CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-012/S-016

CORRESPONDENCE

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

FEB 25 2000

Charles Ganley, MD, Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room, Room S-212
9201 Corporate Boulevard
Rockville, MD 20850

RE: MOTRIN® Migraine Pain
NDA 19-012
Correspondence to S-016

Dear Dr. Ganley:

This letter is in response to the fax of 2/25/00 from Kerry Rothschild containing a mock up of the MOTRIN® Migraine Pain labeling content requirements (Attachment 1). We accept that this labeling serves as a basis of approval for NDA 19-012/S-016 and we agree to submit Final Printed Labeling (FPL) that is identical in content to the labeling text provided with appropriate dosage form-related modifications for tablets, caplets and gelcaps. We further agree, as specified in our correspondence to S-016 to NDA 19-012 on 2/24/00 (Attachment 2; cover letter only), that the tradename will be MOTRIN Migraine Pain. The words "Migraine" and "Pain" will be presented completely in capital lettering in the exact same colors and size in the final printed labeling. The FPL will be formatted in accordance with the OTC labeling final rule (21 CFR 201.66).

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Janet A. Uetz
Associate Director, Regulatory Affairs

cc: Kerry Rothschild, Project Manager (HFD-560)

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

FEB 24 2000

Charles Ganley, MD, Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room, Room S-212
9201 Corporate Boulevard
Rockville, MD 20850

RE: MOTRIN® Migraine Pain, 200 mg
NDA 19-012, S-016
Correspondence

Dear Dr. Ganley:

Attached are copies of correspondence between McNeil and FDA sent via fax on 2/18/00 regarding the product tradename. Attachment 1 includes correspondence in which McNeil proposed the tradename, "MOTRIN Migraine Headache" and FDA's minutes of a teleconference held on 2/18/00 in which the product tradename was discussed. Attachment 2 includes correspondence in which McNeil proposed the alternate tradename "MOTRIN Migraine Pain" and FDA's response in which this alternate tradename was found acceptable.

In follow up to FDA's response, we hereby formally commit to use the tradename, MOTRIN Migraine Pain. The words "Migraine" and "Pain" will be presented completely in capital lettering in the exact same colors and size in the final printed labeling.

A complete response to all of the labeling comments in FDA's fax dated 2/17/00 will be submitted under separate cover.

Should you have any questions, please contact me at (215) 273-8368.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

JAU:dtg
Attachment

cc: Kerry Rothschild, Project Manager (HFD-560)

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Charles Ganley, MD, Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room, Room S-212
9201 Corporate Boulevard
Rockville, MD 20850

FEB 4 2000

RE: Motrin® Migraine, 200 mg
NDA 19-012
Correspondence to SNDA S-016

Dear Dr. Ganley:

We appreciate the feedback we received at our February 1, 2000 meeting with the Agency. We agree with your conclusion that the data provided in S-016 to NDA 19-012 demonstrate a beneficial treatment effect of Motrin® Migraine on migraine pain. As discussed at the meeting, we understand that during the next several weeks there will be internal FDA discussions on the appropriate labeling for Motrin® Migraine. In particular, we understand that discussions will continue on the appropriateness of the 'treats migraine' indication for Motrin® Migraine.

Since our meeting on February 1st, we have again reviewed FDA's most recent review (dated June 15, 1999) of Excedrin® Migraine for the 'treats migraine' indication. We noted that this review included (see page 6 of 8) an analysis of migraine-associated symptoms that we had not previously discussed. This analysis included an evaluation of migraine-associated symptoms defined in the same manner as pain response, ie, going from moderate or severe to mild or none.

The Motrin® Migraine studies provide evidence of the beneficial effect of ibuprofen on the migraine-associated symptoms of photophobia, phonophobia, and functional disability. It appears what primarily needs to be resolved is the treatment effect of Motrin® Migraine on nausea.

As noted by the Agency, the treatment of the pain associated with migraine does not appear to be independent from the treatment of the associated symptoms. The typical migraine studies, including those for Motrin® Migraine, were not designed to assess the efficacy of the drug to specifically treat any individual migraine symptom except pain. Patients were enrolled based on the severity of their pain, not on the severity of their associated symptoms. In fact, these studies were designed to enrich the study population for photophobia, phonophobia, and functional disability, but to limit (see exclusion criteria) enrollment of those with severe nausea. As a consequence, in these studies, only a small percentage (23%) of patients had moderate to severe nausea at the time of treatment. In contrast, 71% of patients had moderate to severe photophobia at baseline, 60% had moderate to severe phonophobia at baseline, and 67% had moderate to severe functional disability.

