least similar, standards used to verify the headache diagnosis in other OTC analgesics for the treatment of migraine (namely, Excedrin Migraine and Advil Liquigels). In these applications, use of the same algorithm enabled me to conclude that ≥96% of the headaches were "definite migraine." This is not possible in the Motrin Migraine application.

Nonetheless, I agree that the 80% figure is an underestimate and it is reasonable at this point to try to "refine" this subgroup a bit better. The sponsor has already suggested including 31 patients that had pain limited to one temple. I agree with this inclusion, although the results of the analyses do not change the conclusions.

In reviewing the data again, I see that there is room for additional refinement in the subgroup of "definite migraine." The patients all recorded location of pain as the following: 1= entire head, 2=front, 3=back, 4=one side, 5=both sides, 6=one temple, 7=other.

I originally included patients with headache location = 4 (one side) in my subgroup analysis. I agree that patients with headache location = 6 should also be included. In reviewing the "other" category, many of those patients included reports of unilateral pain in their description of "other" location (*e.g.*, unilateral front, or unilateral back). Those patients can also be included. Some patients also provided a separate text descriptor of the headache location that sometimes differed from the numeric classification. I included them if their description included some reference to a unilateral pain (the same strategy also applies to pain characteristic – throbbing; *i.e.*, I included some patients who included the term throbbing in the text description, even though their headache characteristic rating may have reflected another predominant type of pain).

One continuing unresolved problem with the data is that information regarding the effect of routine physical activity on the headache is missing. I do note that the sponsor provided a functional ability rating at baseline. This consisted of the following: 0=normal, 1=mildly impaired, 2=moderately impaired, 3=severely impaired. In general, patients who have moderate or severe impairment have to limit or stop routine physical activity. It may not always be true, but it may be reasonable to assume, that patients with moderate/severe impairment at baseline may limit or discontinue physical activity because the activity aggravates their headache. Therefore, it is of interest to me to us a functional ability rating of "2" or "3" to identify patients who may experience aggravation of their headache by physical activity on the headache.

Based on these considerations, I define the following subgroups, and analyzed 2-hour headache response rates, as well as 2-hour incidences of the important secondary measures for each subgroup. I chose not to analyze the 4-hour responses. Although it is true that the Agency at one time in the past relied on 4-hour data for determination of efficacy, most recent applications have all used 2-hour data. With the availability of medications (both prescription and OTC) that are effective at 2 hours, I don't see a compelling reason to approve a medication that is only effective at the 4-hour time point.

I define the following subgroups for analysis:

1. MIG1 – Patients with definite migraine using modified IHS criteria. For pain location, acceptable locations are: unilateral (location = 4), one temple (location = 6), and other (location = 7) but only if unilateral pain appears in the descriptor for "other". Also included were patients who used some reference to unilateral pain in the their text descriptor of the headache, even if it differed from the numeric classification. For throbbing pain, I also included patients who used throbbing in the text description of their headache, even if it differed from the numeric classification.
2. MIG2 – Patients with definite migraine as described in #1 above, while at the same time using baseline functional ability = 2 or 3 (moderate/severe impairment) as a

measure of those patients who's headache may have been aggravated by routine physical activity.

4.1 Migraine Characteristics

The modified IHS criteria used in my review are the following:

1. If the headache has an aura, then it's a migraine. Otherwise,
2. If the headache fulfills IHS criteria 1.1c and 1.1d, then it's a migraine.

Criterion 1.1c states that the headache must be accompanied by at least two of the following:

- unilateral
- throbbing
- moderate/severe
- aggravated by routine physical activity

Criterion 1.1d states that the headache must have at least one of the following:

- nausea or vomiting
- photophobia and phonophobia

Baseline headache information was provided in file base.xpt. I pooled the data from the two studies to facilitate the analysis (although I analyzed each study separately). The files contained one record for each randomized patient (721 in study 22, and 713 in study 30). However, some patient did not treat a headache with study drug. I deleted those from the analysis (61 in study 22, and 64 in study 30). This resulted in 660 patients in study 22 and 649 patients in study 30. All of these patients provided efficacy data and comprise the ITT population (section 4.2, page 6 of my original review).

I describe the distribution of each migraine characteristic below.

4.1.1 Aura

The distribution of aura is shown in Table 4. A total of 320 patients (176 in study 22, and 144 in study 30) reported an aura with their headache.

Table 4: Distribution of Aura

Aura Code	Study 22 (N=660)	Study 30 (N=649)	Total
Missing	1	0	1
0 – absent	483	505	988
1 – present	176	144	320

4.1.2 Unilateral

The distribution of headache location at baseline is shown in Table 5.

Table 5: Distribution of Headache Location at Baseline

Location Code	Study 22 (N=660)	Study 30 (N=649)	Total (N=1309)
1 – entire head	61	63	124
2 – front	115	97	212
3 – back	33	29	62
4 – one side	294	318	612
5 – both sides	45	38	83
6 – one temple	66	66	132
7 – other	46	38	84

Of the 1309 patients in the two studies, 204 supplied additional headache location information in the form of a text field which was coded as "LOC_OTH." I reviewed each of the 204 entries and flagged each record as "unilateral" if there was any reference to unilateral or one sided pain. Sixty-seven (67) of the 204 records had some reference to unilateral or predominantly unilateral pain. The distribution of these patients is shown in Table 6.

Table 6: Distribution of Unilateral "LOC_OTH" Pain

Location Code	Study 22	Study 30	Total
1 – entire head	0	2	2
2 – front	4	1	5
3 – back	0	1	1
4 – one side	3	5	8
5 – both sides	0	0	0
6 – one temple	0	1	1
7 – other	25	25	50
Total	**32**	**35**	**67**

One can see that 50 of these 67 patients were classified as "7 – other." The remaining had various other headache location codes. Eight and one were coded as "4 – one side" and "6 – one temple," respectively, so they are already captured as unilateral pain by examining the location code alone, but the remaining eight patients actually were coded as something other than one side or one temple. Therefore, a total of 58 patients with some reference to unilateral pain in "LOC_OTH" (50 classified as "7," and 8 classified as "1," "2," or "3") can be included as having unilateral pain.

Using the more exhaustive method described above to identify headaches that were unilateral, Table 7 shows the distribution of unilateral pain in the two studies. A total of 802 patients (389 in study 22 and 413 in study 30) had unilateral pain using this classification algorithm.

Table 7: Distribution of Unilateral Pain, by Migraine Location

Character Code	Non-unilateral		Unilateral		Total
	Study 22	Study 30	Study 22	Study 30	
1 – entire head	61	61	0	2	124
2 – front	111	96	4	1	212
3 – back	33	28	0	1	62
4 – one side	0	0	294	318	612
5 – both sides	45	38	0	0	83
6 – one temple	0	0	66	66	132
7 – other	21	13	25	25	84
Total	**271**	**236**	**389**	**413**	**1309**

4.1.3 Throbbing

The distribution of headaches according to character of the pain is shown in Table 8.

Table 8: Distribution of Headache Character

Headache Character Code	Study 22 (N=660)	Study 30 (N=649)	Total
Missing	1	0	1
1 – throbbing/pulsing	395	371	766
2 – pierce/stab	92	102	194
3 – press/tight	163	164	327
4 – other	9	12	21

The same situation arose with headache character as with headache location. There were some patients in the other categories that included "throbbing" in the text descriptor of headache character. There were only 25 such instances where a separate text descriptor was provided. The distribution of throbbing headaches, including patients who provided a descriptor of "throbbing" in other categories, is shown in Table 9. One patient with piercing/stabbing headache also described throbbing pain as well, and 11 patients classifying their headache character as "other" also included throbbing in their description of the pain. In total, 778 (400 in study 22, and 378 in study 30) had at least some throbbing to their headache.

