20603S003

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-603/S-003

APR 15 1999

McNeil Consumer Healthcare
Attention: Vivian A. Chester
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Dear Ms. Chester:

Please refer to your supplemental new drug application dated and received June 15, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infant's Motrin (ibuprofen oral suspension) Concentrated Drops, 50 mg/1.25 mL.

We acknowledge receipt of your correspondences dated April 14 and 15, 1999.

This supplemental new drug application provides for the the expanded use of Infant's Motrin (ibuprofen oral suspension) Concentrated Drops, 50 mg/1.25 mL to include dosing instructions for children 6 months to 23 months of age.

The user fee goal (10 months) for this supplemental new drug application is April 15, 1999.

We have completed the review of this supplemental new drug application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed agreed upon labeling text. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling text. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-603/S-003." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug product becomes available, revision of the labeling may be required.

Please submit three copies of the introductory promotional materials that you propose to use for

this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Over-the-Counter Drug Products and two copies of both the promotional materials and the labeling directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions regarding this application, please contact Kerry Rothschild, Esq., Regulatory Project Manager, at (301) 827-2222.

Sincerely yours,

Linda M. Katz, M.D., M.P.H.
Deputy Director 4/15/99
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

6 pages
Draft Labeling

Copy

MEDICAL OFFICER REVIEW
Division of Over-The-Counter Drug Products

NDA #: 20-603, SE5-~~005~~ 003
NAME: Children's MOTRIN® (ibuprofen oral suspension) Drops, 50 mg/1.25 mL
SPONSOR: McNeil Consumer Products Company
7050 Camp Hill Road
Fort Washington, PA 19034-2299
Tel.:(215)233-7000
TYPE OF SUBMISSION: Commercial Pharmaceutical
DATE OF SUBMISSION: June 15, 1998 **CDER:** June 15, 1998
DATE OF REVIEW: March 15, 1999
REVIEWER: Rosemarie Neuner, MD, MPH
CSO: Mr. Kerry Rothschild, JD

Introduction

Ibuprofen is a propionic acid derivative that belongs to the nonsteroidal anti-inflammatory class of drugs (NSAIDs). A suspension formulation of ibuprofen (100 mg/5 mL) has been marketed in the United States since 1989 by McNeil Consumer Products for use in children (age 6 months and older) as a prescription drug, under the trade names, Pedia-Profen and Children's MOTRIN® Suspension. On June 10, 1995 Children's MOTRIN® (ibuprofen oral suspension) Drops, 50 mg/1.25 mL was approved by the U.S. Food and Drug Administration for marketing as an over-the-counter (OTC) drug product for the temporary relief of fever and pain in children 2-3 years of age. In June 1998, the sponsor of this product, McNeil Consumer Products, submitted a request to the agency for a pediatric exclusivity claim which was subsequently granted. The sponsor has now submitted this efficacy supplement for agency review in which they request the lowering of the currently approved group age range from two to three years of age down to two months of age for this product.

In support of this change in the product's dosing age range, the sponsor has submitted the results of a new subgroup analysis of data generated from 27,000 children less than 2 years of age who participated in the actual use drug -safety trial, the Boston University Fever Study, which evaluated the safety profile of Children's MOTRIN® as an antipyretic agent. (Note: This was the pivotal safety study that supported the approval for the sponsor's NDA 20-516 Children's MOTRIN® Ibuprofen Oral Suspension 100 mg/5 mL in 1995. It also served as the supportive safety study in the approval of the sponsor's other NDA 20-603 Children's MOTRIN® Ibuprofen Drops 50 mg/1.25 mL in 1996.) In addition, the sponsor has included the results of 21 clinical trials where children 2 years old and younger participated as study subjects, in addition to 4 published pharmacokinetic (PK) studies involving children ages 2 months to 2 years. The results from these PK studies are discussed in the PK section of this SNDA review by Dr. E. Dennis Bashaw, FDA Division of Pharmacokinetics (HFD-880).

Since prescription ibuprofen is currently approved for use in infants age 6 months and older, the major regulatory issue to be answered by this application is it

safe for OTC ibuprofen to be used in the pediatric age group 2 months and older at the doses proposed by the sponsor of this supplement. This review will therefore concentrate on the drug's safety profile in this targeted age group.

Efficacy

In support of ibuprofen's efficacy in the targeted pediatric age group of 2 months to 2 years, the sponsor performed an extensive search of the worldwide literature. This search yielded 23 articles and 6 abstracts which described the results of 21 randomized, controlled antipyretic (16) and analgesia (5) trials which evaluated ibuprofen in children ages less than 2 years of age. A complete listing of these articles and abstracts, and their trial summaries written by the sponsor can be found in the following sponsor's tables, Tables 8-10 and 8-12, in Attachment I.

A total of 2,032 febrile children between the ages of 2 months to 13 years participated in the antipyretic studies. (See the following sponsor's table, Table 8-10, found in Appendix I.) Of these 16 studies, 2 were placebo-controlled trials. The other 14 studies compared ibuprofen to active controls such as acetaminophen or aspirin. Five (5) out of the 16 studies were single-dose studies while the remaining 11 trials were multi-dose studies of ibuprofen. These 16 trials tested doses of ibuprofen in the range of 0.5 mg/kg to 10 mg/kg. All 16 studies showed that ibuprofen at the doses tested, with the exception of the lowest dosing range, was an efficacious antipyretic agent in the populations tested. (Refer to Table 8-10 found in Attachment I at the end of this review.)

A total of 504 children between the ages of 6 months to 14 years participated in the 4 postoperative and 1 otitis media analgesic studies. (See the following sponsor's table, Table 8-12, located in Attachment I.) Two out of the 5 trials were placebo-controlled studies, 2 were placebo- and active- controlled studies, and 1 study evaluated ibuprofen as a single-agent with codeine used for rescue pain. Three of the 5 studies evaluated multi-doses while 2 were single-dose trials. The dose range of ibuprofen used in these analgesia studies ranged from 5 mg/kg to 13 mg/kg. All 5 studies showed that ibuprofen at the doses tested was comparable to acetaminophen or more efficacious than placebo in the control of pain in the patients studied.

The sponsor created the following 2 tables, Sponsor's Tables 1 and 2, below, to show how many studies in this collection included study subjects from the targeted pediatric age group. With the exception of one randomized, double-blind, actively controlled antipyretic trial which compared ibuprofen 7.5 mg/kg to acetaminophen 10 mg/kg in 154 children aged 6-months to 5-years, all of the remaining studies used descriptive statistics (i.e., mean, standard deviation, and range) in discussing the age of the subjects who participated in the studies. Thus, it is impossible to know how many children less than 2 years of age actually participated in these studies.