To address this open issue, Table 1 (attached) provides a new summary of the nausea data from the two Motrin® Migraine pivotal studies using an analysis consistent with that used by FDA with respect to Excedrin® Migraine (reviewer's memorandum dated June 15, 1999). This table provides an analysis of nausea at two and four hours based on response defined in the same manner as pain response, ie, going from moderate or severe to mild or none. In addition to study-specific data, pooled data across identically designed studies are presented for nausea at two and four hours. We considered pooling to be appropriate given that 44% of subjects had no nausea at baseline; thus, power was somewhat limited to evaluate nausea within each study.

These data demonstrate a significant beneficial effect of ibuprofen on nausea associated with migraine in the two studies. When comparing the rate of nausea response for the ibuprofen and placebo-treated subjects, the data for individual studies were in favor of ibuprofen but the difference did not usually reach statistical significance. However, when data were pooled across studies of identical design, both ibuprofen 200 mg and ibuprofen 400 mg provided a statistically significant beneficial effect for the relief of nausea at two hours ($p = 0.003$ and $p = 0.046$, respectively) and at four hours ($p = 0.011$ and $p = 0.021$, respectively).

In summary, secondary efficacy results for Motrin® Migraine indicate improvement in the complex of measured migraine-associated symptoms with relief of migraine headache pain. The data submitted in support of this application demonstrate the beneficial effect of ibuprofen on photophobia, phonophobia, and functional disability. Using an analysis consistent with that used in the review of Excedrin® Migraine (ie, reduced from moderate or severe to mild or none), Motrin® Migraine studies demonstrate a statistically significant beneficial effect of ibuprofen on nausea. Based on this, we continue to believe that Motrin® Migraine should be approved for the 'treats migraine' indication.

In view of our user fee deadline later this month, we would appreciate your prompt review of this matter as it directly affects our labeling.

Please call me at (215) 273-7010 if you have any questions and/or would like to discuss the data presented.

Sincerely,

MCNEIL CONSUMER HEALTHCARE

Janet A. Metz for

Vivian A. Chester
Vice President, Regulatory Affairs and Project Management

cc: K. Rothschild, Esq., Project Manager (HFD-560) (via fax)
R. DeLap, MD, Office Director, ODE V (via fax)
C. Ganley, MD, Director (HFD-560) (via fax)
R. Levin, MD, Director (HFD-120) (via fax)

McNeil

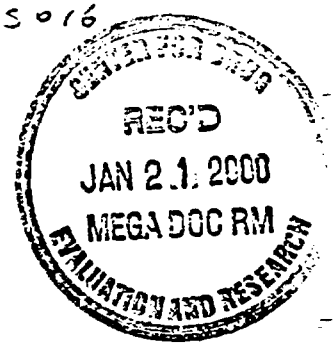
McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

JAN 19 2000

1-19-00 mng

Charles Ganley, MD, Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room, Room S-212
9201 Corporate Boulevard
Rockville, MD 20850

NDA 19-012 S016



RE: MOTRIN® Migraine, 200 mg
NDA 19-012
Correspondence to SNDA S-016

Dear Dr. Ganley:

In follow-up to our submission dated December 9, 1999, we are providing a summary of issues we would like to discuss at our upcoming meeting on MOTRIN® Migraine, as well as a summary of our position regarding them. We would also like to confirm that the meeting to discuss these issues has been scheduled for February 1, 2000 at 3:30pm at FDA's 9201 Corporate Boulevard offices. An updated list of McNeil participants is also provided.

We look forward to meeting with the Agency to discuss MOTRIN® Migraine. If you have any questions, please call Vivian A. Chester at (215) 273-7010 or me at (215) 273-8368.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz
Associate Director, Regulatory Affairs

JAU:dtg

cc: Kerry Rothschild, Project Manager (HFD-560) (via fax)

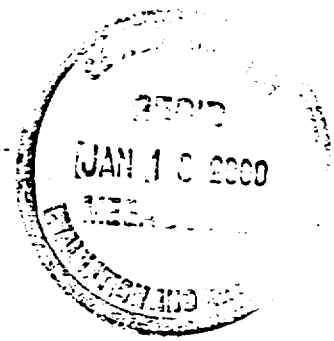
ORIGI

McNeil ORIGINAL

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NDA NO. 19012 REF NO. 004
NDA SUPPL FOR SLR

JAN 17 2000



Charles Ganley, MD, Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room, Room S-212
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 19-012
Supplemental NDA – Labeling in ***Drug Facts***
MOTRIN® IB Ibuprofen Gelcaps

Dear Dr. Ganley:

In accordance with 21 CFR 314.70, we are submitting this supplemental NDA to provide for MOTRIN® IB Gelcaps labeling in ***Drug Facts*** format.