Table 9: Distribution of Throbbing Headaches

Character Code	Non-throbbing		Throbbing		Total
	Study 22	Study 30	Study 22	Study 30	
Missing	1	0	0	0	1
1 – throbbing/pulsing	0	0	395	371	766
2 – pierce/stab	92	101	0	1	194
3 – press/tight	163	164	0	0	327
4 – other	4	6	5	6	21
Total	**260**	**271**	**400**	**378**	**1309**

4.1.4 Moderate/Severe

All patients classified their headache as either moderate or severe in intensity. The distribution of baseline pain is shown in Table 10.

Table 10: Distribution of Baseline Pain

Pain Code	Study 22 (N=660)	Study 30 (N=649)	Total (N=1309)
2 – moderate	456	454	910
3 – severe	204	195	399

4.1.5 Effect of Regular Activity

As stated before, the sponsor did not provide information regarding the effect of regular physical activity on the headache.

4.1.6 Nausea/Vomiting

Nausea at baseline was rated as none, mild, moderate, or severe. The distribution of nausea is shown in Table 11. A total of 734 patients reported nausea at baseline (372 in study 22 and 362 in study 30).

Table 11: Distribution of Nausea

Nausea Code	Study 22	Study 30	Total
Missing	2	1	3
0 – none	286	286	572
1 – mild	219	218	437
2 – moderate	121	126	247
3 – severe	32	18	50
Total	**660**	**649**	**1309**

Nausea	Study 22	Study 30	Total
Absent or Missing	288	287	575
Present	372	362	734
Total	**660**	**649**	**1309**

The number of patients experiencing vomiting at baseline was small. The distribution of vomiting is shown in Table 12.

Table 12: Distribution of Vomiting

Vomiting	Study 22	Study 30	Total
Absent or Missing	644	634	1278
Present	16	15	31
Total	**660**	**649**	**1309**

4.1.7 Photophobia

Photophobia was rated as none, mild, moderate, or severe. The distribution of photophobia is shown in Table 13. The vast majority had photophobia at baseline.

Table 13: Distribution of Photophobia

Photophobia Code	Study 22	Study 30	Total
Missing	0	1	1
0 – none	28	31	59
1 – mild	157	169	326
2 – moderate	328	315	643
3 – severe	147	133	280
Total	**660**	**649**	**1309**

Photophobia	Study 22	Study 30	Total
Absent or Missing	28	32	60
Present	632	617	1249
Total	**660**	**649**	**1309**

4.1.8 Phonophobia

Phonophobia was also rated as none, mild, moderate, or severe. The distribution of phonophobia is shown in Table 13. The vast majority also had photophobia at baseline.

Table 14: Distribution of Phonophobia

Phonophobia Code	Study 22	Study 30	Total
Missing	0	0	0
0 – none	52	64	116
1 – mild	202	212	414
2 – moderate	286	278	564
3 – severe	120	95	215
Total	**660**	**649**	**1309**

Phonophobia	Study 22	Study 30	Total
Absent or Missing	52	64	116
Present	608	585	1193
Total	**660**	**649**	**1309**

4.2 MIG1 – Definite Migraine using "Modified IHS Criteria"

Having identified the distribution of each migraine characteristic described above (while using more exhaustive searches for unilateral and throbbing pain) I was able to select headaches who met the modified IHS criteria for migraine.

As already mentioned before, 320 patients experienced an aura with their headaches and are automatically classified as having migraine.

The distribution of patients who met criteria 1.1c (at least 2 of throbbing, unilateral, mod/sev, aggravated by routine physical activity) is shown in Table 15. Since aggravation by physical activity was not collected, I only used the first three migraine characteristics for the analysis. A total of 1097 headaches (545 in study 22, and 552 in study 30) fulfilled criterion 1.1c using this algorithm.

Table 15: Distribution of Headaches Meeting Criterion 1.1c

Criterion 1.1c	Study 22	Study 30	Total
Not Met	115	97	212
Met	545	552	1097
Total	**660**	**649**	**1309**

The distribution of patients who met criterion 1.1d (either nausea/vomiting or photohobia+phonophobia) is shown in Table 16. The vast majority of headaches met this criterion.

Table 16: Distribution of Headaches Meeting Criterion 1.1d

Criterion 1.1d	Study 22	Study 30	Total
Not Met	37	44	81
Met	623	605	1228
Total	**660**	**649**	**1309**

For purposes of this analysis, the definite migraine population comprised patients who had an aura, or met criteria c and d. The distribution is shown in Table 17.

Table 17: MIG1 - Distribution of Definite Migraines

Migraine Type	Study 22	Study 30	Total
Not Definite	109 (16.5%)	100 (15.4%)	209 (16%)
Definite	551 (83.5%)	549 (84.6%)	1100 (84%)
Total	**660**	**649**	**1309**

Migraine Type	Study	PBO	200mg	400mg	Total
Definite	22	188	179	184	551
Migraine	30	182	182	185	549
Total		**370**	**361**	**369**	**1100**

It shows that 84% of the headaches treated in both studies are "definite migraines" using this classification method. It is slightly higher than the 80% which I originally described

in my efficacy review due to the more exhaustive search for unilateral and throbbing headaches.

4.3 MIG2 – Definite Migraine, Using Functional Ability Rating Scale

I use the same modified IHS criteria to define the MIG2 population, and use baseline functional ability = 2 or 3 (moderate/severe impairment) as a way to identify those patients whose headache may have been aggravated by routine physical activity.

I admit that it is imperfect to use the functional ability rating as a substitute for the true measure in question. I make the assumption (which may or may not be true) that patients who are moderately/severely impaired by their headache, and who, by definition of their functional disability, have limited or interrupted routine physical activity, have done so in part, or in whole, because the physical activity aggravated the pain.

I should point out that the IHS 1.1c criteria, which requires two of the following:

- unilateral
- pulsating
- moderate or severe (inhibits or prohibits daily activities)
- aggravation by walking stairs or similar routine physical activity

includes in the description for "moderate and severe" pain: "inhibits or prohibits daily activities." It can be argued that a functional impairment rating of 2 or 3 merely supports the finding that the pain is moderate/severe and therefore should not be used to judge the presence or absence of the last characteristic. Since the sponsor collected pain severity and functional impairment separately, it does not necessarily follow that just because a headache was rated as moderate or severe, that the functional impairment was also rated as moderate or severe. In fact, the distribution of functional impairment rating, grouped by pain intensity, is shown in Table 18.

Table 18: Distribution of Functional Impairment Rating, grouped by Pain Intensity

Baseline Pain	Functional Impairment	Study 22	Study 30	Total
Moderate	Missing	1	1	2
	0 – none	20	14	34
	1 – mild	164	195	359
	2 – moderate	263	239	502
	3 – severe	8	5	13
Severe	Missing	0	0	0
	0 – none	2	1	3
	1 – mild	19	20	39
	2 – moderate	98	101	199
	3 – severe	85	73	158
Total		**660**	**649**	**1309**

As one can see from the table, it does not necessarily follow that simply because a patient experienced a moderate/severe headache, that functional impairment was also

moderate/severe. Therefore, I think use of moderate/severe impairment as a substitute (albeit imperfect) for pain aggravated by physical activity, is reasonable.

The distribution of patients meeting IHS criterion 1.1c, using this additional parameter, is shown in 13. When compared to Table 15, on page 11, an additional 143 patients meet the criterion (1240 – 1097)

Table 19: Distribution of Headache Meeting Criterion 1.1c (Using Functional Ability Scale)

Criterion 1.1c	Study 22	Study 30	Total
Not Met	36	33	69
Met	624	616	1240
Total	**660**	**649**	**1309**

(Table 15, page 11 is shown below for comparison, which does not use the functional impairment scale)

Criterion 1.1c	Study 22	Study 30	Total
Not Met	115	97	212
Met	545	552	1097
Total	**660**	**649**	**1309**

The MIG2 population is shown in Table 20. When compared to the MIG1 population shown on Table 17, page 11, an additional 99 patients are included (1199 – 1100), comprising almost 92% of the total.

