CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-012/S-016

ADMINISTRATIVE DOCUMENTS

16.0 Debarment Certification

McNeil Consumer Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
McNEIL CONSUMER HEALTHCARE	FEB 24 2000
TELEPHONE NO. *(Include Area Code)* (215) 273-8368	FACSIMILE (FAX) Number *(Include Area Code)* (215) 273-4049
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Camp Hill Road, Fort Washington PA 19034	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 19-012

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ibuprofen	Motrin IB

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Caplet, Tablets, Gelcaps	200mg	Oral

(PROPOSED) INDICATION(S) FOR USE: Migraine Indication

APPLICATION INFORMATION

APPLICATION TYPE (check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

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Name of Drug | Holder of Approved Application

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION

Correspondence to S-016 (Migraine)

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Janet A Uetz	Janet A. Uetz, Associate Director, Regulatory Affairs	2/23/00
ADDRESS *(Street, City, State, and ZIP Code)* Camp Hill Road, Fort Washington, PA 19034		Telephone Number (215) 273-8368

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Paperwork Reduction Project (0910-0338)
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Washington, DC 20201

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
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McNEIL CONSUMER HEALTHCARE	OCT 22 1999
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(215) 273-8368	(215) 273-4049

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NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 19-012

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ibuprofen	MOTRIN IB

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Caplets,Tablets,Gelcaps	200mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

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- ☐ 507

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Name of Drug	Holder of Approved Application

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- ☒ AMENDMENT TO A PENDING APPLICATION
- ☐ RESUBMISSION
- ☐ PRESUBMISSION
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- ☐ LABELING SUPPLEMENT
- ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- ☐ OTHER

REASON FOR SUBMISSION
Amendment to S-016 (Migraine)

PROPOSED MARKETING STATUS (check one)

- ☐ PRESCRIPTION PRODUCT (Rx)
- ☒ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____

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Janet A. Uetz	Janet A. Uetz, Associate Director, Regulatory Affairs	OCT 22 1999
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NAME OF APPLICANT
McNEIL CONSUMER HEALTHCARE

DATE OF SUBMISSION
APR 16 1999

TELEPHONE NO. *(Include Area Code)*
(215) 273-7115

FACSIMILE (FAX) Number *(Include Area Code)*
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PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 19-012

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Ibuprofen

PROPRIETARY NAME *(trade name)* IF ANY NUPRIN / MOTRIN IB

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM: Caplets, Tablets

STRENGTHS: 200mg

ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (check one)
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REASON FOR SUBMISSION
Correspondence to S-016

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M M Barron for	Willie D. Pagsuyuin, Director, Regulatory Affairs	APR 16 1999
ADDRESS *(Street, City, State, and ZIP Code)* Camp Hill Road, Fort Washington, PA 19034		Telephone Number (215)273-7115

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LABELING REVIEW OF NDA SUPPLEMENT

NDA: 19-012/SE1-016 19-012/SE1-016/BL	**Submission Date:** **Received Date:** **Amendment:** **Review Date:** **Amendment:** **Amendment:**	February 26, 1999 February 26, 1999 July 7, 1999 August, 26, 1999 September 22, 1999 October 22, 1999
Applicant:	McNeil Consumer Healthcare 7050 Camp Hill Road Fort Washington, PA 19034-2299	
Applicant's Representative:	Willie D. Pagsuyuin Director, Regulatory Affairs (215) 273-7115	
Drug:	Motrin (ibuprofen 200 mg)	
Pharmacologic Category:	Pain reliever	
Submitted:	Efficacy Supplement – draft labeling for Carton/bottle labeling for 24, 50, 100, 2 (pouch) caplets 24, 50, 100, 2 (pouch-sample) gelcaps 24, 50, 100 tablets + consumer package insert	
Reviewer:	Stephanie A. Mason	

Background:

The sponsor submitted an efficacy supplement (SE1-016) to request approval of a sole indication for Motrin 200 mg tablets, caplets, and gelcaps "for the temporary relief of mild-to-moderate pain associated with migraine headaches" for adults and children over 12 years of age, and provided additional labeling information for the intended migraine headache population. (Per a discussion with FDA on November 9, 1998, this submission includes the ibuprofen-containing gelcap formulation marketed under ANDA 73-019, which has been shown to be bioequivalent to Nuprin/Motrin IB tablets.) The sponsor indicated that the product will be marketed as a new product line under the trade name Motrin Migraine. The sponsor cross-referenced CMC information in support of the gelcap formulation.

The sponsor also pointed out that the gelcap labeling differs from the tablet and caplet labeling for the following items: (1) For 100 gelcap carton size, the statement "This package for households without young children" has been added since there will be no child-resistant package for this count, (2) the inactive ingredient listing contains ingredients specific to the gelcap product, and (3) the phrase "Distributed By" will not be included with the McNeil Consumer Healthcare name since Motrin IB Gelcaps are manufactured by McNeil.

On June 24, 1999, the Agency requested additional safety and efficacy data, and this was received as an amendment to the efficacy supplement on July 8, 1999. A hard copy and diskette (WP 5.1 version) of the labeling text in Drug Facts format for the pain of migraine was also submitted to comply with the OTC Labeling Requirements final rule (64 FR 13254; March 17, 1999).

On September 22, 1999, the sponsor submitted a supplement (SE1-016/BL) in follow-up to its correspondence of July 7, 1999, providing new modified labeling information. Changes included addition of the bulleted statement under Directions, "do not use for more than 48 hours for the pain of migraine, and under Other information for the Gelcaps, "avoid high humidity and excessive heat above 40°C (104°F)." Also, the description of the imprint to be used for Motrin Migraine will read "Motrin M" instead of the current "Motrin IB" and will apply to all three dosage forms when packaged as Motrin Migraine. The sponsor is still developing labeling for a consumer pouch that meets all labeling requirements and plans to submit as soon as available.