Attachment 1 provides copies of thermals (including cartons and bottle labels) for our 8, 24, 50 and 100 count bottles, as well as the consumer leaflet. **Attachment 2** provides a copy of the labeling text in ***Drug Facts*** format. **Attachment 3** provides the labeling text in ***Drug Facts*** format on a 3.5 inch floppy disk in WordPerfect 6.1 for Windows.

In conjunction with this submission, we would like to review the present inclusion of a Consumer Labeling leaflet with this product. The ***Drug Facts*** labeling final rule provides a more structured, organized and compact presentation of text that is more consumer friendly and easier to read. For MOTRIN® IB, all of the information on the carton is repeated on the consumer leaflet. Therefore, the leaflet is redundant and we would like to eliminate it from the package. This approach is consistent with our Children's MOTRIN® line of products, which do not contain a consumer leaflet in the package. At the time of the Children's MOTRIN Rx to OTC switch, FDA determined that such a leaflet was unnecessary because it duplicated information on the product carton.

We would appreciate your evaluation of this request as part of the review of this SNDA. Once the labeling for MOTRIN IB Gelcaps has been approved, we will incorporate the text on MOTRIN IB Caplets and Tablets as well.

If you have any questions on this submission, please contact me at (215) 273-7878.

Very truly yours,

McNEIL CONSUMER HEALTHCARE

Paula J. Oliver
Senior Director, Regulatory Compliance

PJO:dtg
Attachments

cc: (letter only)
Kerry Rothschild, Project Manager

McNeil

ORIGINAL

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

JAN 14 2000

Charles J. Ganley, MD, Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room, Room S-212
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA SUPPL AMEND
SEI-016/RL

RE: Motrin Migraine
NDA 19-012
Amendment No. 2 to SNDA S-016

Dear Dr. Ganley:

In follow-up to a request from Kerry Rothschild on January 12, 2000, we are providing information on formatting specifications associated with the labeling (thermals) included in correspondence to S-016 on 9/22/99. In addition to the information included on the thermals submitted with our SNDA, we have obtained and are providing (attached) the requested type size information for the following:

- Drug Facts (continued)
- Bullets
- Barlines
- Hairlines

We are providing this information for the 24/50/100 count cartons and bottle labels for all three dosage forms. Future labeling submissions will include this information directly on the thermals.

If there are any questions, please contact me at 215-273-7878.

Very truly yours,

MCNEIL CONSUMER HEALTHCARE

Paula J. Oliver
Senior Director, Regulatory Compliance

PJO:dtg
Attachment

cc: Kerry Rothschild, Project Manager (HFD-560)

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Charles J. Ganley, MD, Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd., Room S-212
Rockville, MD 20850

Re: MOTRIN® Migraine, 200mg
NDA 19-012
Correspondence to SNDA S-016

Dear Dr. Ganley:

Thank you for the feedback on our pending MOTRIN Migraine application that the FDA review team provided to us during our teleconference on Friday, December 3, 1999. McNeil's minutes from the teleconference are included in Attachment 1. We appreciate having the opportunity to hear and respond to the issues raised.

We are requesting a follow-up meeting between McNeil and appropriate representatives from FDA to discuss the proposal outlined and supported in this background package for MOTRIN Migraine for the pain of migraine headache. If possible, we would like to meet as soon as possible during the week of December 13, 1999.

Please contact me at (215) 273-8368 if you have any questions on the materials provided and to schedule the requested meeting.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

cc: K. Rothschild, Project Manager (HFD-560) (via fax)

ganley15.doc

McNeil ORIGINAL

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

OCT 22 1999

Charles J. Ganley, MD, Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd., Room S-212
Rockville, MD 20850

Re: MOTRIN® Migraine, 200mg
NDA 19-012
Amendment No. 1 to SNDA S-016

Dear Dr. Ganley:

When SNDA S-016 was submitted on February 26, 1999, the proposed labeling was based on the then current labeling for Excedrin Migraine for the treatment of migraine headache pain. Although the clinical studies that were conducted with MOTRIN Migraine demonstrated efficacy in the constellation of migraine symptoms including headache pain, nausea, photophobia, phonophobia and functional disability, the labeling that was proposed in this SNDA was designed to be consistent with the approved labeling for Excedrin Migraine.