Table 20: MIG2 – Distribution of Definite Migraines (Using Functional Impairment Scale)

Migraine Type	Study 22	Study 30	Total
Not Definite	54 (8.2%)	56 (8.6%)	110 (8.4%)
Definite	606 (91.8%)	593 (91.4%)	1199 (91.6%)
Total	**660**	**649**	**1309**

Migraine Type	Study	PBO	200mg	400mg	Total
Definite	22	205	201	200	606
Migraine	30	195	197	201	593
Total		**400**	**398**	**401**	**1199**

(Table 17, page 11 is shown below for comparison, which does not use the functional impairment scale)

Migraine Type	Study 22	Study 30	Total
Not Definite	109 (16.5%)	100 (15.4%)	209 (16%)
Definite	551 (83.5%)	549 (84.6%)	1100 (84%)
Total	**660**	**649**	**1309**

Migraine Type	Study	PBO	200mg	400mg	Total
Definite	22	188	179	184	551
Migraine	30	182	182	185	549
Total		**370**	**361**	**369**	**1100**

4.4 Efficacy Results

This section contains the efficacy results for each subgroup (MIG1, MIG2) for each study. I performed the following four efficacy analyses:

- Proportion of headache responders at 2 hours (2-hr headache response rate)
- Proportion having nausea at 2 hours
- Proportion having photophobia at 2 hours
- Proportion having phonophobia at 2 hours

I include overall comparisons, and pairwise comparisons vs. placebo for the 2-hour time point. I used a Cochran-Mantel-Haenszel test stratified by baseline pain intensity for headache response, and chi-square for the other three. I used a last post-treatment observation carried forward (LOCF) approach to impute missing data.

4.4.1 MIG1 Population

The MIG1 population, as defined, comprises 84% of the ITT population. The baseline distribution of nausea, photophobia, and phonophobia for this subgroup is shown in Table 21. No significant baseline imbalances were noted, with the possible exception of photophobia in study 22. However, this is not clinically significant with incidences of ≥97% in all three treatment arms.

Table 21: MIG1 – Migraine Associated Symptoms at Baseline

Symptom	200mg	400mg	PBO	p*
Study 22	**n=(179)**	**(n=184)**	**(n=188)**	
Nausea	110 (61%)	106 (58%)	111 (59%)	0.753
Photophobia	178 (99%)	178 (97%)	187 (99%)	0.053
Phonophobia	168 (94%)	178 (97%)	179 (95%)	0.424

Symptom	200mg	400mg	PBO	p*
Study 30	**(n=182)**	**(n=185)**	**(n=182)**	
Nausea	114 (63%)	113 (61%)	100 (55%)	0.288
Photophobia	179 (98%)	184 (99%)	178 (98%)	0.355
Phonophobia	169 (93%)	175 (95%)	167 (92%)	0.552

* chi-square for overall comparison

The 2-hour efficacy results are shown in Table 22. This analysis showed nominally significant p values for 2-hour headache response rates in both studies in favor of drug. Only photophobia in study 30 showed drug-associated nominally significant effects compared with placebo.

Table 22: MIG1 – Two-Hour Efficacy Results

Symptom	Study 22				Study 30			
	200 mg (n=179)	400 mg (n=184)	PBO (n=188)	p*	200 mg (n=182)	400 mg (n=185)	PBO (n=182)	p*
Response Rate, n (%)	71 (40) p=0.032	70 (38) p=0.036	54 (29)	0.031	70 (38) p=0.003	73 (40) p=0.004	47 (26)	0.004
Nausea, present (%)	81 (45) p=0.688	75 (41) p=0.201	89 (47)	0.427	86 (47) p=1.000	86 (46) p=0.883	86 (47)	0.986
Photophobia, present (%)	142 (79) p=0.147	148 (80) p=0.232	160 (85)	0.304	142 (78) p=0.018	143 (77) p=0.011	159 (87)	0.020
Phonophobia, present (%)	129 (72) p=0.983	137 (74) p=0.138	152 (81)	0.120	137 (75) p=0.205	131 (71) p=0.027	147 (81)	0.082

* overall p values: p value for response rate is Cochran-Mantel-Haenszel stratified by baseline intensity; for other analyses is chi-square; other p values in individual cells are pairwise comparison with placebo.

4.4.2 MIG2 Population

The MIG2 population, as defined, comprises approximately 92% of the ITT population. The baseline distribution of nausea, photophobia, and phonophobia for this subgroup is shown in Table 23. No significant baseline imbalances were present.

Table 23: MIG2 – Migraine Associated Symptoms at Baseline

Symptom	200mg	400mg	PBO	p*
Study 22	**(n=201)**	**(n=200)**	**(n=205)**	
Nausea	124 (62%)	117 (58%)	120 (59%)	0.754
Photophobia	199 (99%)	194 (97%)	204 (99%)	0.096

Symptom	200mg	400mg	PBO	p*
Phonophobia	189 (94%)	194 (97%)	195 (95%)	0.342
Study 30	**(n=197)**	**(n=201)**	**(n=195)**	
Nausea	121 (61%)	120 (60%)	108 (55%)	0.458
Photophobia	194 (98%)	200 (99%)	190 (97%)	0.215
Phonophobia	184 (93%)	190 (95%)	179 (92%)	0.555

* chi-square for overall comparison

The 2-hour efficacy results are shown in Table 24. This analysis showed nominally significant p values for 2-hour headache response rates in both studies in favor of drug. As in the analysis in the MIG1 population, only photophobia in study 30 showed drug-associated nominally significant effects compared with placebo.

Table 24: MIG2 – Two-Hour Efficacy Results

Symptom	Study 22				Study 30			
	200 mg (n=201)	400 mg (n=200)	PBO (n=205)	p*	200 mg (n=197)	400 mg (n=201)	PBO (n=195)	p*
Response Rate, n (%)	81 (40) p=0.007	82 (41) p=0.004	56 (27)	0.007	77 (39) p=0.005	80 (40) p=0.008	53 (27)	0.006
Nausea, present (%)	92 (46) p=0.755	78 (39) p=0.091	97 (47)	0.200	90 (46) p=0.767	92 (46) p=0.779	92 (47)	0.946
Photophobia, present (%)	159 (79) p=0.213	162 (81) p=0.442	172 (84)	0.454	151 (77) p=0.006	158 (79) p=0.023	170 (87)	0.016
Phonophobia, present (%)	146 (73) p=0.061	149 (74) p=0.149	165 (80)	0.148	147 (75) p=0.162	143 (71) p=0.030	157 (81)	0.089

* overall p values: p value for response rate is Cochran-Mantel-Haenszel stratified by baseline intensity; for other analyses is chi-square; other p values in individual cells are pairwise comparison with placebo.

5. Discussion

In my original review, I performed an analysis of a subgroup of the ITT population which I determined experienced and treated a "definite migraine" based on modified IHS criteria. This algorithm classified 80% of the headaches treated in both studies as being "definite migraines." I have used this same algorithm in two other applications and have successfully classified ≥96% of headaches treated as "definite migraine" in those sNDA's (Excedrin and Advil Liquigel).

Although the primary analyses were positive in both studies (2-hour pain response in the ITT population), I concluded that Motrin Migraine was effective in the treatment of

headache in a population of migraine sufferers because the subgroup analysis of "definite migraine" failed to demonstrate a nominally significant treatment effect in study 22.

The analyses of the secondary symptoms, both in the ITT population, and in the subgroup analysis, failed to show nominally significant drug-associated treatment effects on the migraine associated symptoms of nausea, photophobia, and phonophobia. Therefore, the drug has not been established as a treatment of migraine for this other reason as well.