Since that time, on October 22, 1999, the sponsor submitted another amendment to the pending efficacy supplement to propose that the indication for Motrin Migraine be similarly revised to "treats migraine." To support its request, the sponsor submitted a draft prototype label for the treats migraine indication. The labeling contained in this supplement will be the focus of this review. However, additional general comments on the color labeling in the September submission are also provided.

Reviewer's Comments:

1. **Indication:**
The Medical Reviewer (Division of Neuropharmacological Drug Products, HFD-120) , concludes, based on its review of the data, that Motrin Migraine is effective for the temporary reduction of pain associated with migraine headache. The indication has been revised to read: "treats pain associated with migraine headache." While the clinical findings support the claim that Motrin is effective for the temporary reduction of pain associated with a migraine headache, the data do not support the relief from the other symptoms of migraine (i.e., nausea, phonophobia, photophobia, and functional disability) necessary for the treatment of migraines. Therefore, this indication is not supported by the available data. (See medical and statistical reviews - HFD-120 attached.)

2. **Ask a doctor before use if you have:**
Given the above change in the sponsor's proposed indication, all bulleted statements pertaining to "treats migraine" need to be deleted. The bulleted statements under this heading should be revised to reflect the supported indication and be presented in the following order:

- the worst headache of your life
- fever and stiff neck
- headaches beginning after or caused by head injury, exertion, coughing or bending
- experienced your first headache after the age of 50
- daily headaches
- a migraine headaches so severe as to require bed rest
- bleeding problems
- asthma
- ulcers
- liver disease
- kidney disease
- stomach problems such as heartburn, upset stomach, or stomach pain that do not go away or recur
- vomiting with your migraine

3. **When using this product:**
This section is unnecessary and should be deleted.

5. **Directions:**
In the sponsor's draft prototype, it provides directions for adults and children 12 years and older, and for children under 12 years of age. The sponsor states that the studies

demonstrate that ibuprofen at OTC doses of 200 mg and 400 mg is an effective treatment for pain of migraine headache, and that the current labeling to direct consumers to take 400 mg if migraine symptoms do not respond to 200 mg is consistent with its findings. Per the medical reviewers, HFD-120 and HFD-560, it is concluded that Motrin Migraine was effective in the treatment of headache pain in a population of migraine sufferers. However, the clinical trials submitted included insufficient subjects under 18 to support the product's use in adolescents 12 to 18 years of age. Because the clinical trials did not include sufficient adolescents 12 to 18 years of age, the Directions section is revised as follows:

Directions

adults:	• take 1 or 2 tablets with a glass of water • do not take more than directed • if symptoms persist or worsen, ask your doctor
under 18 years of age:	• ask a doctor

5. **Principal Display Panel**:

The name of the product is not acceptable because it promotes or implies use of the product as a treatment for migraine. The sponsor should modify its proposed tradename to emphasize that the product is useful for relief of migraine pain.

The flag statement "New" should be deleted after 6 months of marketing.

For consistency with other approved labeling, we recommend that the quantity of the therapeutically active ingredient contained in each dosage unit, (e.g., ibuprofen tablets USP, 200 mg) follow after the established name of the drug.

Review of New Drug Format Labeling for color labeling submitted in September 22, 1999 submission (SE1-016/BL).

The Drug Facts checklist below reflects comments for the Motrin Migraine (temporary relief of pain associated with migraine) 2s (pouch), 24s, 50s, and 100s count size cartons for the tablets, caplets, and gelcaps. This also includes the consumer leaflet. The paragraphs not listed have been found acceptable.

Principal Display Panel

Paragraph 21 CFR	Description of Paragraph	Adequate (yes/no)	Comments
201.60	Principal Display Panel	N	**The tradename Motrin Migraine needs to be revised to go with the revised indication.**
201.61	Statement of Identity • Established name of drug • Statement of general pharmacological category(ies) or the principal intended actions • Bold type • Size related to the most prominent printed matter	N	**The established name of the drug is not in a size related to the most prominent printed matter on the panel. Also, for consistency, the quantity of the therapeutically active ingredient contained in each dosage unit should follow after the established name of the drug.**

Labeling Content [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
(c)(1)	Drug Facts, Drug Facts (continued)	N	**The word "Continued" should be unbolded and in regular print.**
(c)(4)	Use(s)	N	**Needs to be revised to read "treats pain associated with migraine headache."**
(c)(5)	Warning(s)	Y	
(c)(5)	(iii) Do not use	N	**Statement needs to be revised to include the word "other" to read: "if you have ever had an allergic reaction to any other pain reliever/fever reducer."**
(c)(5)	(iv)Ask a doctor before use if you have	N	**Needs to be revised to include other conditions. Refer to prototype for guidance.**
(c)(5)	(v) Ask a doctor or pharmacist before use if you are	Y	
(c)(5)	(vi) When using this product	N	**This statement is not necessary and should be deleted.**
(c)(5)	(vii) Stop use and ask a doctor if	N	**A period should be added at the end of the second sentence in the first bulleted statement.**
(c)(5)	(ix) The pregnancy/breast feeding warning	N	**A hyphen should be added between the words "breast" and "feeding. " Second sentence, the word "specifically" should be changed to "definitely" to read "...during the last 3 months of pregnancy unless definitely directed to do so..."**
(c)(6)	Directions	N	**The first letters in the words "Adults" and "Children" should be lower case. Directions need to be revised.**
(c)(9)	Questions	N	**Telephone number should be bolded**

Labeling Format [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
(d)(3)	Bold subheading except (continued)	N	**"Continued" should be unbolded and in regular type**

The **Drug Facts** specifications for the modified carton labeling are:

Drug Facts title – 8.25 point type size Drug Facts (continued) – 7 point type size
Headers – 8 point type size Subheaders and body text – 6 point type size
Box bar line and Barlines – 2.5 point type size
Hairlines – 0.5 point type size Leading – 6.5 point type size Bullets – 5 point type size

This is acceptable.