Since the OTC labeling for Excedrin Migraine has recently been approved for the broader migraine indication, this Amendment proposes that the indication for MOTRIN Migraine be similarly revised to "treats migraine". As appropriate for ibuprofen, revisions to the **Warnings** and **Directions** for MOTRIN Migraine were made to be consistent with the recently approved labeling for Excedrin Migraine in Drug Facts format (copy attached).

In support of this request, we are providing the following documentation.

Attachment 1 provides revised labeling text incorporating the proposed labeling revisions. New text is underlined and deleted text is indicated with a strike through mark.

Attachment 2 highlights efficacy data previously submitted in SNDA S-016 supporting the revised indication; no new data or additional analyses are being introduced with this Amendment. In particular, in addition to the primary efficacy endpoints, Reduction in Baseline Pain Intensity to mild or no pain at 2 hours and Pain Intensity Difference at 2 hours, migraine associated symptoms such as nausea, phonophobia, photophobia and functional disability were also assessed in the clinical studies 97-022 and 97-033. As demonstrated by the data referenced, ibuprofen at OTC doses of 200 mg and 400 mg is an effective treatment for migraine headache pain and the

associated symptoms of migraine including nausea, photophobia, phonophobia, and functional disability. The demonstrated efficacy in this constellation of symptoms supports the proposed revised labeling.

To minimize the potential for consumer confusion, it is appropriate that the labeling for MOTRIN Migraine be consistent with currently approved OTC labeling for migraine. It is likewise appropriate that ingredient-specific **Warnings** and **Directions** may be necessary. The labeling proposed in this Amendment incorporates as much as appropriate from the approved labeling for Excedrin Migraine. Should you have any questions, please give me a call at 215-273-8368.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz

Janet A. Uetz, MS
Associate Director, Regulatory Affairs

Attachment

Cc: Kerry Rothschild (HFD-560)

Jau012

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 19-012/S-016

JUL 28 1999

McNeil Consumer Healthcare
Attention: Janet Uetz
Director, Regulatory Affairs
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Dear Ms. Uetz:

Please refer to your pending supplemental new drug application (NDA) 19-012/S-016 for Motrin Migraine Tablets, Caplets, and Gelcaps, submitted February 26, 1999, under section 505(b) of the Federal Food , Drug and Cosmetic Act.

We are reviewing your submission and have identified the following comments and information requests with regard to your supplemental NDA:

1. The following additional data should be submitted for review:

   A. Reports of CNS toxicity or serious adverse events related to the CNS (e.g., subarachnoid hemorrhages, strokes, etc.) collected by the McNeil Consumer Healthcare event safety monitoring system and/or by FDA=s Spontaneous Reporting System (SRS) associated with the use of ibuprofen, 200 and 400 mg; and

   B. Reports of bleeding diaphesis collected by the McNeil Consumer Healthcare event safety monitoring system and/or by FDA=s Spontaneous Reporting System (SRS) associated with the use of ibuprofen, 200 and 400 mg.

2. The submission does not contain any clinical data for anyone under 18 years of age. Any available data for 12 to 18 year olds should be submitted.

3. The submission did not contain: (1) a statement that all clinical trials were conducted in accordance with the IRB/Declaration of Helsinki provisions of the CFR; and (2) a statement that the integrated summary of safety includes all safety data of which you are aware, from all sources, foreign or domestic. Please provide such statements.

4. We have not received the comparative table of differences in the gelcoat and filmcoat products, previously requested during a telecon on February 24, 1999. The table is to contain comparisons of specifications, methodologies, formulations of the core, manufacturing process of the core, manufacturing sites, and sources of the drug substance. Please provide the comparative table.

We would appreciate your prompt written response so that we can continue our evaluation of your supplemental NDA.

These comments are being provided to you to give you notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

Should you have any questions regarding this application, please contact Kerry Rothschild, Esq., Regulatory Project Manager, at 301-827-2284.

Sincerely yours,

/S/ 7/28/99

Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-012/S-016

MAR 31 1999

McNeil Consumer Healthcare
Attention: Willie D. Pagsuyuin
Director, Regulatory Affairs
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Dear Mr. Pagusuyuin:

Please refer to your pending supplemental new drug application (NDA) 19-012/S-016 for Motrin Migraine Tablets, Caplets, and Gelcaps, submitted February 26, 1999, under section 505(b) of the Federal Food , Drug and Cosmetic Act.