Sponsor's Table 1 - Age of the Youngest Patient Included in Published Efficacy Antipyretic Trials

Age	Number of Studies	Literature Reference [one study]
2-3 months	6	[8] [19,49] [20] [25] [26] [27]
4-11 months	9	[6] [7] [10,13] [11,17] [12] [15,22] [14,16,24] [18,21] [23]
12-23 months	1	[9]

Sponsor's Table 2 - Age of the Youngest Patient Included in Published Efficacy Analgesic Trials

Age	Number of Studies	Literature Reference [one study]
2-3 months	0	None
4-11 months	1	[30]
12-23 months	4	[28] [29,33] [31] [32]

Since these studies are not proprietary studies, and their actual case reports and data sets were not included in this submission for review, they can only be considered supportive of the already established efficacy profile of ibuprofen in children ≤ 2 years old. As previously discussed, ibuprofen as a prescription drug is considered to be efficacious in the sponsor's requested pediatric target age group for this submission. Thus, these studies are being included in this review at this time for completeness and reference.

Medical Reviewer's Comments: All 21 studies showed that ibuprofen was an efficacious agent for the indications studied when compared to placebo and other recognized antipyretic and analgesic agents. Thus, these studies can be used in support of ibuprofen's already recognized effectiveness as an antipyretic and analgesic agent in the sponsor's requested targeted age group.

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Safety

As discussed in the preceding introduction, the focus of this review is to determine whether ibuprofen is safe to be used as an OTC agent in the sponsor's requested targeted pediatric age group of 2-months to 2-years. In support of this product's safety profile the sponsor has submitted for review the following safety data for children less than 2-years of age:

1. The Boston University Fever Study subgroup analysis of children less than 2-years of age.
2. McNeil CPC controlled clinical trial data on subjects ≤ 2-years of age enrolled on or after November 17, 1993 and treated with ibuprofen.
3. McNeil CPC Spontaneous Reporting System for McNeil CPC ibuprofen products in children ≤ 2-years of age for the time period November 17, 1993 through October 2, 1997, including serious reports in the published literature.
4. FDA Spontaneous Reporting System for all ibuprofen products in children ≤ 2-years of age for the time period November 1, 1993 through August 25, 1997. (Note: Adverse events reported through McNeil Spontaneous Reporting System are not included here.)
5. Published randomized controlled clinical trials and human pharmacokinetic studies of ibuprofen products for the years 1966 through October 1997 that reported including children ≤ 2-years of age.
6. AAPCC TESS ibuprofen data from the years 1994 through 1996 for children ≤ 2-years of age. (The 1997 report was not yet available.)

The sponsor has compiled the following summary table, Table 8-13, which outlines the total number of serious adverse events that have been reported to have occurred in children < 2-years of age since November 1993 from the above submitted safety data base. (See sponsor's table, Table 8-13, below.)

The cornerstone of this safety data base for children (see sponsor's table, Table 8-13, below) is generated from the actual use safety study, the Boston Fever Study. Although this study was reviewed by the agency in support of a regulatory action for NDA 20-516 Children's MOTRIN® Ibuprofen Oral Suspension 100 mg/5 mL in 1995, the sponsor has submitted for review a new subcohort analysis of the 27,065 children < 2 years of age who participated in this study which compares the incidence of adverse events that occurred during the trial in this group to that of subjects age ≥ 2 years. This study will be discussed first followed by reviews of the other safety data as listed above.

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Table 8-13. Summary of Ibuprofen Safety Data For Children Less Than Two Years of Age (data since November 1993, except where noted otherwise)

Boston University Fever Study (children < two years of age)	(Total Patients)	27,065
Total Ibuprofen Exposures		17,938
Hospitalizations for events of primary interest		3
Other hospitalizations (excluding deaths)		258
Deaths		0
McNeil CPC Controlled Clinical Studies (children < two years of age)		
Antipyretic Study	(Total Patients)	1
Total Ibuprofen Exposures[1]		1
Reports of AEs with serious outcomes (excluding deaths)[2]		0
Deaths		0
Commercial Marketing Experience		
• Dosage Units (50 mg) Shipped: OTC Children's Motrin Ibuprofen Products (all ages)		
• Total Prescriptions Filled: Pediatric Ibuprofen Suspension and Drops (all ages)		
• Total Physician Recommendations for Pediatric Ibuprofen Products (estimate for children < two years of age)		
McNeil CPC Drug Safety Reporting System (pediatric ibuprofen products) (children < two years of age)		
Total Ibuprofen Reports		314
Reports of AEs with serious outcomes (excluding deaths)[2]		7
Deaths		2
FDA Spontaneous Reporting System (pediatric, adult and unknown ibuprofen products) (children < two years of age)		
Total Ibuprofen Reports (excludes McNeil CPC reports)		72
Reports of AEs with serious outcomes (excluding deaths)[2]		20
Deaths		5
AAPCC TESS Database (pediatric, adult and unknown ibuprofen products) (children < two years of age)		
Total Ibuprofen Exposure Cases (1994 through 1996)		17,635
Moderate or major outcomes (excluding deaths)[3]		29
Deaths		0
Published Randomized Controlled Studies (inclusive of, but not limited to, children < two years of age[4]) (first study published in 1976)		
Antipyretic Studies	(Total Patients)	2032
Total Ibuprofen Exposures		974
Serious AEs (excluding deaths)[5]		0
Deaths		0
Analgesic Studies	(Total Patients)	504
Total Ibuprofen Exposures		213
Serious AEs (excluding deaths)[5]		0
Deaths		0
Pharmacokinetic/Pharmacodynamic Studies	(Total Patients)	340
Total Ibuprofen Exposures		194
Serious AEs (excluding deaths)[5]		0
Deaths		0

1 One child less than two years of age was unintentionally enrolled in a McNeil CPC controlled trial of ibuprofen for which enrollment was planned for children two to 11 years of age (Protocol No. 95-516).

2 A serious outcome is defined as an adverse event that is life threatening (immediate risk of death from the reaction), requires inpatient hospitalization, prolonged hospitalization, or is permanently or severely disabling. Outcomes of death, congenital anomaly, or cancer are also considered serious.

3 Generally, a moderate outcome involves a patient who exhibits signs or symptoms as a result of the exposure which are pronounced, prolonged, or of a systemic nature; usually some form of treatment is required. Symptoms are not life-threatening and the patient has no residual disability or disfigurement. A major outcome generally involves a patient who exhibits signs or symptoms as a result of the exposure which are life-threatening or result in significant residual disability or disfigurement.