Regarding the use of the modified version for this product, the sponsor will need to demonstrate that more than 60 percent of the total surface area available to bear labeling on the entire outside container would be needed to present the required labeling.

Recommendations: The draft prototype does not reflect true specifications (i.e., fonts, type size, etc.) or format (i.e.,horizontal barlines or hairlines) and should be used for guidance. The labeling is approvable contingent upon agreement of the following revisions:

1. **Use** - revise the indication to read "treats pain associated with migraine headache."

2. **Ask a doctor before use if you have**
- the worst headache of your life
- fever and stiff neck
- headaches beginning after or caused by head injury, exertion, coughing or bending
- experienced your first headache after the age of 50
- daily headaches
- a migraine headaches so severe as to require bed rest
- bleeding problems
- asthma
- ulcers
- liver disease
- kidney disease
- stomach problems such as heartburn, upset stomach, or stomach pain that do not go away or recur
- vomiting with your migraine

3. **Direction**

The Directions have been revised to read as follows:

Directions

adults:	• take 1 or 2 tablets with a glass of water • do not take more than directed • if symptoms persist or worsen, ask your doctor
under 18 years of age:	• ask a doctor

4. The name of the product is not acceptable as it promotes or implies use of the product as a treatment for migraine. The sponsor should modify its proposed tradename to emphasize that the product is useful for treatment of pain associated with migraine headache.

5. Regarding the 2s pouch labeling, the number "2" is placed too closely to the word "migraine" and therefore gives the appearance that it is part of the product name (i.e., Motrin Migraine 2). This needs to be corrected.

6. The established name of the drug is not in a size related to the most prominent printed matter, i.e., Motrin. The established name should be larger.

7. For consistency, we recommend that the quantity of the therapeutically active ingredient contained in each dosage unit, (e.g., ibuprofen tablets USP, 200 mg) follow after the established name of the drug.

8. The word "continued" in "Drug Facts (continued)" should be unbolded and in regular type.

9. **Do not use:**
The word "other" should be added so that the bulleted statement reads "if you have ever had an allergic reaction to any other pain reliever/fever reducer."

10. **Stop use and ask a doctor if**
A period should be placed at the end of the second sentence to read: "Seek medical help right away."

11. **If pregnant for breast-feeding –**
A hyphen should be placed between the words "breast" and "feeding." The second sentence should be revised to read: "It is especially Important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery."

12. **Directions**
The first letters in the words "Adults" and "Children" should be lower case.

13. **Questions or Comments?** – The telephone number needs to be bolded

14. The flag statement "New" should be deleted after 6 months of marketing.

15. Regarding the use of the modified version for its products, the sponsor will need to demonstrate that more than 60 percent of the total surface area available to bear labeling on the entire outside container would be needed to present the required labeling.

/S/
Stephanie A. Mason, IDS Reviewer

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

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

LABELING REVIEW OF NDA SUPPLEMENT—ADDENDUM

NDA: 19-012/SE1-016 19-012/SE1-016/BL	**Submission Date:** **Received Date:** **Review Date:**	February 26, 1999 February 26, 1999 February 22, 2000
Applicant:	McNeil Consumer Healthcare 7050 Camp Hill Road Fort Washington, PA 19034-2299	
Applicant's Representative:	Janet A. Uetz Regulatory Affairs (215) 273-8368	
Drug:	Motrin (ibuprofen 200 mg)	
Pharmacologic Category:	Pain reliever	
Submitted:	Efficacy Supplement – draft labeling for Carton/bottle labeling for 24, 50, 100, 2 (pouch) caplets 24, 50, 100, 2 (pouch-sample) gelcaps 24, 50, 100 tablets + consumer package insert	
Reviewer:	Stephanie A. Mason	

Background:

On February 17, 2000, the Agency faxed to the sponsor, a revised draft prototype labeling for the product Motrin Migraine. In its review of the labeling, the Agency states that the name of the product (i.e., Motrin Migraine) is not acceptable because it promotes or implies use of the product as a treatment for migraine, The sponsor was asked to modify its proposed tradename to emphasize that the product is useful for relief of migraine pain.

On February 18, 2000, in response to the Agency's fax dated February 17, 2000, the sponsor provided its response to the Agency's fax regarding the tradename, and proposed to rename its product from "Motrin Migraine" to "Motrin Migraine Headache." The Agency also found this name unacceptable, and suggested via fax that the product be renamed "Motrin Headache for Migraine Pain." The sponsor responded with a request for a meeting via telephone with the Agency to discuss the tradename issue. In conclusions, both parties agreed that "Motrin Migraine Pain" is an acceptable name for the product. A complete response to other labeling issues will be forthcoming.

On February 22, 2000, the sponsor faxed its complete response to the Agency's draft prototype labeling. The Agency has evaluated the sponsor's proposed labeling and conclude that the following will be acceptable:

1. **Use** – The indication proposed by the sponsor, "treats migraine headache pain," was revised to read "treats pain of migraine headache" rather than "treats pain associated with migraine headache."