In my review, I also admitted that the subgroup of "definite migraine" was an underestimate of the true percentage of migraine headaches treated. This is because information regarding the effect of routine physical activity on the headache was not captured in the headache diary or case report form. The sponsor confirms this in the response to our comments. They also correctly point out that the estimate was also low because I failed to include some patients who described pain in one temple. These were coded separately in the datasets. They also point out that patients were asked to perform a self-administered and self-rated questionnaire prior to treatment of the headache in order to verify that the headache treated was a migraine. Patients were also asked whether their headache was typical of their usual migraine, and 97% responded in the affirmative.

Migraine studies, by their nature, rely completely on subjective data for interpretation, since there is no objective measure of a migraine, or of its severity. There are global measures (*e.g.*, is this headache typical of your usual migraine?), and there are more "symptom-specific" measures (*e.g.*, is the headache unilateral? Is the headache throbbing?). I believe that using symptom-specific measures to identify a migraine is preferable, since they resemble more closely the IHS established guidelines for migraine diagnosis. It is for this reason, that I have chosen not to rely on the analysis of the 97% of patients who reported treating a "typical migraine," as provided by the sponsor in their response.

Instead, in this review, I have provided details of a more exhaustive search for "definite migraines" while at the same time, allowing application of the same modified IHS criteria for migraine diagnosis. I have identified two subgroups, one comprising 84% of the ITT population (designated as MIG1) and the other comprising approximately 92% of the ITT population (designated as MIG2). In my analyses of the 2-hour headache response rates in these subgroups, both studies show nominally significant drug-associated treatment effects when compared to placebo. I have asked our biostatistician, Dr. Kallappa Koti, to repeat these subgroup analyses. His analyses differ from mine in that he, like the sponsor, [redacted] His findings are, however, similar to mine. Although Dr. Koti's analyses fail to show nominally significant drug-associated treatment effects on severe pain (pain intensity = 3), the numbers are directionally in favor of drug and I think this may simply be a power issue. I agree with Dr. Koti's comment that it "unscientific" to use the results of these subgroup analyses for statistical inference; however, I do believe the results are useful to better interpret the results of the

[1] I chose not to do so because the sponsor had already provided an analysis in the original NDA showing that inclusion or exclusion of this site from the analysis had no effect on the study's outcome.

protocol-specified primary analyses in both studies. I conclude, therefore, that Motrin Migraine is effective in the treatment of migraine headache pain.

Both my and Dr. Koti's analyses of the secondary symptoms in these subgroups once again fail to reveal consistent and reproducible drug-associated nominally significant treatment effects on nausea, photophobia, and phonophobia. Therefore, I still cannot conclude that Motrin Migraine is an effective treatment of migraine, the syndrome.

It remains for discussion whether the pain of migraine is a valid indication for approval. Certainly, at one time, Excedrin Migraine was approved for this indication, but with the recent approval of the Excedrin NDA supplement for the treatment of migraine, there is no other drug now on the market that has this indication. There is some reason to believe that having separate drugs on the market for the treatment of migraine and for the treatment of the pain of migraine is confusing and should be avoided. Since Motrin is a known and approved analgesic, it seems to make little sense to approve a product for one type of pain (resulting in a "pseudo-specific" claim), when essentially the same product is already approved for the treatment of pain in general. This issue will be addressed more fully by the Division of OTC.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. /S/

See my memo

ao 12/29/99
cc:
HFD-120
NDA 19-012
electronic copy-Levin

MEDICAL OFFICER'S SAFETY REVIEW UPDATE
Division of Over-The-Counter Drug Products

NDA #: 19-012, S016
NAME: MOTRIN® IB Tablets/Caplets
SPONSOR: McNeil Consumer Healthcare
7050 Camp Hill road
Fort Washington, PA 19034-2299
TYPE OF SUBMISSION: Commercial Pharmaceutical
DATE OF SUBMISSION: February 26, 1999 **CDER:** February 26, 1999
Addendum: September 22, 1999
DATE OF REVIEW: November 29, 1999
REVIEWER: Rosemarie Neuner, MD, MPH
PM: Mr. Kerry Rothschild, JD

Background

This medical officer review is a safety profile update of MOTRIN® IB (ibuprofen) Tablets/Caplets that was done as part of the agency's overall review of McNeil Consumer Healthcare's supplemental submission NDA 19-012, S016 in which they request a new migraine indication for this product. Ibuprofen, a member of the nonsteroidal anti-inflammatory class of drugs, has been available in the U.S. as an over-the-counter (OTC) analgesic since 1984. It is indicated for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever. The recommended dose of OTC ibuprofen is 200 mg tablets/caplets every 4-6 hours. If symptoms persist, 2 (400 mg) tablets/caplets may be taken. The maximum total daily dosage of OTC ibuprofen is 1200 mg, or 6 tablets/caplets in a 24-hour period.

In support of this application, the sponsor has submitted for agency review the following safety information:

1. The clinical trial safety database for the 2 randomized, placebo-controlled, single-dose migraine efficacy studies submitted in support of this application (Protocols 97-022 and 97-030).

2. The results of a literature search of published randomized clinical trials which studied single-ingredient ibuprofen in the treatment of migraine headache for the period from 1966 through September 30, 1998.

3. Postmarketing adverse event data collected by the McNeil Drug Safety Reporting System for all single-ingredient McNeil and other OTC adult strength ibuprofen products (i.e., Motrin® IB, Arthritis Foundation™, Haltran®, Nuprin®, Medipren®, Excedrin® IB, and unknown OTC ibuprofen brands) for the 5-year

period of October 1, 1993 through September 30, 1998.

4. A summary of ibuprofen overdose case reports from the McNeil Drug Safety Reporting System for the 5-year period of October 1, 1993 through September 30, 1998 for the sponsor's OTC adult ibuprofen products. Included in this data are case reports that were published in the literature.

5. Additional postmarketing reports of Central Nervous System (CNS) toxicity or serious CNS adverse events (e.g., subarachnoid hemorrhages, strokes, seizures and meningitis) collected by the McNeil Drug Safety Reporting System and by the FDA's Spontaneous Reporting System (SRS) associated with the use of 200 mg and 400 mg doses of ibuprofen. (Note: This information was submitted to the application on September 22, 1999 in response to a request for additional information made by the agency's OTC reviewer.)

6. Postmarketing reports of bleeding diathesis collected by the McNeil Drug Safety Reporting System and by the FDA's Spontaneous Reporting System (SRS) associated wtih the use of 200 mg and 400 mg doses of ibuprofen. (Note: This information was submitted to the application on September 22, 1999 in response to a request for additional information made by the agency's OTC reviewer.)

Since a review of the clinical trial safety database contained in this submission can be found in the medical officer's efficacy review dated 8/18/99 by Dr. Armando Oliva of HFD-120, this safety profile update will focus on the remaining 5 sources of safety data as listed above and summarized in Sponsor's Table 8.7-1 found on the following page.

Table 8.7-1. Summary of OTC Ibuprofen Safety Data Included in Motrin® Migraine SNDA

McNeil Pivotal Controlled Clinical Studies (Protocol 97-022 and 97-030)		
Migraine Studies	(Total Patients)	1309
Total Ibuprofen Exposures		874
Reports of AE with serious outcomes[a]		0
Death		0
Published Randomized Controlled Studies (first study published in 1983)		
Migraine Studies	(Total Patients)	477
Total Ibuprofen Exposures		245
Reports of serious AE[b]		0
Death		0

• Use for Migraine			
Reports of AE - other than FDA subgroups			12
Reports with serious outcome[c]	1		
Death	0		
Reports of AE - FDA subgroups			0
Hepatic system		0	
Reports with serious outcome	0		
Death	0		
Gastrointestinal bleeding		0	
Reports with serious outcome	0		
Death	0		
Kidney failure		0	
Reports with serious outcome	0		
Death	0		
Concomitant alcohol use or abuse		0	
Reports with serious outcome	0		
Death	0		
• Uses Other Than Migraine			
Reports of AE - other than FDA subgroups			1220
Reports with serious outcome[c]	37		
Death	2		
Reports of AE - FDA subgroups			53
Hepatic system		7	
Reports with serious outcome	4		
Death	0		
Gastrointestinal bleeding		28	
Reports with serious outcome	12		
Death	1		
Kidney failure		14	
Reports with serious outcome	12		
Death	0		
Concomitant alcohol use or abuse		6[d]	
Reports with serious outcome	3		
Death	0		

a: Serious adverse event: a definite hazard or handicap to the subject, which includes those events defined as a serious outcome. For Table 8.7-1, a report of death is listed separately from other serious outcomes.

b: Serious as defined by the investigator.

c: Serious outcome: adverse event that is life-threatening, requires inpatient or prolonged hospitalization, intervention to prevent permanent impairment or damage, or is permanently or severely disabling. Outcomes of death, congenital anomaly, or cancer are also considered serious.

d: Two concomitant alcohol use reports are both listed in the alcohol use and gastrointestinal FDA subgroups.