4 While overall safety information was reported, such information for children less than two years of age was not specified.

5 Serious as defined by the investigator.

1. The Boston Fever Study Subcohort Analysis of Children Less Than 2 Years of Age.

This was a 4-week, multicenter, double-blind, randomized, acetaminophen-controlled antipyretic study conducted by the Slone Epidemiology Unit of Boston University in office-based pediatric population from the continental United States. The study's objective was to assess the risk of serious adverse events such as gastrointestinal bleeding, acute renal failure, anaphylaxis and Reye syndrome associated with the use of ibuprofen in febrile children. Children between 6 months to 12 years of age weighing between 7-50 kg were recruited after presenting for a pediatric evaluation of an acute febrile illness to any one of the 1,735 pediatricians or family practitioners who participated in the trial. In order to be eligible for study entry, the children had to be able to take the study medication by mouth, and have a parent/guardian able to administer the study medication while observing and caring for them. Children who were dehydrated, unable to take medication by mouth, or with histories of hypersensitivity to acetaminophen or NSAIDS, renal or hepatic diseases, bleeding disorders, anemia, neoplasia, endocrine or metabolic problems, or peptic ulcer disease were ineligible for study entry. A total of 84,192 patients were entered into the trial out of which 83,915 patients were randomized and received 1 of the following 3 treatments: 5 mg/kg ibuprofen, 10 mg/kg ibuprofen, or 12 mg/kg acetaminophen.

Out of the total of 83,915 children entered into the study, 27,065 were < 2 years and 56,850 were ≥ 2 years of age. Demographically, the 2 age groups on comparison as well as the 3 randomized treatment groups were very similar in make up as shown in the following 2 tables, Sponsor's Tables 3 and 4, below.

Sponsor's Table 3 - Demographic Characteristics of All Participants

Characteristic	Age	
	< 2 years (n =27,065)	≥ 2 years (n = 56,850)
Median Age (Months)	13	59
Median Weight (kg)	10	18
Sex, %Male % Female	54 46	50 50
Race, %White % African-American %Hispanic	81 7.2 7.2	82 7.3 6.6

Sponsor's Table 4 - Demographic Characteristics of 27,065 Participants ≤ 2 Years Old According to Treatment Group

Characteristic	Acetaminophen	Ibuprofen (5 mg/kg)	Ibuprofen (10 mg/kg)
Total Number	9,127	9,159	8,779
Median Age (Months)	14	13	13
Median Weight (kg)	10	10	10
Sex, % Male	54	54	55
Race, % White	82	81	80
% African-American	7.3	6.8	7.4
% Hispanic	6.7	7.2	7.7

Three-hundred nineteen (319) children (1.1%) ≤ 6 months of age were entered into the study despite an entry age requirement of being at least 6 months or older. Table 5 below lists the numbers of infants ≤ 6 months who participated in the study. (Note: In the official study report the sponsor states that because age was not routinely confirmed, children ≤ 6 months of age were only included in the analysis of the study data if their reported weight was between the 5th and 95th percentile for month of reported age.).

Table 5 - Age Distribution For 319 Children Younger than 6-Months of the 27,065 Participants ≤ 2 Years Old at Enrollment

Age in Months	Number	Percent
1	4	0.015%
2	13	0.048%
3	27	0.010%
4	76	0.281%
5	199	0.735%

The 2 age groups differed in the reported causes of their fevers as shown in Sponsor's Table 6. Although upper respiratory tract infection was the most commonly reported cause of fever for both age groups, in children < 2 years of age, otitis media was more common ($p<0.001$) as compared to children ≥ 2 years of age, who were more commonly afflicted with pharyngitis and lower respiratory tract infections ($p<0.001$ for

both comparisons).

Sponsor's Table 6 - Cause of Fever Among All Participants

Illness (%)	Age	
	< 2 years (n =27,065)	≥ 2 years (n = 56,850)
Upper Respiratory Infection	43	42
Otitis Media	48[1]	27
Pharyngitis	19	40[2]
Lower Respiratory Infection	6.3	8.8[3]
Gastrointestinal Infection	3.0	3.2

[1]Statistically significant difference at (p<0.001).
[2]Statistically significant difference at (p<0.001).
[3]Statistically significant difference at (p<0.001).

Sponsor's Table 7 shown immediately below demonstrates that there were no differences in the causes of fever in the 27,065 participants ≤ 2 years of age when examined by randomized antipyretic treatment group.

Sponsor's Table 7 - Cause of Fever Among 27,065 Participants ≤ 2 Years Old According to Treatment Group

Illness (%)	Acetaminophen	Ibuprofen (5 mg/kg)	Ibuprofen (10 mg/kg)
Upper Respiratory Infection	43	43	43
Otitis Media	48	48	48
Pharyngitis	20	19	20
Lower Respiratory Infection	6.5	6.2	6.2
Gastrointestinal Infection	3.0	3.3	2.8

The following 2 tables, Sponsor's Tables 8 and 9, show by age and randomized treatment group the numbers and percentages of children who were randomized, but did not receive study medications. The tables also show that the median number of doses and the median duration of treatment by those who did receive medications was very similar for the subcohort and the original cohort groups, as well as all 3 treatment groups ≤ 2 years of age.

Sponsor's Table 8 - Study Medication Use Among All Participants

Exposure	Age	
	< 2 years (n =27,065)	≥ 2 years (n = 56,850)
Treated, %	96.1	95.1
Not Treated, %	3.9	4.9
Doses Received (Median)	6-10	6-10
Duration in Days (Median)	3	3

Sponsor's Table 9 - Study Medication Use Among 27,065 Participants ≤ 2 Years Old According to Treatment Group

Exposure	Acetaminophen	Ibuprofen (5 mg/kg)	Ibuprofen (10 mg/kg)
Treated, %	96.1	96.1	96.0
Not Treated, %	3.9	3.9	4.0
Doses Received (Median)	6-10	6-10	6-10
Duration in Days (Median)	3	3	3
Dose (mg/kg) (Median)	12	4.8	9.6

Study Outcomes:

Although no deaths were reported to have occurred during the duration of the study, 2 children did die during the follow-up period. Both deaths were unrelated to the study medications. The first case involved a 15-month-old black male randomized to the acetaminophen treatment group who died as a result of injuries sustained in a motor vehicle accident. The second case involved an 11-year-old male randomized to ibuprofen 5 mg/kg who died due to complications of meningitis.