2. **Do not use** – For consistency, the Agency believes this section should remain the same. Therefore, the word "other" can not be deleted as requested by the sponsor.

3. **Ask a doctor before use if you have** – The following bulleted statements are added as requested by the sponsor:

- never had migraines diagnosed by a health professional
- a headache that is different from your usual migraine
- stomach pain

The following bulleted statements are deleted as requested by the sponsor:

- bleeding problems
- asthma
- ulcers
- liver disease
- kidney disease
- stomach problems such as heartburn, upset stomach, or stomach pain that do not go away or recur

The bulleted statement "vomiting with your migraine" should remain in the labeling.

4. **Stop use and ask a doctor if** – The second bulleted statement can be revised to read:
- migraine headache pain is not relieved or gets worse

5. **Directions** – The section should be revised to read as follows:

adults:	• take 1 or 2 tablets with a glass of water at the onset of pain • the smallest effective dose should be used • do not take more than 2 caplets in 24 hours for pain of migraine unless directed by a doctor
under 18 years of age:	• ask a doctor

/S/

Stephanie A. Mason, IDS, Reviewer

/S/

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

/S/

Rosemarie Neuner, M.D., M.P.H.,
Medical Reviewer

LABELING REVIEW OF NDA SUPPLEMENT—ADDENDUM #2

NDA: 19-012/SE1-016 19-012/SE1-016/BL	**Submission Date**: February 26, 1999 **Received Date**: February 26, 1999 **Review Date**: February 25, 2000
Applicant:	McNeil Consumer Healthcare 7050 Camp Hill Road Fort Washington, PA 19034-2299
Applicant's Representative:	Janet A. Uetz Regulatory Affairs (215) 273-8368
Drug:	Motrin (ibuprofen 200 mg)
Pharmacologic Category:	Pain reliever
Submitted:	Efficacy Supplement – draft labeling for Carton/bottle labeling for 24, 50, 100, 2 (pouch) caplets 24, 50, 100, 2 (pouch-sample) gelcaps 24, 50, 100 tablets + consumer package insert
Reviewer:	Stephanie A. Mason

Background:

On February 23, 2000, the sponsor sent a fax in response to the Agency's draft labeling that was also sent on the same day. The sponsor had problems with the Directions section of the proposed labeling and requested a teleconference. On February 24, 2000, a meeting was held via telephone between the sponsor and the Agency to discuss further revisions to the Directions section of the labeling as proposed by the Agency . The sponsor revised its labeling and fax to the Agency the same day. On February 25, 2000, it was agreed between both parties that the following revisions should be made:

1. **Stop use and ask a doctor if** – The second bulleted statement "migraine headache pain is not relieved or gets worse" should be revised to read ""migraine headache pain is not relieved or gets worse after first dose."

2. **Directions** – The section should be revised to read as follows:

adults:	• take 1 or 2 tablets with a glass of water • the smallest effective dose should be used • if symptoms persist or worsen, ask your doctor • do not take more than 2 caplets in 24 hours for pain of migraine unless directed by a doctor
under 18 years of age:	• ask a doctor

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Ref: OTC #99-6

RECEIVED
JAN 21 2000
By

MEMORANDUM

DATE: January 20, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Dr. Charles Ganley
Director, Division of OTC Drug Products

SUBJECT: Consultative Review, NDA 19-012, Motrin Migraine

The enclosed reviews by Dr. Armando Oliva (12/29/99) and Dr. Randy Levin (1/3/00) are in response to your request to evaluate the sponsor's proposal (included in a submission of 12/9/99 from McNeil), that they be granted a claim for "the pain of migraine", while other issues related to an overall migraine indication are being discussed.

As the enclosed reviews make clear, a statistically significant between treatment difference has been demonstrated in the two studies for the primary outcome, Headache Response Rate at 2 Hours. In particular, Dr. Oliva has re-analyzed the studies after a diligent attempt to identify additional treated headaches as bona fide migraine headaches (an issue in his first review), and has shown that the results on pain are reproduced. Also of note, there continues to be a lack of consistent statistically significant between treatment differences on the associated symptoms of migraine.

The question of whether or not these data support any migraine related claim is a difficult one. It is fair to say that traditionally (that is, since the approval of sumatriptan), drugs have been granted (overall) migraine claims on the basis of a finding of substantial evidence of effectiveness on Headache Response Rate (as defined in the Motrin studies) at 2 hours; that is, this measure is the sole primary outcome in studies of these agents. One could argue that granting a migraine claim on this basis was (is) ill-advised because it is possible that any drug approved on the basis of such a finding is no more than an analgesic, and should not, therefore, be granted any migraine claim, and certainly not a claim as a specific treatment for the entire symptom complex known as "migraine" (after all, the diagnosis of migraine requires other symptomatology besides pain). As it has turned out, however, for all of the recently (post-sumatriptan) approved prescription migraine treatments, nominally statistically significant between treatment differences have been seen for the other secondary symptoms considered relevant (nausea, photophobia, and phonophobia). We have not been faced with a proposed treatment for migraine that has had a consistent beneficial effect on pain, but not on these associated symptoms.

If such a result had been seen (as is the case here with Motrin), the question could fairly be raised about what, if any, migraine related claim would be supportable. Specifically, as the sponsor is asking here, could not a claim for the "pain of migraine" be granted?