We are reviewing your submission and have identified the following comments and information requests with regard to your supplemental NDA:

The supplemental NDA cross references abbreviated new drug application (ANDA) 73-019 for information relevant to the gelcap formulation. As previously discussed, the agency has determined that it is inappropriate to cross reference an ANDA in a supplemental NDA of this type. Consequently, certain information necessary to allow an adequate review of the gelcap formulation for the proposed indications/uses is contained in neither the NDA nor the supplemental NDA.

We recommend that you send a letter to the Office of Generic Drugs requesting that the volumes associated with ANDA 73-019 be administratively transferred to NDA 19-012.

We would appreciate your prompt written response so that we can continue our evaluation of your supplemental NDA.

These comments are being provided to you to give you notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond

to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, please contact Kerry Rothschild, Esq., Regulatory Project Manager, at 301-827-2284

Sincerely,

/S/

for: Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Rosemary Cook
Supervisory Project Manager
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Central Document Room #N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

FEB 24 1999

RE: NDA 19-012
Correspondence

Dear Ms. Cook:

The attached correspondence supports our understanding of an acceptable filing strategy for Motrin Migraine Tablets, Caplets and Gelcaps. This provides for these three new products to be filed under an SNDA to NDA 19-012 with cross-reference to ANDA 73-019 for the CMC information for the gelcap form.

The SNDA for the migraine indication is complete and ready for submission to FDA on Friday, February 26, 1999. Since this SNDA provides for Motrin Migraine Gelcap as a new product, instead of a new indication added on to the Motrin IB Gelcap labeling, this approach is acceptable under current regulations and offers an efficient review mechanism for three new related products.

For future efficiency, we propose also to concurrently request consolidation of ANDA 73-019 under NDA 19-012. We have prepared our SNDA for the migraine indication based on our understanding reflected on the attached correspondence, and are concerned at this point that alternative approaches separating out the gelcap product will delay its review and approval.

We appreciate your cooperation in assisting to expeditiously resolve this situation. Should you have any questions, please contact me at (215) 273-7115 or Vivian Chester at (215) 273-7010.

Very truly yours,

McNEIL CONSUMER HEALTHCARE

Willie D. Pagsuyuin
Director, Regulatory Affairs

cc: Linda Katz, MD
Debra Bowen, MD
Kerry Rothschild

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FACSIMILE TRANSMISSION RECORD

DATE: 2/25/00

FROM: Kerry G. Rothschild, Esq.
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2284 FAX: 301-827-2316 or
301-827-2315

TO: Name: Janet Uetz
Company: McNeil Consumer Healthcare
Phone: 215-273-8368

FAX #: 215-273-4049 No. Of Pages (including cover) 5 4

****

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Message: Please refer to your supplemental new drug application NDA 19-012/S016, for Motrin (ibuprofen) tablets, caplets, and gelcaps 200 mg, with amended labeling submitted February 21, 2000.

Please find attached, a revised mock-up of the product labeling reflecting the content requirements of the March 17, 1999 FEDERAL REGISTER document "Over-The-Counter Human Drugs; Labeling Requirements; Final Rule" (64 FR 13254), incorporated into the drug regulations at 21 CFR 201.66. Please note that the attached labeling example is not intended to reflect formatting requirements under the OTC labeling final rule. Please refer to the OTC labeling final rule for specific formatting requirements.

In order to ensure a timely action for this supplemental new drug application, we request that you provide a commitment letter acknowledging the following:

1. The enclosed labeling serves as a basis of approval for NDA 19-012/S-016; and

2. You agree to submit Final Printed Labeling (FPL) that is identical in content to the enclosed labeling text, and formatted consistent with 21 CFR 201.66.

Furthermore, if you have not already submitted a letter of commitment in response to the agency's fax dated 2/28/00 (copy attached), please also include a commitment that the

proprietary name of the product will be presented consistent with that fax.

If you have any questions, please contact Kerry Rothschild, Esq., Regulatory Project Manager, at 301-827-2284.

McNEIL CONSUMER HEALTHCARE, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034 (215) 273-7000

URGENT DELIVERY REQUESTED
FAX TRANSMITTAL

DATE: ~~February 24, 2000~~ NUMBER OF PAGES (including cover page): 2

TO: Kerry Rothschild FROM: Janet A. Uetz

FAX NUMBER: (301) 827-2315 FAX NUMBER: (215) 273-4049
TELEPHONE NUMBER: (215) 273-8368

MESSAGE:

Dear Kerry:

Attached are revised Directions for MOTRIN® Migraine Pain based on the discussion at our teleconference this morning. Please let me know as soon as you can when we will be able to have the follow up call with Dr. Ganley as discussed this morning.