The original objective of this study was to assess the risk associated with the use of ibuprofen in febrile children for the occurrence of serious adverse events. The objective of the subcohort analysis was to describe the risk of serious adverse clinical events following the use of ibuprofen in a study subcohort of children < 2 years of age. The original analysis of the entire study cohort found that only 795 (1%) participants out of the 83,915 randomized to receive study medications were hospitalized for any reason during the 4 weeks following study entry. In the subcohort analysis, 385 out of the 27,065 children < 2 years of age and 410 out of 56,850 children ≥ 2 years of age were hospitalized for any reason. (See Sponsor's Table 10, below.)

As part of the statistical analysis of this new subcohort examination, absolute risk and relative risk for the development of serious outcomes were designated to be calculated for comparison purposes by both age and treatment groups for "any" as well as for specifically predesignated adverse events that are of a safety concern in pediatric populations exposed to ibuprofen (i.e., GI bleeding, acute renal failure, anaphylaxis, or Reye Syndrome.) In the < 2 years of age subcohort, the absolute risk for hospitalization due to any reason was found to be 1.4% (95% confidence interval, 1.3-1.6%) vs 0.72% (95% CI, 0.65-0.79%) for children ≥ 2 years of age. (Refer to Sponsor's Table 10 below.) The relative risk for hospitalization due to any reason in the < 2 years of age subcohort as compared to the subcohort ≥ 2 years was found to be 2.0 (95% CI, 1.7-2.3). (See Sponsor's Table 10.)

Sponsor's Table 10 - Risk of Hospitalization for Any Reason According to Age

Age	Total Number	No.Hospitalized	Absolute Risk (95% CI[1])	Relative Risk[2] (95% CI)
<2 yrs.	27,065	385	1.4% (1.3-1.6%)	2.0 (1.7-2.3)
≥2 yrs.	56,850	410	0.72% (0.65-0.79%)	1.0 (--)

[1]Confidence interval.
[2]Risk of hospitalization among children < 2 years of age compared to the risk of hospitalization among children ≥ 2 years of age.
[3]Reference category.

Only 2 out of the 319 infants < 6 months of age who were included in the study were hospitalized. The first case involved an infant hospitalized for the treatment of a viral infection who had been assigned to ibuprofen 5 mg/kg. The other case involved an infant hospitalized with pneumonia who had been assigned to the ibuprofen 10 mg/kg treatment group.

As part of the new "sub" subcohort analysis, the absolute risk of hospitalization for any reason for the 319 infants < 6 months old regardless of antipyretic treatment was 0.63% (95% CI, 0.08-2.2%). When compared to the risk of hospitalization in children ≥ 6 months of age, no significant difference was shown (p=0.8) between these 2 age groups. No significant difference (p=0.5) was also found when comparing the risk of hospitalization for any reason according to assigned antipyretic treatment in infants < 6 months of age.

The following table, Sponsor's Table 11, shows that when comparing the risk for hospitalization for any reason by treatment group assignment according to age, children < 2 years of age treated with ibuprofen (relative risk: 2.1 [95% CI, 1.8-2.5]) and acetaminophen (relative risk - 1.7 [95% CI, 1.8-2.5]) were at a significantly higher risk than children ≥ 2 years old (ibuprofen - relative risk: 1.0 [95% CI]; acetaminophen - relative risk - 1.0 [95%, CI]). (Refer to Sponsor's Table 11 below.) No increase in the risk for hospitalization was noted on comparison of within age groups according to treatment as shown in the next table, Sponsor's Table 12, as shown below. (See the

following table, Sponsor's Table 12.)

Sponsor's Table 11 - Risk of Hospitalization for Any Reason According to Antipyretic Assignment and Age

Antipyretic	Age	Total Number	No. Hospitalized	Absolute Risk/100,000 (95% CI[1])	Rel. Risk[2] 95% CI
Ibuprofen	<2 yrs.	17,938	261	1.5% (1.3-1.6%)	2.1 (1.8-2.5)
	≥2yrs.	37,847	262	0.69% (0.61-0.78%)	1.0[3] (---)
Acetaminophen	<2 yrs.	9,127	124	1.4% (1.1-1.6%)	1.7 (1.4-2.2)
	≥2yrs.	19,003	148	0.78 (0.66-0.91%)	1.0[3] (---)

[1]Confidence Interval.
[2]Risk of hospitalization among children < 2 years of age compared to the risk of hospitalization with among children randomized to ≥ 2 years of age.
[3]Reference category.

Sponsor's Table 12 - Risk of Hospitalization for Any Reason According to Age and Antipyretic Assignment

Age	Antipyretic	Total Number	Number Hospitalized	Absolute Risk (95% CI[1])	Relative Risk[2] (95% CI)
<2 years	Ibuprofen	17,938	261	1.5% (1.3-1.6%)	1.1 (0.87-1.3)
	Acetaminophen	9,127	124	1.4% (1.1-1.6%)	1.0[3] (---)
≥2 years	Ibuprofen	37,847	262	0.69% (0.61-0.78%)	0.89 (0.73-1.1)
	Acetaminophen	19,003	148	0.78 (0.66-0.91%)	1.0[3] (---)

[1]Confidence Interval.
[2]Risk of hospitalization among children randomized to ibuprofen compared to the risk of hospitalization among children randomized to acetaminophen.
[3]Reference category.

As stated earlier, one of the original aims of the Boston Fever Study was to assess the risk for the occurrence of GI bleeding, acute renal failure, anaphylaxis and Reye Syndrome in the pediatric population studied. In the original cohort of 83,915 patients that were entered into the study, there were only 4 reported cases of GI bleeding, and no cases of acute renal failure, anaphylaxis, or Reye Syndrome. Sponsor's Table 13 (see below) shows the distribution and the absolute risk by age group for a hospitalization due to acute GI bleeding in the subcohort analysis. In children < 2 years of age, this risk was found to be 11 per 100,000 (95% CI, 2.2 to 32 per 100,000). Since these numbers were so low, there was insufficient data to show a significant difference (Fisher's exact test, p=0.1) when compared with the risk for acute GI bleeding in children ≥ 2 years of age.

Sponsor's Table 13 - Risk of Hospitalization With Acute Gastrointestinal (GI) Bleeding According to Age

Age	Total Number	No.Hospitalized	Absolute Risk per 100,000	95% CI[1]
<2 years	27,065	3	11	2.2-32
≥2 years	56,850	1	1.8	0.05-9.8

[1]Confidence Interval

As seen in Sponsor's Table 14 (below), all of the GI bleeds occurred in children treated with ibuprofen. Although the highest absolute risk of hospitalization due to an acute GI bleed was found to be associated with children < 2 years of age treated with ibuprofen (17 per 100,000 [95% CI, 3.5-49 per 100,000]), the sponsor reported the risk for the two ibuprofen treatment groups within that age group was similar. However, it was not found to be significantly increased (p=0.6) when compared to the risk associated with children < 2 years of age who were treated with acetaminophen (0 per 9,127 [95% CI, 0-33 per 100,000]). (Refer to Sponsor's Table 14.) In children ≥ 2 years of age, the risk of a hospitalization due to acute GI bleeding in the ibuprofen treated group was 2.6 per 100,000 (95% CI, 0.05-15 per 100,000), and in the acetaminophen treated group it was 0 per 19,003 (95% CI, 0-16 per 100,000). On comparison of the 2 age groups, the risk for hospitalization due to an ibuprofen-induced acute GI bleed was not found to be significantly different (p=0.1).