The answer is not obvious. As noted above, such a finding raises the question about whether or not the drug is simply an analgesic. If it were, granting a claim for the "pain of migraine" would be a pseudospecific, and therefore misleading, claim. In other words, the specific nature of the claim (pain of ***migraine***) would be an artifact of the population studied. Had only patients with toothache been studied, a similar (pseudospecific) line of reasoning would support a claim for the pain of toothache. Clearly, for a symptom like pain that occurs in numerous clinical settings, such individual claims seem inappropriate, and sponsors are required to study pain in several models so that an appropriate general analgesic claim can be granted. Of course, if these studies demonstrated a **specific** effect on the pain arising in only one of the settings studied, this would raise the question about granting a claim for the pain of that specific clinical setting. In the case of Motrin, we of course know that it is effective in treating pain in various clinical settings.

Does this settle the question? Not necessarily.

Strictly speaking, as I noted above, we grant a general migraine claim (not restricted to a pain claim) to a drug on the basis of a finding on pain relief only. Why? For several reasons, I believe. First, we have made the (usually unstated) assumption that migraine pain is somehow a different clinical entity than the pain arising in other clinical settings. This is based on our (still largely incomplete) understanding of the pathophysiology of migraine, and the resultant pain, which has been considered different from the pathophysiology underlying pain in other settings. In addition, the presumed mechanism of action of the triptans (and other approved migraine treatments) suggests that they are not analgesics, but act in other ways that seem to be more "migraine specific". These factors, taken together, I believe, explain why we have granted a migraine claim for the typical drug we see in this division without requiring additional studies in other pain models. It is critical to note, however, that our granting this claim is based on a number of assumptions that could be wrong.

Why, though, do we grant a general migraine claim, and not limit the claim to one for pain of migraine only?

Again, the diagnosis of migraine requires more than headache. The generic question about how many symptoms of a condition need to be successfully treated before a general claim for that condition should be granted is an interesting one. In the case of migraine, however, pain is the most prominent and disabling symptom for most people, and this, in the context of the current thinking about the "uniqueness" of the pathophysiology of migraine and the purported mechanism of action of the triptans (and other drugs), has been the primary basis for our granting the global claim, at least historically. But, in addition, as I noted earlier, we have been "lucky" in a real sense, because all the drugs we've approved recently do have beneficial effects on the associated symptoms. While these have not been primary outcomes, these findings have provided comfort that the drugs in question actually do treat the whole syndrome (or the most relevant parts of it), and not just the pain.

We are currently re-thinking the requirements for granting a general migraine claim. For example, we seem to be moving in the direction of **requiring** a statistically significant between group difference on the associated symptoms (or some of them) in order to grant the general claim. I believe it is also fair to say that we are seriously thinking about the view that an effect on migraine pain alone is not only insufficient to grant a general migraine claim, but that it would be insufficient to support a migraine specific pain claim as well, even for drugs that are believed to have a "migraine specific" mechanism of action. As a general rule, relying on presumed mechanisms of action to support a specific claim for a drug is, in my view, wrong, and in the case of migraine there is still enough that is not known both about the pathophysiology of the disorder and the mechanism(s) of action of the "migraine specific" drugs that there seems to be no compelling reason to assume much about either. For example, we do not really know if the triptans might not successfully treat pain arising in other clinical settings. As I have said, though, in the case of the triptans, they are known to have clear beneficial effects on the associated symptoms.

Given these considerations, and especially given the fact that Motrin is known to be an analgesic in other settings, it seems to me that a "pain of migraine" claim would be, in this case, and at this time, a pseudospecific claim, and therefore misleading, and I would recommend against granting such a claim. Motrin's current pain claim can be reasonably read to include migraine pain. I have not commented, of course, on the additional issue of whether or not a pain of migraine claim in the OTC setting is confusing vis-a-vis a general claim; my personal view is that it may be confusing, but this decision is rightly the purview of the OTC division.

/S/

Russell Katz, M.D.

Cc:
HFD-120/Katz/Levin/Oliva

MEMORANDUM

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

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

Date: January 3, 2000
From: Randy Levin, M.D., Neurology Team Leader
Subject: Motrin NDA 19-012 S016 correspondence date 12/9/99
To: file

Summary:

The sponsor is providing follow up from a teleconference where we explained the problems with their applications in terms of determining efficacy of Motrin for the treatment of migraine. Among other things, the differences between groups for associated symptoms were not considered supportive for the claim of the drug in the treatment of migraine. The sponsor is asking to address the issue of Motrin as a migraine treatment at a later time and wants to pursue the claim as a treatment for the pain of migraine.

The issue on the indication was discussed in length internally during the Excedrin NDA review. Initially, the claim of pain of migraine was used because the treatment of migraine was not an "OTC indication" and in order to approve Excedrin as an OTC migraine treatment, the use was confined to the treatment of pain. Subsequently, it was decided that the distinction between a migraine treatment and a treatment for the pain of migraine was unclear and treatment of migraines could be an OTC indication. The results from the Excedrin studies supported the claim of a migraine treatment since the differences between groups on the associated symptoms of nausea, photophobia and phonophobia favored Excedrin at a nominal p value of < 0.05.

The criteria used to determine that a drug is a migraine treatment is also an issue. The sponsor notes that we have relied on the headache response rate at 2 hours to establish the efficacy of drugs for migraines. This criteria was used for "triptans" migraine treatments. This data was also supported by a difference in the incidence of associated symptoms. There were concerns about relying on resolution of headache symptoms alone since simple analgesics could lead to a reduction in pain without being a "migraine treatment". However, the triptans were not considered to be analgesics and the effect on the associated symptoms was consistent with the effect expected for a migraine treatment.