Thanks for your efforts in arranging these calls on such short notice.

Janet A. Uetz

McNEIL CONSUMER HEALTHCARE, 7060 CAMP HILL ROAD, FORT WASHINGTON, PA 19034 (215) 273-7000

URGENT DELIVERY REQUESTED
FAX TRANSMITTAL

DATE: ~~February 23, 2000~~ NUMBER OF PAGES (including cover page): 3

TO: Kerry Rothschild FROM: Janet A. Uetz

FAX NUMBER: (301) 827-2315 FAX NUMBER: (215) 273-4049
TELEPHONE NUMBER: (215) 273-8368

MESSAGE:

URGENT

RE: NDA 19-012, S-016
MOTRIN® Migraine Pain
Response to FDA Fax dated 2/23/00

Dear Kerry:

Attached is our response to the labeling sent by FDA on 2/23/00. Except for the Directions, we accept the labeling as presented in the Fax. In order to expeditiously resolve the wording for the Directions, we are requesting a teleconference today, if possible, with appropriate FDA representatives.

Thanks for your help.

Janet A. Uetz

McNEIL CONSUMER HEALTHCARE, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034 (215) 273-7000

URGENT DELIVERY REQUESTED
FAX TRANSMITTAL

DATE: ~~February 21, 2000~~ NUMBER OF PAGES (including cover page): 10

TO: Kerry Rothschild FROM: Janet A. Uetz

FAX NUMBER: (301) 827-2315 FAX NUMBER: (215) 273-4049
TELEPHONE NUMBER: (215) 273-8368

MESSAGE:

Dear Kerry:

Attached is our response to FDA's faxed comments of February 17, 2000.

PRD/jau

Janet A. Uetz

McNEIL CONSUMER HEALTHCARE, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034 (215) 273-7000

URGENT DELIVERY REQUESTED
FAX TRANSMITTAL

DATE: ~~February 18, 2000~~ NUMBER OF PAGES (including cover page): 2

TO: Kerry Rothschild FROM: Janet A. Uetz
CC: Charles Ganley, MD

FAX NUMBER: (301) 827-2315 FAX NUMBER: (215) 273-4049
TELEPHONE NUMBER: (215) 273-8368

MESSAGE:

URGENT

RE: NDA 19-012, S-016

Dear Kerry:

In response your fax dated 2/17/00, we are proposing the tradename "MOTRIN Migraine Headache" as illustrated in the attached principal display panel mock up. In order to meet our product launch timeline, it is very important that we bring the tradename to closure TODAY. This is especially important because we understand that Monday, February 21, 2000 is a Federal holiday. We are working on a complete response to your fax, which I hope to be able to send to you shortly. In the mean time, I would greatly appreciate anything you could do to provide feedback on the tradename as soon as possible. Thanks for your help.

Janet A. Uetz

McNeil

McNEIL CONSUMER HEALTHCARE, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034 (215) 273-7000

URGENT DELIVERY REQUESTED
FAX TRANSMITTAL

DATE: February 18, 2000 NUMBER OF PAGES (including cover page): 1

TO: Liz Yuan FROM: Janet A. Uetz

FAX NUMBER: (301) 827-2315 FAX NUMBER: (215) 273-4049
TELEPHONE NUMBER: (215) 273-8368

MESSAGE:

Dear Liz:

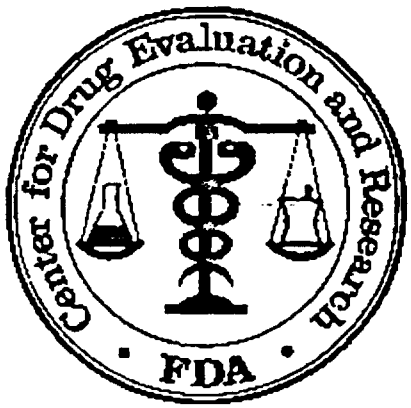
The following people will be representing McNeil at our 2:30pm teleconference today (2/18/00):

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

Thanks for arranging this teleconference for us.