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Sponsor's Table 14 - Risk of Hospitalization with Acute GI bleeding According to Age and Antipyretic

Age	Antipyretic	Total Number	Number Hospitalized	Absolute Risk per 100,000	95% CI
<2 yrs.	Ibuprofen	17,938	3	17	3.5-49
	Acetaminophen	9,127	0	--	0-33
≥2 yrs.	Ibuprofen	37,847	1	2.6	0.05-15
	Acetaminophen	19,003	0	--	0-16

None of the 3 cases of acute GI bleed that occurred in the subcohort study population of < 2 years of age died. The first case (Subject ID 78468989) occurred in a 19-month-old male with a history of Hirschsprung's disease, status post colostomy and Swenson pull-through, and enterocolitis who was randomized to the ibuprofen 50 mg/5 mL treatment group when he presented with a fever due to otitis media. In addition, he also received a course of an unknown antibiotic. This subject received 3 doses of ibuprofen over the next 2-days. On the third day he was hospitalized for evaluation of abdominal pain and vomiting. Records state that his vomitus appeared to look like coffee grounds, and his stool was guaiac positive. He was treated with enemas and stool softeners for a possible bowel obstruction, and improved without further recurrence of GI bleeding during the 9 months of post-study follow up.

The second case (Subject ID 43135762) of acute GI bleed occurred in a 19-month-old male randomized to the ibuprofen 100 mg/5 mL treatment group who hospitalized the day after receiving just 1 dose of the study medication due to guaiac positive diarrhea associated with persistent vomiting. His stool assay was positive for rotavirus antigen. He improved after treatment with IV fluids, antibiotics, and acetaminophen without further episodes of bleeding during the 20 months of post-study follow up.

The last case (Subject ID 85496241) of acute GI bleeding occurred in a 8-month-old female randomized to the ibuprofen 100 mg/5 mL treatment group who had a fever due to a persistent case of otitis media which was treated with Augmentin. She was admitted on the third study day, 48 hours after receiving 2 doses of the study medication over a 24-hour period for evaluation of hematochezia and guaiac positive stools associated with dehydration, vomiting and otitis media. The subject improved with IV hydration and antibiotics and the treating physician attributed the hematochezia to the study medication. There were no reports of the hematochezia recurring during the 2 week post-study follow up.

Although there were no reported cases of acute renal failure, anaphylaxis or Reye syndrome which occurred during this study, the sponsor did calculate the observed risk for both the original study cohort population as well as that of the new subcohort analysis. Since there were no reported cases of these 3 specific adverse

events during the study, only the upper-bound of the 95% confidence interval (CI)could be calculated. In children < 2 years of age, the upper bound of the 95% CI for the risk of hospitalization due to acute renal failure, anaphylaxis, or Reye Syndrome was found regardless of the treatment group was 11 per 100,000; in children ≥ 2 years of age the upper bound for these events was 5.1 per 100,000. (Refer to Sponsor's Table 13.) In children < 2 years of age, the upper bound of the 95% CI for the risk of hospitalization due to these events treated with acetaminophen was found to be 0 per 9,127(95% CI, 0-33 per 100,000); in children < 2 years of age treated with ibuprofen the upper bound for these events was 0 per 17,938 (95% CI, 0-17 per 100,000). (Refer to Sponsor's Table 14.) In infants < 6 months of age, the observed risk of hospitalization for each of the above specific adverse events regardless treatment was 0 per 319 (95% CI, 0-0.94); among infants who received treatment with acetaminophen the observed risk was 0 per 112 (95% CI, 0 to 2.7%); among infants who received treatment with ibuprofen the observed risk was 0 per 207 (95% CI, 0 to 1.5%). (Note: The differences noted in the upper bound of the 95% CI for the infant population is due to its small sample size.)

In view of the fact that there were no cases of acute renal failure which occurred during this trial, the sponsor decided to look at changes in subjects' serum creatinine levels as another means of possibly determining the nephrotoxicity of ibuprofen in the pediatric population. Since the original protocol did not require the measurement and collection of entry and exit serum creatinines, they did a post hoc analysis from lab data collected from 222 (28%) out of the 795 children who were hospitalized while participating in the study. (Note: Only serum creatinines obtained within the first 24-hours of admission were used in this analysis.) The mean creatinine level on admission was 0.48 mg/dL, and 9% of them were higher than 0.7 mg/dL which is the upper limit of normal for children. No significant difference in mean serum creatinine levels was noted when compared by treatment group. Only 112 (29%) out of the 385 children < 2 years of age who were admitted during this study had serum creatinine levels available for analysis. The following table, Sponsor's Table 15 shown below, lists the distribution, mean and range for the serum creatinines collected for data analysis in this age group. (See Sponsor's Table 15.) On cross-treatment group comparison, the difference in mean serum creatinine between the acetaminophen group (0.34 mg/dL) and the ibuprofen treatment group (0.42 mg/dL) was found to be statistically significant (p=0.03) via calculation of an unpaired student's t-test, but when analysis of covariance is used to calculate the p-value taking into account subjects' ages, weight, sex and dehydration, no significant difference was found. Comparison of the prevalence of serum creatinines > 0.07 mg/dL in the acetaminophen and ibuprofen treatment groups, was not found to be significantly different (p=0.32). (See Sponsor's Table 15 below.) (Note: The sponsor reports that although they repeated this analysis with lower thresholds set for an "elevated" serum creatinine, the numbers of cases increased in both treatment groups but the difference was still not statistically significant. Although this data was not included in the submission for review, it needs to be mentioned to document the scope of the sponsor's post hoc analysis.)

Sponsor's Table 15 - Serum Creatinine Among Hospitalized Children < 2 Years Old

	Acetaminophen	Ibuprofen
Total Number	29	83
Serum Creatinine (mg/dL) **Mean** **(SEM)** **Range**	 0.34 (0.025) 0.1-0.7	 0.42 (0.023) 0.1-1.4
Serum Creatinine >0.7 mg/dL **Number** **(%)**	 0 (0)	 5 (6)

The following table, Sponsor's Table 16, lists the mean serum creatinines by treatment group for the subcohort of children < 2 years of age. The sponsor states that they did not do a subanalysis of mean serum creatinines in the subgroup infant population < 6 months of age because too few of these subjects were hospitalized.