Because the differences in incidence for these associated symptoms were associated with a nominal p value of less than 0.05, we did include the information in labeling.

This importance of the effect on the associated symptoms changed with the Excedrin NDA. Excedrin is approved as an analgesic and the associated symptoms become important for distinguishing a migraine effect from an analgesic effect. This might not be a valid way to distinguish the different treatment effects since headache relief alone might lead to resolution of the associated symptoms. However, there was some evidence to suggest that the analgesic effect was not always associated with resolution of the associated symptoms. In the Excedrin studies, the associated symptoms were consistent with the headache response, and the conclusion was that Excedrin was a migraine treatment.

This was not true for the data provided in the Motrin NDA. Motrin and Excedrin were analyzed in a similar fashion. With both drugs, there was a concern that not all patients treated a migraine. Dr. Oliva and the sponsor have divided the patients into 2 groups based on different ways to assess whether the patient treated a migraine. One group was based on whether the patient noted in the diary that they treated a "typical migraine". 97% of the headaches were migraines by this method. The second group was defined by using a set of criteria to identify headaches more likely to be migraines. Dr. Oliva used these criteria when evaluating the Excedrin studies. In the Excedrin studies <5% of the headaches treated did not fulfill the criteria, while in the Motrin studies the number was closer to 20%. The sponsor subsequently provided additional information that brings this number to 15%. The sponsor did not collect information on whether a headache is aggravated by activity which is one of the criteria used to determine if the patient had a migraine. Instead Dr. Oliva proposed using moderate to severe functional impairment as equivalent to the criteria that the headache was aggravated by activity. Using this information, 8% of the patients did not fulfill the migraine criteria.

A reanalysis of the data using these migraine criteria modified by the sponsor's resubmission are summarized in the following table.

Symptom	Study 22			Study 30		
	200 mg	400 mg	PBO	200 mg	400 mg	PBO
	(n=201)	(n=200)	(n=205)	(n=197)	(n=201)	(n=195)
Headache Response Rate, %	40%	41%	27%	39%	40%	27%
	p=0.007	p=0.004		p=0.005	p=0.008	
Nausea, present %	46%	39%	47%	46%	46%	47%
	p=0.755	p=.091		p=0.767	p=0.779	
Photophobia, present (%)	79%	81%	84%	77%	79%	87%
	p=0.213	p=0.442		p=0.006	p=0.023	
Phonophobia, resent (%)	73%	74%	80%	75%	71%	81%
	p=0.061	p=0.149		p=0.162	p=0.030	

* p values re pairwise comparison with placebo.

Comments:

Migraine is characterized by multiple symptoms including, among others, headache, nausea, photophobia, and phonophobia. The results of the studies support the claim that Motrin is effective for the temporary reduction of pain associated with a migraine headache. However, the data does not show the same with the other symptoms of migraine and, therefore, does not support a claim for Motrin as a treatment for migraines. I should also note that the use of '"relief" of pain has been reserved for elimination of pain. The current analyses look at pain "response" rates which is a reduction of pain to mild pain as well as elimination of pain. With the original NDA submission, the sponsor's analyses suggested significant differences in the percentage of patients with headache "relief".

The immediate question that is being raised by the sponsor is that since Motrin appears to reduce the pain associated with a migraine can the drug be marketed as a "treatment for the pain of migraine". This would be instead of the claim of the currently approved drugs as a "treatment for migraine". This was previously discussed for the Excedrin application and my understanding is that there is a perception that patients will not readily make a distinction between a "treatment for the pain of migraine" and a "treatment for migraine". If this is true, then giving this claim to a drug that has not been shown to treat the associated symptoms could mislead patients since all drugs currently approved as migraine treatments treat more than the headache pain.

/S/

Randy Levin, M.D.
Neurology Team Leader

(OTC#99-6) COMPLETED OCT 0 5 199

MEMORANDUM

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

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

Date: September 29, 1999

From: Acting Director, Russell Katz, M.D.
/S/ 01599
Division of Neuropharmacological Drug Products, HFD-120

Subject: NDA 19-012, Motrin Migraine

To: Director, Division of OTC Drug Products
HFD-560

Document type: Consultative Review
ODE1 number:

See the attached review for the Division's comments.

OCT 7 1999

/S/

MEMORANDUM

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

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

Date: September 23, 1999
From: Randy Levin, M.D., Neurology Team Leader
Subject: Motrin NDA 19-012
To: file

Background

The sponsor has provided an efficacy supplement for the use of Motrin IB for the acute treatment of mild to moderate pain associated with migraines for adults and children over the age of 12. Currently, the drug is approved for the reduction of fever and the temporary relief of headaches, muscular aches, minor pain of arthritis, toothache, backache, minor aches and pains associated with common cold, and the pain of menstrual cramps in adults and children 12 years old and older.

Dr. Oliva reviewed the efficacy portion of the supplement. A statistical consult was provided by Kallappa Koti.

Efficacy studies

The supplement includes the results of 2 adequate and well controlled studies (study 22 and 30) evaluating the efficacy of the drug in the treatment of migraines. The design of the two studies were identical. In an attempt to exclude patients with severe migraines, patients who experienced vomiting in over 20% of attaches and those requiring bed rest or prohibiting normal daily activities in more than 50% of their migraines were excluded from the study. Doses of 200, 400 and placebo were compared for headaches response rates at 0.5, 1, 1.5, 2, 4, 5 and 6 hours following treatment with rescue being allowed 2 hours following treatment.