Janet A. Uetz

FOOD AND DRUG ADMINISTRATION DATE 02-18-00
DIVISION OF OVER-THE-COUNTER DRUG PRODUCTS
DOCUMENT CONTROL ROOM HFD-560
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857



TO:

Name Vivian Chester

Fax No. 215-273-4049

Phone No. 215-273-7010

Location McNeil Consumer Healthcare

FROM:

Name Elizabeth F. Yuan

Fax No. 301-827-2315

Phone No. 301-827-2293
9201 Corporate Blvd. Rm. S210
Location Rockville, MD 20850

Comments:

We acknowledge receipt of your facsimile dated 2-18-00 providing to propose "Motrin Migraine Pain" as the tradename for NDA 19-012/S-016. Provided that the 2 words "Migraine" and "Pain" are both completely in capital lettering, and presenting in the exact same colors and size, the agency finds "Motrin Migrain Pain" acceptable. Please submit a letter of commitment regarding the lettering, colors, and size to this NDA if you propose to use "Motrin Migraine Pain" as the tradename to your NDA supplemental application.

Please be reminded that this correspondence only addresses the tradename and not the complete labeling for this drug product. A complete response to our facsimile dated 2-17-2000 is still pending to the agency for the review of this supplemental new drug application.

Thank you.

Attachment: Facsimile proposing "Motrin Migraine Pain"

McNeil

McNEIL CONSUMER HEALTHCARE, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034 (215) 273-7000

URGENT DELIVERY REQUESTED
FAX TRANSMITTAL

DATE: February 18, 2000 NUMBER OF PAGES (including cover page): 2

TO: Liz Yuan FROM: Janet A. Uetz

FAX NUMBER: (301) 827-2315 FAX NUMBER: (215) 273-4049
TELEPHONE NUMBER: (215) 273-8368

MESSAGE:

Dear Liz:

Attached is a copy of the principal display panel depicting the proposed tradename MOTRIN® Migraine Pain.

Janet A. Uetz

Janet A. Uetz

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FACSIMILE TRANSMISSION RECORD

DATE: 2/17/00

FROM: Kerry G. Rothschild, Esq.
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2284 FAX: 301-827-2316 or
301-827-2315

TO: Name: Janet Uetz
Company: McNeil Consumer Healthcare
Phone: 215-273-8368

FAX #: 215-273-4049 No. Of Pages (including cover) 4

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Message:
Please refer to your supplemental new drug application NDA 19-012/S-016, for Motrin (ibuprofen) tablets, caplets and geltabs, 200 mg.

Please find attached, a mock-up of the product labeling reflecting the content requirements of the March 17, 1999 FEDERAL REGISTER document "Over-The-Counter Human Drugs; Labeling Requirements; Final Rule" (64 FR 13254), incorporated into the drug regulations at 21 CFR 201.66. Please note that the attached labeling example is not intended to reflect formatting requirements under the OTC labeling final rule. Please refer to the OTC labeling final rule for specific formatting requirements.

In order to ensure an action today for this supplemental new drug application, we request that you provide a commitment letter acknowledging the following:

1. The enclosed labeling serves as a basis of approval for NDA 19-012/S-016; and

2. You agree to submit Final Printed Labeling (FPL) that is identical in content to the enclosed labeling text, and formatted consistent with 21 CFR 201.66.

To assist you in reformatting your labeling , the reviewer has provided the following comments:

1. 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.

2. 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.

3. 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.

4. 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.

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

6. **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."

7. **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."

8. **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."

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

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

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

12. 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.

If you have any questions regarding this submission, please contact Kerry Rothschild, Esq., Regulatory Project manager, at 301-827-2284.

M.M.B.
DEC 21 1998

McNEIL CH
RECORD OF CONTACT

Agency:
FDA X
Other

Date of contact:
12/18/98

Medium:
Telephone X
Meeting at

Date of Record:
12/18/98

Between:
FDA
Peter Rickman
Branch Chief
Regulatory Affairs, Office of Generic Drugs
(telephone - (301) 827-5845)

Subject:
Consolidation of NDA/ANDAs
for OTC MOTRIN Products

Representing McNeil CH:
Willie D. Pagsuyuin

IND:
NDA:
Other:
ANDA: 19-012
73-019
71-215
70-475

I called the Office of Generic Drugs and spoke with Peter Rickman. I explained to him that McNeil now owns both the parent NDA (19-012) for Motrin IB and several approved ANDAs for OTC Motrin products. Further, I told him that we would like to consolidate these files by incorporating our approved ANDAs into NDA 19-012. Rick said that our proposal is acceptable to him; however, he said that we will need to submit a letter withdrawing the ANDAs and requesting that information in these ANDAs be incorporated into NDA 19-012. Once they receive this request, they will transfer the "jackets" (files) to the Drug Evaluation group. He also asked me to work out the logistics with the Drug Evaluation group to ensure that there is no interruption in the regulatory status of products covered under the ANDAs.