Sponsor's Table 16 - Mean Serum Creatinine Among Hospitalized Children < 2 Years Old By Age and Treatment Group

Age	Mean Creatinine	(No.)	Mean Creatinine	(No.)	Mean Creatinine	(No.)
All	0.34	(29)	0.43	(46)	0.40	(73)
12-23 mos.	0.37	(17)	0.44	(25)	0.43	(21)
<12 mos.	0.32	(12)	0.43	(21)	0.36	(16)

The sponsor also looked at the risk for hospitalizations associated with other adverse events or conditions that may be of potential risk in this younger pediatric age group. They looked at asthma, bronchiolitis, and vomiting/gastritis since these occurred in at least 5 or more subjects in the subcohort population. Sponsor's Table 17, below, shows that there were 32 children < 2 years of age and 36 children ≥ 2 years of age who were hospitalized due to asthma while participating in the trial. The relative risk for hospitalization with asthma in children < 2 years of age was found to be 1.9 (95% CI 1.2 to 3.0) when compared to that in children ≥ 2 years of age.

Sponsor's Table 17 - Risk of Hospitalization with Asthma According to Age

Age	Total Number	No.Hospitalized	Absolute Risk/100,000 (95%CI)	Relative Risk[2] (95% CI)
<2 yrs.	27,065	32	120 (81-70)	1.9 (1.2-3.0)
≥2 yrs.	56,850	410	63 (44-88)	1.0[3] (--)

[1]Confidence interval.
[2]Risk of hospitalization with asthma among children < 2 years of age compared to the risk of hospitalization with asthma among children ≥ 2 years of age.
[3]Reference category.

The following table, Sponsor's Table 18 below, lists in a table the associated absolute and relative risks for the 2 age groups by treatment for hospitalization with asthma. This table shows that regardless of the antipyretic treatment, the risk of hospitalization is inversely related to the child's age.

Sponsor's Table 18 - Risk of Hospitalization with Asthma According to Antipyretic Assignment and Age

Age	Antipyretic	Total Number	Number Hospitalized	Absolute Risk/100,000 (95% CI[1])	Relative Risk[2] 95% CI
<2 yrs.	Ibuprofen	17,938	20	110 (68-170)	1.8 (1.0-3.2)
	Acetaminophen	9,127	24	63 (41-94)	1.0[3] (---)
≥2 yrs.	Ibuprofen	37,847	12	130 (70-230)	2.0 (0.9-4.6)
	Acetaminophen	19,003	12	63 (33-110)	1.0[3] (---)

[1]Confidence Interval.
[2]Risk of hospitalization with asthma among children randomized to ibuprofen compared to the risk of hospitalization with asthma among children randomized to acetaminophen.
[3]Reference category.

Sponsor's Table 19 below, shows the distribution of children hospitalized by age and treatment group for the risk of hospitalization due to asthma. The data in this table demonstrates that treatment with either antipyretic agent was not associated with the risk of hospitalization in either age group. (Refer to Sponsor's Table 19 shown below.)

Sponsor's Table 19 - Risk of Hospitalization with Asthma According to Age and Antipyretic Assignment.

Age	Antipyretic	Total Number	Number Hospitalized	Absolute Risk/100,000 (95% CI[1])	Relative Risk[2] 95% CI
<2 years	Ibuprofen	17,938	20	110 (68-170)	0.9 (0.4-1.7)
	Acetaminophen	9,127	12	130 (70-230)	1.0[3] (---)
≥2 years	Ibuprofen	37,847	24	63 (41-94)	1.0 (0.5-2.0)
	Acetaminophen	19,003	12	63 (33-110)	1.0[3] (---)

[1]Confidence Interval.
[2]Risk of hospitalization with asthma among children randomized to ibuprofen compared to the risk of hospitalization with asthma among children randomized to acetaminophen.
[3]Reference category.

Since it can be difficult to discern between asthma and bronchiolitis in very young children, the sponsor looked at the 37 hospitalized cases of bronchiolitis which occurred during the study. The following 2 tables, Sponsor's Tables 20 and 21, show the study data describing the risk associated with hospitalizations due to bronchiolitis in both subcohort age groups by age as well as treatment group.

Sponsor's Table 20 - Risk of Hospitalization With Bronchiolitis According to Age

Age	Total Number	No.Hospitalized	Absolute Risk per 100,000	95% CI[1]
<2 years	27,065	33	120	84-170
≥2 years	56,850	4	7	2-18

[1]Confidence Interval

Sponsor's Table 21, below, shows that on comparison of the 2 treatment groups, the risk for hospitalization due to bronchiolitis did not vary.

Sponsor's Table 21 - Risk of Hospitalization with Bronchiolitis Among Participants <2 Years of Age According to Antipyretic Assignment

Antipyretic	Total Number	Number Hospitalized	Absolute Risk/100,000 (95% CI[1])	Relative Risk[2] (95% CI)
Ibuprofen	17,938 9,127	21	120 (72-180)	0.9 (0.4-1.8)
Acetaminophen	9,127	21	130 (70-230)	1.0[3] (---)

[1]Confidence Interval.
[2]Risk of hospitalization with bronchiolitis among children randomized to ibuprofen compared to the risk of hospitalization with bronchiolitis among children randomized to acetaminophen.
[3]Reference category.

The sponsor also looked at the number of cases who were hospitalized due to vomiting/gastritis during the study. Sponsor's Table 22, below, shows the numbers of children and the associated risks for hospitalization due to vomiting/gastritis for both subcohort populations. On comparison between age groups, the risk for hospitalization due to vomiting/gastritis did not vary.

Sponsor's Table 22 - Risk of Hospitalization With Vomiting/Gastritis According to Age

Age	Total Number	No.Hospitalized	Absolute Risk/100,000 (95% CI[1])	Relative Risk[2] (95% CI)
<2 years	27,065	9	33 (15-63)	1.1 (0.5-2.5)
≥2 years	56,850	17	30 (17-48)	1.0[3] (---)

[1]Confidence Interval.
[2]Risk of hospitalization with vomiting/gastritis among children randomized to ibuprofen compared to the risk of hospitalization with vomiting/gastritis among children randomized to acetaminophen.
[3]Reference category.