Patients, age 18 to 71 (mean 39), were enrolled and treated a single moderate to severe migraine headache. Approximately one third of the headaches were rated as severe. 85% of the patients were female. About 25% of the migraines were preceded by an aura, 60% were associated with nausea, 2% were associated with vomiting, 92% were associated with phonophobia and 95% were associated with photophobia.

The 2 hour headache response rate, defined as headache pain going from moderate or severe to mild or no pain 2 hours after treatment, was the primary outcome measure. The results are summarized in the following table. Dr. Koti noted a statistically significant association between treatment and headache response (adjusted p value 0.01). He performed a subgroup analysis. The response rates were not associated with a nominal p value of < 0.05 for the patients with severe pain at baseline. The results of this analysis is summarized in the following table. Of the 577 patients evaluated in study 22, 96 were males. The 2 hour headache response rate was 51, 37 and 48% for the 200, 400 and placebo groups, respectively. Dr. Koti also noted a significant treatment-by investigator interaction.

2 hour headache response rates and percentage of patients with associated symptoms at 2 hours (p value < 0.05)						
	Study 22			Study 30		
Symptom	200 mg	400 mg	PBO	200 mg	400 mg	PBO
Number of patients (a)	(n=188)	(n=196)	(n=194)	(n=216)	(n=219)	(n=214)
Response Rate - all headaches (a)	43%*	44%*	29%	40%*	41%*	26%
Response rate - moderate headache at baseline (a)	51%* (n=128)	47%* (n=134)	32% (n=127)	49%* (n=144)	45%* (n=158)	29% (n=152)
Response rates - severe headache at baseline (a)	27% (n=60)	38% (n=61)	22% (n=67)	21% (n=72)	30% (n=61)	18% (n=62)
Response rates - males	51% (n=41)	37% (n=30)	48% (n=25)	42% (n=36)	52% (n=33)	34% (n=29)
Nausea, present	44%	39%	47%	45%	43%	46%
Photophobia, present	71%	72%	79%	75%*	75%*	86%
Phonophobia, present	78%	78%	82%	73%	68%*	79%

Because patients were selected who did not have a history of severe migraines, Dr. Oliva evaluated each the recorded characteristics of each headache to estimate if the headaches were migraine headaches. Dr. Oliva used criteria from the International Headache Society criteria to estimate if the patients had migraines. From the criteria, the migraine should have two of the following features: moderate or severe intensity, aggravated by activity, unilateral pain, pulsating pain. The headache should also be associated with at least one of the following: nausea and/or vomiting, photophobia, phonophobia. Any headache associated with an aura was automatically considered to be a migraine. Using this criteria, 20% (261 of the 1309 headaches) did not fulfill the criteria. These numbers were fairly evenly distributed between all treatment groups in both studies. It is not known if these headaches were migraines or other type of headache. A reanalysis of the headache response rate is summarized in the following table. The difference between drug an placebo was associated with nominal p value of > 0.05 for study 022 and < 0.05 for study 030.

2 hour response rates for patients with migraines based on Dr. Oliva's criteria						
	Study 22			Study 30		
Symptom	200 mg	400 mg	PBO	200 mg	400 mg	PBO
	(n=169)	(n=177)	(n=179)	(n=176)	(n=177)	(n=170)
Response Rate - all headaches	40%	36%	29%	39%	39%	25%
Response rate - moderate headache at baseline	47%	36%	33%	48%	42%	29%
Response rates - severe headache at baseline	24%	36%	21%	23%	30%	13%
Nausea, present	44%	41%	48%	48%	48%	48%
Photophobia, present	72%	76%	80%	80%	78%	87%
Phonophobia, present	79%	81%	84%	77%	71%	81%

Comments

Migraine is a type of headache characterized by pain associated with a variety of symptoms including nausea, photophobia and/or phonophobia. We have evaluated a number of drugs as acute treatments for migraines. To assess efficacy in migraine trials, we have used the primary outcome measure of the 2 hour headache response rate defined as a reduction in the headache severity from moderate or severe to mild or no pain. A significant increase in the headache response rate compared to patients receiving placebo is required for a drug to receive the indication for an acute treatment of migraine.

Supportive evidence for the migraine claim includes a reduction in the associated migraine symptoms of nausea, photophobia and phonophobia. We have used a nominal p value of < 0.05 to define a difference in the incidence of these associated symptoms when compared to placebo. We have felt that the response to the associated migraine symptoms would be helpful for distinguishing a migraine treatment from a simple analgesic. A migraine treatment would not only lead to a reduction in the headache pain, it should also reduce the associated migraine symptoms while an analgesic would essentially only treat the pain. One of the problems with this assumption is that the headache pain and the associated symptoms might not be independent. The relief of pain might also lead to a reduction in the associated symptoms.

The findings in the studies provided in this NDA suggest that the treatment of pain might be independent from the treatment of the associated symptoms. While a statistically significant treatment difference was seen for the primary outcome measure of headache pain, there was less difference between groups for the associated symptoms. This was the most clear for nausea.

There was an issue of that some of the headache treated might not have been migraines. Even when the patients with the more definite migraines were analyzed, the disconnect between the analgesic effect and the effect on the associated symptoms remained.

In addition to the lack of effect on the associated symptoms of migraine, the drug did not appear to be effective for those headaches classified by the patients as being severe. The treatment effect appeared to come from the patients with moderate headache pain.

This results of the study suggest that Motrin IB may not be a specific migraine treatment. The benefits seen in the study may simply be related to the analgesic effect of the drug.

Recommendation

I agree with Dr. Oliva that the studies did not provide the evidence needed to support the claim that Motrin is an acute treatment for migraines. The findings do support the current labeling claim for the temporary relief of headache.