I. Published randomized controlled clinical studies of migraine headache using single-ingredient ibuprofen for the period of 1966 through September 1998.

In support of OTC ibuprofen's safety profile the sponsor submitted the following 5 articles and abstracts that were identified via a worldwide literature search during the period of 1966 through September 1998:

1. Nebe J, Heier M, Diener HC. Low-dose ibuprofen in self-medication of mild to moderate headache: A comparison with acetylsalicylic acid and placebo. Cephalalgia 1996; 16:231-238.
2. Hamalainen ML, Hoppu K, Vqalkeila E, et al. Ibuprofen or acetaminophen for the acute treatment of migraine attacks in children: A double-blind, randomized, placebo-controlled, crossover study. Neurology 1997; 48:103-107.
3. Hamalainen ML, Hoppu K, Santavuori P. Ibuprofen or acetaminophen for acute treatment of migraine attacks in children: A double-blind, randomized, placebo-controlled, crossover study. Cephalalgia 1995;15:260 (abstract).
4. Hoernecke R, Doenicke A, Roizen MF, et al. Ibuprofen alone in the treatment of migraine. Anesthesiology 1993; 79:A837 (abstract).
5. Pearce I, Frank GJ, Pearce JMS. Ibuprofen compared with paracetamol in migraine. Practitioner 1983: 227:465-467.

These 5 citations describe the results from 4 randomized, placebo-controlled clinical trials of single-ingredient ibuprofen versus acetaminophen, aspirin or dihydroergotamine in the treatment of migraine headache pain in adults and children 12 years and older. (Note: The 2 citations by Hamalainen et al, describe the same study. A complete listing of the citations along with study summaries can be found in Attachment I at the end of this review.) Approximately 245 subjects with migraines were treated in these studies with single or multiple doses of 200 mg or 400 mg of ibuprofen. The total maximum daily dose of ibuprofen in each study did not exceed 1200 mg. (Refer to Attachment I for additional study information.) No serious adverse events or deaths were reported to have occurred in any of the 4 studies. Although the study by Nebe et al, did not report any ibuprofen-related adverse events, the remaining 3 studies reported low incidences of nonserious adverse events (nausea, vomiting, gastric pain, drowsiness and weakness) during the trials, which were similar to that of the control and active comparator groups. (See Attachment I for further information.)

Medical Reviewer's Comments: The nonserious adverse events reported to have occurred in these trials is consistent with OTC ibuprofen's current safety profile.

II. Postmarketing adverse event data collected by the McNeil Drug Safety Reporting System for all single-ingredient McNeil and other OTC adult strength ibuprofen products (i.e., Motrin® IB, Arthritis Foundation™, Haltran®, Nuprin®, Medipren®, Excedrin® IB, and unknown OTC ibuprofen brands) for the 5-year period of October 1, 1993 through September 30, 1998.

The sponsor estimates during the 5-year period for October 1, 1993 through September 30, 1998 that they sold 7.1 billion 200 mg strength tablets of OTC adult ibuprofen. As shown in the preceding table, Sponsor's Table 8.7-1, there were a total of 1,285 adverse event reports associated with the use of OTC adult ibuprofen collected by the McNeil Drug Safety Reporting System for OTC ibuprofen products marketed by the sponsor. To ease the reviewing process, the sponsor was requested to organize the submitted postmarketing adverse event data into reports associated with the use of ibuprofen for the treatment of migraine versus other uses, and then by the following 4 subcategories: hepatotoxicity, kidney failure, gastrointestinal bleeding, and concomitant alcohol use or abuse. Each of these subgroups are discussed separately in this section. (Note: In preparing this section of the supplement in support of OTC ibuprofen's safety profile, the sponsor did not query the FDA's Spontaneous Reporting System for adverse event reports that were called in directly to the agency's Medwatch program for McNeil OTC ibuprofen products, or for adverse event reports associated with OTC ibuprofen manufactured by other sponsors. Some of the case reports collected by the sponsor were published literature reports of adverse events where the brand of OTC ibuprofen used was unknown. Thus, the postmarketing data reviewed in this safety profile update is not a true reflection of the magnitude of adverse events and drug-related toxicity for OTC ibuprofen overall.)

IIA. Adverse event reports in individuals who used OTC ibuprofen to treat migraines:

Twelve (12) out of the 1,285 adverse event reports occurred in individuals who used OTC ibuprofen to treat migraines. (See Sponsor's Table 8.7-1.) Only 1 out of these 12 adverse event reports resulted in a serious outcome. This occurred in a 29-year old female (MR0981094A) who was hospitalized after developing severe headache pain after taking two 400 mg doses of Nuprin over an 8-hour period of time. During the 2 years prior to this event, she had reportedly been taking 2 Nuprin tablets once to twice a day as needed for the relief of regular headache pain and dysmenorrhea. On the basis of clinical physical findings, lumbar puncture results and repeat negative bacterial cultures, this individual was diagnosed as having aseptic meningitis which her physicians attributed to ibuprofen.

Sponsor's Table 8.7-24, shown in Attachment II at the end of this review, summarizes the remaining 11 reports of nonserious adverse events associated with the use ibuprofen in the treatment of migraine which include the following reactions: lack of efficacy (6), overdose (3), amblyopia (1), and constipation (1).

IIB. Adverse event reports associated with McNeil OTC ibuprofen products for non-migraine uses:

As noted in the preceding table, Sponsor's Table 8.7-1, there were 1,220 reports of adverse events associated with the use of the sponsor's OTC ibuprofen during the period of October 1, 1993 through September 30, 1998. Thirty-seven (37) out of the

1,220 reports were classified as serious and included 2 deaths. Sponsor's Table 8.7-28 found in Attachment III of this review summarizes these 37 ibuprofen-associated serious case reports. The COSTART systems most commonly cited in these cases were: body as a whole (36), nervous system (19), digestive system (16), cardiovascular system (9), metabolic and nutritional disorders (6), hemic and lymphatic system (5), and respiratory system (2). (Note: Some of these serious case reports listed more than 1 event, and thus were counted more than once.)

Of the 2 ibuprofen-associated deaths, 1 occurred in a 78 year-old male (MR326/154) with a diagnosis of arthritis on systemic steroid treatment who had been taking ibuprofen 200 mg as needed for 9 months. He developed convulsions with delirium following the ingestion of 200 mg of ibuprofen for a headache; was hospitalized and subsequently died. The cause of death was listed as unknown. The other death was generated from foreign postmarketing data and involved a 40-year-old female (MR0516874A) with a history of childhood asthma, but no history of drug (aspirin) allergy or nasal polyps, who took two (2) 200-mg tablets of ibuprofen for a toothache. Immediately post-ingestion of the ibuprofen, this individual developed an asthma attack and started to treat herself with fenoterol and inhaled steroids without success. Intramuscular steroids failed to improve her bronchospasms which continued to worsen until she lost consciousness and had a respiratory arrest. Attempts to resuscitate her in the local emergency room failed. She subsequently died due to acute respiratory failure. Findings on autopsy were consistent with acute emphysema, scattered edema of the lung, with thickening of bronchial walls and mucus plugging.