The last table, Sponsor's Table 23, below, demonstrates that the risk for hospitalization due to vomiting/gastritis did not increase with treatment with either acetaminophen or ibuprofen, nor was it shown to vary with age or antipyretic treatment.

Sponsor's Table 23 - Risk of Hospitalization with Vomiting/Gastritis According to Antipyretic Assignment and Age

Antipyretic	Age	Total Number	No. Hospitalized	Absolute Risk/100,000 (95% CI[1])	Rel. Risk 95% CI
Ibuprofen	<2 yrs.	17,938	7	39 (16-80)	1.1 (0.5-2.9)
	≥2yrs.	37,847	13	34 (18-59)	1.0[3] (---)
Acetaminophen	<2 yrs.	9,127	2	22 (2.6-79)	NA[4]
	≥2yrs.	19,003	4	21 (5.8-54)	1.0[3] (---)

[1]Confidence Interval.
[2]Risk of hospitalization with vomiting/gastritis among children < 2 years of age compared to the risk of hospitalization with vomiting/gastritis among children randomized to ≥ 2 years of age.
[3]Reference category.
[4]Relative risk not calculated because the number hospitalized in at least one group was < 5.

Medical Reviewer's Comments: There are many methodological problems associated with this subcohort analysis of the Boston Fever Study. The original study was unable to accomplish one of its aims which was to assess the risk associated with the use of ibuprofen in a pediatric population for developing GI bleeds, acute renal failure, anaphylaxis and Reye syndrome. It is unclear if this was due to problems failing to measure or capture these adverse events or if the design introduced selection bias based on having health care providers "select" good candidates (i.e., children who were not too sick and had intelligent caretakers.) Since the new subcohort analysis was a post hoc analysis of the original trial data, the validity of its findings are subject to the same issue.

Some of the laboratory data subanalyses performed in this submission did not make good sense to this reviewer such as using the serum creatinines as surrogate markers for more significant problems were not validated.

The original protocol also had an age entry criteria of > 6 months, but the subanalysis reveals that 319 infants ≤ 5 months old were entered into the study. These enrollments constitute trial violations and thus, both the subcohort and "sub-subcohort" infant analysis which draw on this data for support technically should be discounted.

Despite these methodological flaws, the study's size does provide some useful information. Thus, based on the above study data reviewed, and the paucity of adverse events that actually occurred in such a large pediatric population (subcohort population

of n=27,065), it is fairly obvious that ibuprofen at the 2 doses tested is safe to be used in an OTC pediatric population < 2 years of age. The real question posed to this reviewer is at what age is it no longer safe to be used as an OTC product? Unfortunately, there is no answer to that question based on the data submitted in this SNDA. Sponsor's Table 5, demonstrates numerically how few infants between the ages of 2 and 5 months actually participated (as protocol violations no less) in the study (n=319), with the percentage of infants < 6 months of age enrolled in the study comes to only < 1.2% of the total subcohort population. Thus, it is the opinion of this medical reviewer that this study fails to generate sufficient support for a pediatric OTC claim in children < 6 months of age.

2. McNeil CPC controlled clinical trial data on subjects ≤ 2-years of age enrolled on or after November 17, 1993 and treated with ibuprofen.

Since the above listed date, sponsor states in this submission that they have not conducted any clinical trials in children ≤ 2 years of age. One 19-month-old child was inadvertently randomized to the ibuprofen suspension 7.5 mg/kg treatment group of a 2-arm, single-dose, randomized, investigator-blinded antipyresis trial that compared ibuprofen to acetaminophen 12.5 mg/kg. The child reportedly did not experience any adverse effects from this exposure.

Medical Reviewer's Comments: Noted.

3. McNeil CPC Spontaneous Reporting System for McNeil CPC ibuprofen products in children ≤ 2-years of age for the time period November 17, 1993 through October 2, 1997, including serious reports in the published literature.

A search of the sponsor's own CPC Spontaneous Reporting System (SRS) for both serious and nonserious adverse event reports in children ≤ 2 years of age who ingested either the prescription or OTC formulations of Children's Motrin® yielded 9 serious and 305 nonserious reports from health care professionals and consumers. A total of 18 and 361 adverse events were generated by COSTART terminology respectively for serious and nonserious adverse events. Two (2) out of the 9 serious cases resulted in the deaths of the children due to Invasive Group A streptococcal infection post-varicella infection (1) and renal failure (1). The 7 remaining serious cases resulted in the hospitalizations of the children involved due to the following adverse events: drug-induced anaphylaxis (1), dehydration (1), anemia (1), and sepsis syndrome secondary to varicella lesions (4). The sponsor has provided the following summary table, Table 8-40, which describes and lists these 9 serious cases in tabular format in children ≤ 2 years of age. Table 8-41, lists all of the 361 nonserious adverse event reports by body system. The sponsor reported in this submission that out of the original 305 nonserious reports received by them in this age group, 272 reports were associated with their (OTC) Children's Motrin® Suspension formulation, 14 reports were

Table 8-40. AE Reports with Serious Outcomes in Children Less Than Two Years of Age Received by McNeil CPC from November 17, 1993 through October 2, 1997 for Motrin® Ibuprofen Products, Children's Motrin® Ibuprofen Products, and Unknown Pediatric Ibuprofen Products

Case No.	Product Form[1]	Date Received	Age	Sex	AE	COSTART Term	Daily Dose	Duration of Drug	Outcome
1	MOS	04/06/95	8 mo	Female	Cellulitis Anemia	Cellulitis, Anemia	Unknown	Unknown	Hospitalization
2	CMS	01/27/97	11 mo	Male	Lips and eyes swelled Increase in number of hives Trouble breathing	Edema face Urticaria Dyspnea	Unknown	1 dose	Hospitalization
3	MOS	09/23/97	11 mo	Male	Renal failure	Kidney failure	10 mg/kg per dose	Unknown	Hospitalization[2]
4	MOS	10/26/94	1 yr	Male	Creatine phosphokinase increased Convulsion Septic shock Gastrointestinal hemorrhage	Creatine phosphokinase increased Convulsion Sepsis Gastrointestinal hemorrhage	100 mg, q4h	6-8 months	Hospitalization
5	MOS	02/23/95	1 yr	Female	Dehydration	Dehydration	Unknown	Unknown	Hospitalization
6	MOS	02/23/95	1 yr	Male	Cellulitis face Bilateral otitis media	Cellulitis Otitis media	Unknown	Unknown	Hospitalization
7	MOS	02/23/95	1 yr	Female	Infection	Infection	Unknown	Unknown	Hospitalization
8	CMS	02/09/96	15 mo	Male	Hemoglobin and hematocrit decreased	Hypochromic anemia	10mg/kg, q8h	8 days	Hospitalization
9	MOS	02/23/95	1.5 yr	Male	Sepsis Meningitis Cardiac arrest	Sepsis Meningitis Heart arrest	Unknown	Unknown	Death

[1] MOS = Prescription Motrin® Ibuprofen suspension, CMS = OTC Children's Motrin® Ibuprofen suspension.
[2] The infant's renal function recovered. The physician reported that the infant died some time later due to unknown complications unrelated to the reported event.