/S/

Randy Levin, M.D.
Neurology Team Leader

MEMORANDUM OF TELECONFERENCE

Meeting Date:	2-18-2000
Time:	2:30pm
Location:	9201 Corporate Blvd. Rockville, MD 20876
Application:	NDA 19-012/S-016
Type of Meeting:	Teleconference
Meeting Chair:	Charles J. Ganley
Meeting Recorder:	Elizabeth F. Yuan

FDA Attendees, titles, and Office/Division:
Robert Delap, M.D., Ph.D., Director, ODEV, CDER, FDA
Charles J. Ganley, M.D., Director, DOTCDP, ODEV, CDER, FDA
Elizabeth Yuan, R.Ph, Regulatory Project Manager, DOTCDP, ODEV, CDER, FDA

External Constituent Attendees and titles from Mcneil Consumer HealthCare:
Vivian Chester, Vice President, Regulatory Affairs
Aaron See, Associate Marketing Manager
Scott Snyder, Franchise Marketing Director
Janet Uetz, Associate Director, Regulatory Affairs
Tony Vernon, President

Meeting Objectives:
To discuss the proposed tradename "MOTRIN Migraine Headache" faxed to the agency on 2-18-00

Discussion Points (bullet format):

1. "Motrin Migraine Headache" is not an acceptable tradename, because the clinical efficacy data submitted with this supplement supports relief of pain/headache associated with migraines, but not migraines themselves. The agency has proposed the tradename "Motrin Headache for Migraine Pain" to adequately address the efficacy of this drug product, and also to distinguish the clinical difference with Excedrin Migraine. If McNeil were to do a Label Comprehension Study in support of "Motrin Migraine Headache", the study must include consumers' understanding of the comparison between "Motrin Migraine Headache" and Excedrin Migraine.

2. McNeil found the proposed tradename "Motrin Headache for Migraine Pain unacceptable. The counterproposal from McNeil was "Motrin Migraine Pain".

3. The agency agreed to take a look at "Motrin Migraine Pain" and its presentation on paper to determine whether "Motrin Migraine Pain" is an adequate tradename for this drug product.

Minutes Prepare /S/

Chair Concurrer /S/

Attachments/Handouts:
Facsimile dated 2-18-00 to the agency

MEMORANDUM OF TELECON

DATE: February 24, 1999

APPLICATION NUMBER: NDA 19-012, ANDA 73-019, Motrin IB formulations

BETWEEN:

Willie Pagsuyuin,
Director, Regulatory Affairs
McNeil Consumer Healthcare
215-273-7115

AND

Kerry Rothschild, HFD-560
Rosemary Cook, HFD-560
Charlotte Yaciw, HFD-550

SUBJECT:

McNeil Consumer Healthcare has asked for guidance on how to consolidate their ANDA 73-019 for Motrin gelcaps into their NDA 19-012 for Motrin tablets and caplets. Through various conversations, it has become apparent that the consolidation was desired so that the gelcap formulation could be included in the efficacy supplement McNeil intends to file to their NDA for a migraine indication. McNeil believes that we have already concurred with their strategy.

Following an internal meeting, sponsor was contacted with the following feedback:

- An efficacy supplement may be submitted to NDA 19-012, but the ANDA must be transferred to the NDA before review of the gelcap formulation is possible.

- In order to transfer the ANDA to the NDA, a letter must be sent to the Office of Generic Drugs requesting that the folders for ANDA 73-019 be transferred to the NDA, and that the ANDA number be cancelled. The request may be done as a general correspondence to OGD, and a copy should be submitted to the NDA.

- Once the transfer is complete, the review of the efficacy supplement for the gelcap formulation may procede. The transfer is complete when the sponsor is notified that the volumes have arrived to the NDA. Transfer and cancellation of ANDA number will not interrupt the marketing status of the gelcap product. Any changes to the gelcap product should be submitted as supplements to the NDA AFTER the transfer is complete.

- DOTCDP requested a comparative table of differences between the gelcoat and filmcoat products. The table may be submitted as correspondence to NDA 19-012. The table should contain comparasons of Specs, methodology, formulation of the core, manufacturing process for the core, manufacturing sites, and sources of the drug

substance.

Timing issueswere addressed as follows:

- The agency cannot review an efficacy supplement to the gelcap formulation unless it is already part of the NDA. Ideally, sponsor would wait until transfer is complete, then submit efficacy supplement for all formulations covered under the NDA.

- As an alternative, sponsor could submit the efficacy supplement as it is prepared (i.e., for tablet, caplet, and gelcap), and state in the cover letter that the gelcap formulation is not to be considered as part of efficacy supplement. When the transfer is complete, the agency would check its review timeline for the supplement to determine whether an amendment to the supplement is appropriate. The agency would not risk missing its goal date for the review of the supplement, but if possible, the agency would also prefer handling the three formulations as a single supplement.

Sponsor was also strongly reminded that the Meetings MaPP is designed to foster communication and concurrence between the agency and sponsors. When sponsors deviate from the MaPP, and ask informal questions in various telephone calls, the advise they receive is not official, and concurrence is not obtained. Although McNeil believes they received concurrence on their plan to consolidate the ANDA and NDA while simultaneously submitting their efficacy supplement for a migraine indication, the agency does not believe this is the case.

Kerry Rothschild
Project manager, HFD-560

cc: Original N19-012
HFD-560/Div. File
HFD-560/Rothschildk
HFD-560/Cookr
HFD-560/Katzl
HFD-560/Lumpkins
HFD-550/Yaciw
HFD-550/Patelh