IIC. Adverse event reports for the subcategories of hepatotoxicity, kidney failure, gastrointestinal bleeding, and concomitant alcohol use or abuse.

Hepatoxicity -

As noted in Sponsor's Table 8.7-1, shown above, there were a total of 7 case reports of adverse events related to the hepatic system collected by the sponsor. Four (4) out of the seven reports were classified as serious while the remaining 3 were nonserious in nature. Although none of the serious cases died, or required an emergent liver transplantation, 3 out of the 4 serious hepatotoxicity cases had to be hospitalized due to elevated liver function tests. These 4 cases are summarized in the listing prepared by the sponsor, Sponsor's Table 8.7-32, found in Attachment IV of this review. (Note: Only 1 of these 4 cases of hepatotoxicity was reported directly to the sponsor by a physician; the remaining 3 cases were case reports published in the literature.) Of the 4 serious hepatic cases, 1 case was due to an intentional overdose (MR1031739A), another case (MR1040922A) involved a 44-year-old male with chronic active hepatitis, the third case was an 8-year-old female (MR314/154) with a concomitant viral illness who developed cholestatic jaundice with symptoms of serum sickness following the use of 200 mg of ibuprofen 4-5 times a day for a few days, while the fourth case involved a 29-year-old male (MR0633909A) who developed cholastatic jaundice with documented vanishing bile duct syndrome on subsequent liver biopsy

after taking 200 mg of ibuprofen three times a day for 3 weeks. Although there was no concomitant use of alcohol in the first 2 cases, this information was reported to be unknown in the latter 2 cases. (Refer to Sponsor's Table 8.7-32 in Attachment IV for further information.)

Sponsor's Table 8.7-34 in Attachment IV located at the end of this review lists the 3 remaining nonserious cases of OTC ibuprofen toxicity which included elevated liver enzymes, jaundice and drug-induced hepatitis. The results of viral hepatitis testing in these 3 cases was not included in the information submitted by the sponsor. In addition, the use of concomitant alcohol was reportedly unknown in 2 (MR660/19012 and MR597/154) out of the 3 cases. (See Sponsor's Table 8.7-34 found in Attachment IV for additional information.)

Gastrointestinal Bleeding -

As demonstrated on Sponsor's Table 8.7-1, shown above there were 28 case reports of gastrointestinal (GI) bleeding submitted by the sponsor in support of OTC ibuprofen's safety profile. Thirteen (13) of these reports were classified as serious while the remaining 15 reports were listed as nonserious in nature. [Note: The 13 case reports were collected from a variety of sources: published literature (3), healthcare providers (2), consumers (5), and an attorney (1).] A summary table, Sponsor's Table 8.7-36, of the 13 serious GI bleeding cases associated with the use of OTC ibuprofen which can be found at the end of this review in Attachment IV. Only 1 case out of the 13 serious GI bleeding cases resulted in the death of the individual. An unknown adult male (MR0934619A) who ingested an unspecified dose of OTC ibuprofen over 24 hours, for relief of a work-related injury was hospitalized due to a GI bleed secondary to gastric ulceration. This individual reportedly died after developing hepatic encephalopathy and liver failure. No additional background information regarding the use of alcohol or pre-existing liver disease was contained in the case report submitted for review. (See Sponsor's Table 8.7-36 located in Attachment IV.) Although the current labeling for OTC analgesics carries a warning against concomitant alcohol use, 2 (MR0184804A and MR738/19012) out of the 13 serious GI bleeding cases reportedly used alcohol. One GI bleeding case (MR-581/1540) reportedly was taking an anticoagulant, warfarin, while another case was taking aspirin (MR0782985A) which increased the risk for developing a GI bleed. In 6 of the serious cases, the individuals deveioped GI bleeding after ingesting 1 or 2 doses of OTC ibuprofen or within the recommended limited duration of use for the product. The duration of product use was unknown in 5 cases, and only 2 cases took OTC ibuprofen longer than recommended. (Refer to Sponsor's Table 8.7-36 found in Attachment IV.)

Of the remaining 15 nonserious GI bleeding cases associated with the use of OTC ibuprofen listed in Sponsor's Table 8.7-38 shown in Attachment IV, the concomitant use of alcohol was reportedly unknown. In 3 (MR387/154, MR1162/19012, and MR1191/19012) of these 15 cases of nonserious GI bleeding were individuals taking other aspirin containing products that increased their risk for developing a GI bleed despite the existing consumer warning on the products' labels. In 8 out of these 15 nonserious GI bleed cases, the amount and duration of ibuprofen

ingested was listed as unknown. Of the remaining 7 cases, only 2 cases (MR428/154 and MR1255/19012) exceeded the recommended dose and duration of use of the product. (See Sponsor's Table 8.7-38 in Attachment IV.)

Renal Failure -

There were a total of 14 case reports of renal failure associated with the use of OTC ibuprofen. (Refer to the preceding Sponsor's Table, Sponsor's Table 8.7-1, shown above.) Twelve (12) out of the 14 case reports were considered to be serious in nature. [Note: Ten (10) of these 12 serious case reports were from the published literature. Of the remaining 2 case reports, 1 was reported to the sponsor by a healthcare provider, while the other was reported to the sponsor by a consumer.] The 12 cases of serious renal toxicity which are summarized in the sponsor's table, Sponsor's Table 8.7-40, located at the end of this review in Attachment IV include the following: acute renal failure (3 cases), membranous nephropathy (3 cases), and renal dysfunction (6 cases). None of these individuals who developed serious renal toxicity from ibuprofen died, and all recovered once the drug was discontinued. Very limited background information was contained in the reports submitted by the sponsor for review regarding other risk factors for renal failure such as concomitant hypertension (MR356/154), diabetes, or use of diuretics or other nephrotoxic drugs. Although 4 (MR1238/19012, MR0683683A, MR0790207A, and MR0392412A479/154) of the 12 cases of renal toxicity were due to overdoses of ibuprofen, and 1 case (MR0823635A623/154) occurred in an individual who had rhabdomyolysis, no other risk factor other than prolonged duration of use of ibuprofen could be identified in the majority of these cases. (Refer to Sponsor's Table 8.7-40 in Attachment IV.)

Sponsor's Table 8.7-42 found in Attachment IV summarizes the 2 nonserious cases of renal toxicity. Again, the reports submitted in both of these cases contained limited information for review. (See Sponsor's Table 8.7-42 in Attachment IV.)

Concomitant Alcohol Use or Abuse -

There were a total of 6 case reports of concomitant alcohol use or abuse as listed in the preceding table, Sponsor's Table 8.7-1. Three (3) of these 6 cases were classified as serious, while the remaining 3 cases were considered to be nonserious in nature. None of these 3 serious cases died due to the concomitant use of alcohol and ibuprofen. (Note: A summary table of these 3 case reports, Sponsor's Table 8.7-44, can be found in Attachment IV at the end of this review.) Two of the serious case reports (MR0184804A and MR738/19012) developed GI bleeding and are also found under that subcategory. (Refer to the above section on Gastrointestinal Bleeding.) The third case (MR906/19012) involved a newborn male who developed tonic-clonic seizure activity immediately post-birth. The infant's mother reportedly took ibuprofen during the last trimester of pregnancy due to back spasms, while continuing to smoke cigarettes and having minimal alcohol ingestion. The infant was subsequently diagnosed as having microcephaly on MRI, with an abnormal EEG consistent with permanent brain damage, spastic quadriparesis and delayed motor skills. The etiology of the infant's

brain damage ranged from cord compression, nonketotic hyperglycemia, or because of premature closure of the ductus arteriosus due to the use of ibuprofen during the last trimester of pregnancy. (Refer to Sponsor's Table 8.7-44 in Attachment IV for additional information.)