Willie D. Pagsuyuin

M.M.B.

McNEIL CH
RECORD OF CONTACT

DEC : 1998

Agency:
FDA X
Other

Date of contact:
11/9/98

Medium:
Telephone X
Meeting at

Date of Record:
12/1/98

Between:
FDA - OTC Division
Linda Katz, MD
Marina Chang
Stephanie Mason
Debbie Lumpkin

Subject:

Representing McNeil CH:
Vivian Chester
Paula Oliver
Willie Pagsuyuin

IND:
NDA: NDA 19-012 Motrin IB Tablets/Caplets
NDA 19-899 Motrin IB Sinus Tablets/Caplets
NDA 20-516 Children's Motrin Suspension
NDA 20-601 Children's/Jr Strength Motrin Chewable Tablets
NDA 20-602 Jr Strength Motrin Caplets
NDA 20-603 Children's Motrin Drops
ANDA 73-019 Motrin IB Gelcaps
NDA 19-872 Tylenol ER Caplet
Other:

Background:
At FDA's request, a telephone conference was held 11/9/98 to discuss the following:

1. Product name: Tylenol Arthritis Extended Relief Caplets
2. Allergy warnings for adult and children's OTC Motrin products
3. Proposed application to add migraine indication to our adult OTC Motrin products

Tylenol Arthritis Extended Relief Caplets

FDA advised McNeil that labeling for Tylenol Arthritis Extended Relief insufficiently communicates that the product is intended for pain relief. To address this issue, McNeil agreed to either:

- Modify the product name to include the word "Pain" or,
- Include a statement on the principal display panel to indicate that the product is intended for the treatment of the pain of arthritis.

We were asked to submit revised labeling under an SNDA for FDA approval.

In a follow-up conversation later that day, FDA also requested that we submit representative promotional materials for Tylenol Arthritis ER.

Allergy Warnings for OTC Adult and Children's Motrin Products

FDA advised us to use the allergy warning as outlined in their letter of September 15, 1998.

Proposed Application to Add Migraine Indication to our adult OTC Motrin Products

FDA indicated that it is acceptable to submit the application for migraine indication for the OTC Motrin Tablets and Caplets under an SNDA to NDA 19-012. The marketed gelcap product can be included in the same SNDA and the CMC information for this formulation can be incorporated by cross-referencing the approved ANDA 73-019.

The OTC Division also did not object to our proposal to consolidate ANDA 73-019 for Motrin Gelcap under NDA 19-012 for Motrin Tablet and Caplet but suggested we also obtain agreement from the Office of Generic Drugs before doing so.

Willie D. Pagsuyoin

19-012 / 73-019

McNEIL

URGENT DELIVERY REQUESTED

McNEIL CONSUMER PRODUCTS COMPANY, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034-2299 (215) 233-7000

FAX TRANSMITTAL

FAX NUMBER: (301) 827-2315 **DATE:** November 2, 1998

TO: Stephanie Mason, Project Manager

FROM: Willie D. Pagsuyuin (telephone number- (215) 233-7115)

FROM FAX NUMBER: (215) 233-7168

RE: NDA 19-012
Motrin IB Tablets & Caplets, 200 mg
ANDA 73-019
Motrin IB Gelcaps, 200 mg

Dear Stephanie:

This is regarding our plans to submit an application to add migraine as an indication for our existing OTC Motrin IB products.

I. For Motrin IB Tablets and Caplets, 200 mg, covered under our approved NDA 19-012:

We wish to confirm the acceptability of submitting an SNDA to NDA 19-012. The products will have separate labeling with the migraine indication.

II. For Motrin IB Gelcaps, 200 mg, covered under our approved ANDA 73-019:

We wish to determine which of the following submission route is acceptable to the FDA for adding the migraine indication:

A. Submit an SNDA to our approved ANDA 73-019. Safety and efficacy data will be incorporated by cross-reference to the SNDA to NDA 19-012 (indicated above in Item I). The product will have separate labeling with the migraine indication.

B. Include the gelcap in our SNDA listed in Item I above, and submit it to our approved NDA 19-012. CMC information will be incorporated by cross-reference to our approved ANDA 73-019. The product will have separate labeling with the migraine indication.

We would appreciate your prompt response. Thank you. Willie Pagsuyuin

NUMBER OF PAGES (INCLUDING TRANSMITTAL SHEET): 1

IF YOU HAVE ANY PROBLEMS RECEIVING THIS FAX, CALL: (215) 233-7115