The remaining 3 nonserious cases of concomitant alcohol ibuprofen use are listed in Sponsor's Table 8.7-46 shown in Attachment IV. The most serious of these 3 cases, MR1190/19012, reportedly developed seizures while taking an antidepressant, Prozac, with the alcohol and ibuprofen.

Medical Reviewer's Comments: With the exception of the renal failure postmarketing case reports, the postmarketing adverse event reports discussed in the above section reveal little, if any, new information regarding OTC-ibuprofen associated toxicity. The current label for this product contains consumer warning regarding the risk for GI bleeds, and the concomitant use of alcohol, other analgesics and medications with ibuprofen. The relatively few case reports related to already labeled adverse events suggests that the current warnings are appropriate and do not need to be changed or updated with the exception of perhaps specifically mentioning anticoagulants as a minor contraindication to decrease the risk of GI bleeding, or strengthening the existing recommended duration of product use (i.e., 10 days or less for pain). The latter may be beneficial since it may decrease the number of GI bleeds due to prolonged exposure to ibuprofen which is a known risk factor for developing an NSAID-induced GI bleed, as well as decreasing the risk of developing renal toxicity.

At prescription dosages, ibuprofen is known to cause nephrotoxicity. It is not surprising to this medical reviewer that cases of renal toxicity and failure occurred in consumers taking OTC ibuprofen. Review of the cases submitted by the sponsor demonstrated that many of the individuals who developed nephrotoxicity continued to take ibuprofen longer than what is currently recommended on the product's label (i.e., for more than 10 days). This risk may be minimized by either adding a separate renal warning for consumers who are at an increased risk for developing renal toxicity due to pre-existing conditions such as hypertension, diabetes, or concomitant use of nephrotoxic drugs, or by strengthening the current recommendations for the maximum duration of use of this product.

III. A summary of ibuprofen overdose case reports from the McNeil Drug Safety Reporting System for the 5-year period of October 1, 1993 through September 30, 1998 for the sponsor's OTC adult ibuprofen products. Included in this data are case reports that were published in the literature.

As defined by the sponsor, an overdose of OTC ibuprofen was defined as follows: any use of an adult-strength OTC ibuprofen product in a child less than 12 years of age, a dose greater than 400 mg in an adult without a physician's supervision, or a total dose of greater than 1200 mg in 24 hours without a physician's supervision. Instances where a physician had prescribed OTC ibuprofen at doses of more than 1200 mg per day did not constitute an overdose situation by the above criteria. During the 5-

year period of October 1, 1993 through September 30, 1998, the McNeil Drug Safety Reporting System collected a total of 181 case reports as defined by the above criteria, out of which there were 2 duplicate reports leaving 179 case reports. Only 12 cases (7%) out of these 179 reports resulted in a serious outcome, none of which resulted in a fatality. The remaining 167 case reports (93%) were classified as nonserious in nature, out of which 132 cases (79%) did not report any signs or symptoms of toxicity, or resulted in conditions that required medical intervention versus 35 cases (21%) which reported nonserious signs or symptoms of toxicity but did not require or seek medical attention. All of the 167 nonserious ibuprofen overdose case reports were reported directly to the sponsor by consumers.

The 12 serious case reports are listed and summarized in Sponsor's Table 8.8-3 located in Attachment V at the end of this review. Two (2) out of these 12 serious overdose cases were treated in the emergency room and released on the same day, while the remaining 10 cases were hospitalized and released at a later date. There are 3 case reports which describe accidental ingestion of an adult-strength ibuprofen containing product by a child versus 6 cases of intentional overdoses by adults. The information sent in for review on the remaining 3 cases did not capture the type of overdose which had occurred. Half of the overdose reports were generated from case reports that had been published in the literature. (Refer to Sponsor's Table 8.8-3 in Attachment V for further information.)

A tabular listing and summary of the 35 nonserious ibuprofen overdose cases who developed signs or symptoms of toxicity is shown in Sponsor's Table 8.8-5 which is found in Attachment V. Nine (9) out of these 35 nonserious overdose cases describe accidental overdose situations with adult formulations of ibuprofen in children. Of the remaining 26 nonserious overdose case reports, only 2 case reports were cases of either accidental or intentional overdoses in adults. In the remaining 24 cases the type of overdose situation was undetermined. The most frequently reported side effects in these nonserious overdose cases were complaints involving the nervous and digestive system, and included somnolence, dizziness, nausea, vomiting, and upset stomach.

Medical Reviewer's Comments: Review of the overdose data did not reveal any new information regarding ibuprofen-related drug toxicity. From the information submitted by the sponsor, it is impossible for this medical reviewer to draw any conclusions regarding the possibility of accidental overdoses in adults due to misinterpretation of the current dosing instructions present on ibuprofen product labels.

IV. Additional postmarketing reports of central nervous system (CNS) toxicity or serious CNS adverse events (e.g., subarachnoid hemorrhages, strokes, seizures and meningitis) collected by the McNeil Drug Safety Reporting System and by the FDA's Spontaneous Reporting System (SRS) associated with the use of 200 mg and 400 mg doses of ibuprofen. (Note: This information was submitted to the application on September 22, 1999 in response to a request for additional information made by agency's OTC reviewer.)

In response to this request, the sponsor identified 19 case reports from the previously submitted postmarketing safety data base for this efficacy supplement. Review of the reports demonstrated that only 10 out of the 19 reports met criteria for serious central nervous system (CNS) toxicity (e.g., subarachnoid hemorrhages, strokes, seizures, meningitis, etc...) . Of the 9 cases that did meet CNS adverse event criteria 1 was a duplicate case report (MR0454419A and MR508/154), 3 were due to hepatic encephalopathy secondary to alcoholism and/or hepatic toxicity, and the 5 remaining cases were a mixture of nonrelated events such as an allergic reaction, panic attacks, birth trauma, or using non-OTC doses of ibuprofen.

The 10 CNS adverse event reports are listed and summarized in the following table, Table 1 shown below. The first 2 cases (MR0981094A and MR326/154) are discussed in Sections IIA and IIB of this review and will not be commented on here. (Refer to the above sections, Sect. IIA and IIB for further information and discussion.) Of the remaining 8 cases there was 1 case report of aseptic meningitis due to ibuprofen (MR0985394A), 2 cases of coma due to overdoses with the drug (MR0454419A and MR1031739A), 1 case of de novo seizures after ingesting ibuprofen with a history of head trauma (MR568/154), and 1 case of loss of consciousness following ingestion of ibuprofen (MR1172/19012). The 3 remaining reports (MR1041375A, MR377/154, and MR967/19012) are consistent with strokes following the ingestion of OTC ibuprofen. (See Table 1 shown below for further information.)

APPEARS THIS WAY
ON ORIGINAL

Table 1 - Serious CNS Adverse Events Associated with the Use of OTC Ibuprofen During the Period of October 1, 1993 to September 30, 1998.

Report No.	Age/Sex	Adverse Event
MR0981094A	29yo/F	H/O intermittent OTC ibuprofen use for dysmenorrhea. S/P ingestion of 2 400-mg doses of CTC ibuprofen for treatment of migraine developed aseptic meningitis. Recovered but migraine persisted.
MR326/154	78yo/M	H/O arthritis treated with systemic steroids and OTC ibuprofen. Developed seizures and delirium S/P ingestion of 200 mg ibuprofen for headache. Hospitalized and died. Cause of death unknown.
MR1172/19012	43yo/F	S/P accident due to loss of consciousness after taking 2 400-mg doses of OTC ibuprofen.
MR568/154	74yo/M	H/O head trauma 10 years ago S/P de novo seizure after taking 1200 mg in divided doses of OTC ibuprofen in 24 hrs.
MR0985394A	78yo/M	Developed aseptic meningitis following positive dechallenge-rechallenge with OTC ibuprofen.
MR1041375A	17yo/F	Hospitalized for evaluation of ambylopia, deafness, confusion, and convulsions following the ingestion of OTC doses of ibuprofen for 4 days. Neurological work-up unremarkable. Symptoms resolved S/P discontinuing ibuprofen.
MR0454419A (MR508/154)	6yo/M	S/P accidental overdose of 30 200-mg tablets of ibuprofen. Developed shock, coma and metabolic acidosis. Hospitalized and recovered. (Note: Duplicate case report submitted from published literature.)
MR377/154	19yo/F	Developed vomiting, blurred vision, weakness, loss of balance, difficulty swallowing and dysarthria S/P ingestion of 2 200-mg tablets of OTC ibuprofen. Neurological work-up unremarkable. Reported to have residual weakness, dysarthria and difficulty swallowing.
MR967/19012	unk/M	Consumer reported to sponsor that he had a "mini-stroke" after taking OTC ibuprofen. No further information given.
MR1031739A	16yo/M	Hospitalized after developing coma, hypothermia, hypoventilation, metabolic acidosis and elevated liver enzymes S/P intentional overdose with OTC ibuprofen. Recovered.

Medical Reviewer's Comments: Aseptic meningitis is a relatively rare side effect of ibuprofen. The paucity of cases noted in this review do not justify the addition of a warning to the product's label for this adverse event. Review of the 3 stroke case reports did not reveal any information that demonstrated the use of ibuprofen was causally related to these neurological events.

V. Postmarketing reports of bleeding diathesis collected by the McNeil Drug Safety Reporting System and by the FDA's Spontaneous Reporting System (SRS) associated with the use of 200 mg and 400 mg doses of ibuprofen. (Note: This information was submitted to the application on September 22, 1999 in response to a request for additional information made by agency's OTC reviewer.)

In response to this request, the sponsor submitted 1 report (MR0683683A) that was originally published in the literature describing the case of a 21-year-old female who was found unconscious following an intentional overdose of an unknown amount of an ibuprofen containing product. Over a 16-day hospital course the patient developed metabolic acidosis, hypotension, renal failure, adult respiratory distress disorder and disseminated intravascular coagulation. She made a full recovery with aggressive medical treatment and support. Toxic drug screening including tests for alcohol and aspirin were all negative in this case.

Medical Reviewer's Comments: No comments.

Final Recommendations: Review of the safety data submitted by the sponsor in support of ibuprofen's safety profile does not reveal any new or unexpected adverse events for this product. The addition of either an OTC-analgesic drug class renal warning, or strengthening the present consumer recommendation regarding the short-term duration of use of these products such as, "Prolonged product use may result in serious health problems" to further minimize consumer risk of developing a GI bleed and/or renal failure should be considered by the reviewing division.

/S/

Rosemarie Neuner, MD, MPH
Medical Reviewer, HFD-560

/S/

Linda M. Katz, MD, MPH 12/6/99
Deputy Dir., HFD-560

CC: NDA 20-802 File
HFD-120 Div. File
HFD-550 Div. File
HFD-560 Dir/Ganley
HFD-560 Dep Dir/Katz
HFD-560 Team Leader/Lumpkins
HFD-120 Team Leader/RLevin
HFD-120 MO/Oliva
HFD-560 MO/Neuner
HFD-560 PM/KRothschild

Attachment I

to

Safety Review Update

Table 8.7-19. Summary of Published Controlled Clinical Trials Using Ibuprofen to Treat Migraine Headache

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy/ Safety	Mean Age (range), y Gender	Study Results
Placebo-control						
Hämäläinen et al *Neurol* 1997;48: 103-107. [20,21]	R DB PC CO	Ibu 10 mg/kg APAP 15 mg/kg Pbo cellulose Single dose	Syrup Oral Syrup Oral Syrup Oral	78/81 80/83 78/81	Overall: 10.7 (4-16) 44 F, 44 M	**Population:** Children with at least 2 moderate or severe migraine attacks per month **Efficacy:** A 2-grade reduction in migraine severity at 2 hours (scale= 1-5): APAP- 54%, Ibu- 68%, and Pbo- 37% (chi-square p= 0.02). Complete relief at 2 hours: APAP- 39%, Ibu- 60%, and Pbo- 28%. Rescue medicine use ≤2 hrs: APAP- 7.5%, Ibu- 7.7%, and Pbo- 10.3%, p= NS. **Safety:** AEs reported in 4/83 APAP, 8/81 Ibu, 9/81 Pbo, p= NS. Ibu- 3 nausea, 4 vomiting, 1 gastric pain; APAP- 2 nausea, 2 vomiting; Pbo- 3 nausea, 6 vomiting.
Nebe et al *Cephalagia* 1995;15:531-5. [19]	R DB PC DD 3-fold CO	Ibu 200 mg ASA 500 mg Pbo Single dose	Tablet Oral Tablet Oral Tablet Oral	65/65 65/65 65/65	Overall: 36 50 F, 15 M	**Population:** Adults with 1-6 mild-to-moderate headaches per month for at least 6 months (55% with migraine alone or migraine + tension headache) **Efficacy:** At 1 hour, mean headache reduction (VAS intensity) was significantly lower in Ibu-treated headaches when compared with Pbo (p<0.001) or ASA (p=0.021). ASA was significantly better than Pbo (p=0.046). **Safety:** No adverse events were reported.

Abbreviations: AE = adverse event, APAP = acetaminophen, ASA = acetylsalicylic acid, CO = crossover, DB = double-blind, DD = double-dummy, DHE= dihydroergotamine, F= female, IBU = ibuprofen, M= male, OTC= over-the-counter, Par = Parallel, Pbo = placebo, PC = placebo-controlled, PID = pain intensity difference, R = randomized, SPID= sum of pain intensity difference, TOTPAR = total of pain relief, VAS = visual analog scales.

Table 8.7-19. Summary of Published Controlled Clinical Trials Using Ibuprofen to Treat Migraine Headache

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy/ Safety	Mean Age (range), y Gender	Study Results
Placebo-control						
Hoernecke et al. *Anesthesiol* 1993;79:A837 (abstract). [22]	Random order PC Par	Ibu 400 mg DHE 2.5 mg Both Pbo Single dose	Oral Oral Oral Oral	Total: 303/303	Not specified	**Population:** Outpatients with migraine **Efficacy:** VAS score (10-point) at 2 h : Ibu- 2.3, Both- 2.4, DHE- 2.7, Pbo- 3.3 (Ibu or Both vs. Pbo, $p \leq 0.05$). Ibu alone or in combination with DHE was effective in treating migraine headache. DHE alone was directionally less effective than Ibu. **Safety:** The incidence of AEs was low and not different between groups. No serious AEs were reported.
Active Control						
Pearce et al. *Practitioner* 1983;227:465-7. [23]	R DB CO	Ibu 400 mg APAP 900 mg Multidose q4-6h	Capsules Oral Capsules Oral	23/23 26/26	Overall: 39 22 F, 5 M	**Population:** Adults with classical or common migraine headaches. **Efficacy:** Patient assessment vs their usual medication: APAP and Ibu reduced headache severity vs patient's usual medication, $p<0.01$. Within-patient assessment for relief (Ibu vs APAP): Ibu better- 11, Ibu same- 7, Ibu worse- 4, $p>0.05$. **Safety:** Two patients reported AEs while taking Ibu (drowsiness and weakness); three patients reported AEs while taking APAP (nausea, dyspepsia, and increased vomiting).

Abbreviations: AE = adverse event, APAP = acetaminophen, ASA = acetylsalicylic acid, CO = crossover, DB = double-blind, DD = double-dummy, DHE= dihydroergotamine, F= female, IBU = ibuprofen, M= male, OTC= over-the-counter, Par = Parallel, Pbo = placebo, PC = placebo-controlled, PID = pain intensity difference, R = randomized, SPID= sum of pain intensity difference, TOTPAR = total of pain relief, VAS = visual analog scales.