Table 8-41. Body System Summary for AE Reports with Nonserious Outcomes For Children Less Than Two Years of Age Received by McNeil CPC from November 17, 1993 through October 2, 1997 for Motrin® Ibuprofen Products, Children's Motrin® Ibuprofen Products, and Unknown Pediatric Ibuprofen Products

Body System Adverse Event	Number
Body as a whole	**87**
Asthenia	2
Edema face	8
Hypothermia	3
Lab test abnormal	2
Malaise	2
No drug effect	21
Overdose	1
Accidental Overdose	40
Pain	1
Abdominal pain	7
Cardiovascular system	**2**
Tachycardia	1
Peripheral vascular disease	1
Digestive system	**62**
Anorexia	1
Constipation	4
Diarrhea	14
Dyspepsia	3
Dysphagia	2
Eructation	1
Flatulence	3
Hemorrhagic gastritis	1
Glossitis	2
Gastrointestinal hemorrhage	1
Nausea	1
Stomatitis ulcer	1
Abnormal stools	5
Vomiting	23
Hemic and lymphatic system	**2**
Ecchymosis	1
Eosinophilia	1
Metabolic and nutritive disorder	**2**
Peripheral edema	1
Hyperglycemia	1
Musculoskeletal system	**1**
Arthralgia	1
Nervous system	**119**
Confusion	1
Convulsion	1
Dizziness	2
Abnormal dreams	1
Emotional lability	2
Abnormal gait	1
Hallucinations	1
Hyperkinesia	13
Insomnia	30
Nervousness	36
Restlessness	12
Screaming syndrome	6
Somnolence	10
Stupor	1
Tremor	2

Table 8-41. Body System Summary for AE Reports with Nonserious Outcomes For Children Less Than Two Years of Age Received by McNeil CPC from November 17, 1993 through October 2, 1997 for Motrin® Ibuprofen Products, Children's Motrin® Ibuprofen Products, and Unknown Pediatric Ibuprofen Products

Body System Adverse Event	Number
Respiratory system	
Burning of the throat	10
Cough increased	1
Dyspnea	1
Epistaxis	3
Pharyngitis	3
Rhinitis	1
	1
Skin and appendages	
Erythema multiforme	71
Pruritus	1
Rash	4
Skin discolor	46
Sweat	1
Urticaria	3
	16
Urogenital system	
Oliguria	5
Urine abnormality	1
	4
Total for all body systems	361

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for their Children's Motrin® Drops, 1 report was for their Children's Motrin® Chewable tablets, 17 were for their prescription Motrin® Suspension, and 1 was for their prescription Motrin® Drops.

Medical Reviewer's Comments: Review of the narratives of these 9 serious adverse event cases does not reveal any information that could signal any unforeseen adverse event associated with the use of OTC ibuprofen in children ≤ 2 years of age. Cases associated with Invasive Group A Streptococcal infections have been reviewed by the agency's epidemiologists in the past, and no association was found.

4. FDA Spontaneous Reporting System (SRS) for all ibuprofen products in children ≤ 2-years of age for the time period November 1, 1993 through August 25, 1997. (Note: Adverse events reported through McNeil Spontaneous Reporting System are not included here.)

A query of the FDA's SRS database yielded 20 serious adverse event reports in children < 2 years of age which were related to either the use of a prescription or OTC formulation of ibuprofen. Two out of the 20 cases were reports which describe the same fatal overdose case in a 23-month-old female who died due to aspiration pneumonia that were submitted by the sponsor's competitor. (Note: This was a case of an accidental overdose, a further description of which can be found in the following 6b. Overdose Section below.) The sponsor has prepared the following 2 tables, Tables 8-42 and 8-43, which list by COSTART body system terminology all 51 of the adverse events coded for these 19 serious cases (Table 8-42), and a tabular summary of the 19 cases themselves (Table 8-43). Four (4) out of these 19 serious cases resulted in the death of the child due to pulmonary hemorrhage (1), sepsis with cardiac arrest (2), and aspiration pneumonia (1). (Note: The last case is the case that was reported twice to the system.)

The next table, Table 8-44, lists the 145 nonserious adverse events generated from a total of 52 case reports in the FDA's SRS database by COSTART terminology.

Medical Reviewer's Comments: Review of these 19 serious cases does not reveal any information that could signal any unforeseen adverse event associated with the use of OTC ibuprofen in children ≤ 2 years of age. However, one must keep in mind that these cases occurred in situations where access to the drug was controlled by a health care provider (i.e., via a prescription). Thus, this reviewer is unable to predict if the occurrence of these events will increase in frequency when this product is available to a pediatric population ≤ 2 years of age.

5. Published randomized controlled clinical trials and human pharmacokinetic studies of ibuprofen products for the years 1966 through October 1997 that reported including children ≤ 2-years of age.

An extensive literature search of the worldwide literature by the sponsor yielded a total of 29 articles which discussed the data from 21 single-dose and multi-dose clinical studies with a total combined pediatric population of 3,006 subjects. (Note: More information about these studies can be found in the preceding efficacy section, and in the Sponsor's Tables 8-10 and 8-12, in Attachment I.) No serious adverse events were reported to have occurred in any of these studies. Two studies did not report any safety data and thus are excluded from this safety review. Nine out of the remaining 19 trials did report the occurrence of non-serious adverse events in ibuprofen-treated children which included: nausea, vomiting, diarrhea, rash, hypoglycemia, agitation, febrile seizures, exanthem, insomnia, hypothermia, epistaxis, sweating, GI complaints, discomfort, and hypothermia. Many of these adverse events were not considered by the authors of these published studies to be related to treatment with ibuprofen. Since these trials only used descriptive statistics in discussing their patient populations, it is impossible for this reviewer to determine if any of the above listed adverse events occurred in subjects < 2 years of age based on the data presented.

A total of 340 children between the ages of 3 months to 12 years were enrolled in the 5 pharmacokinetic studies submitted in support of this application. The investigators of these studies did not report the occurrence of any serious or non-serious adverse event during these trials. (Refer to the PK review of this NDA review for more information.)

Medical Reviewer's Comments: This reviewer agrees with the authors of these studies that most of the adverse events reported associated with these trials were probably related to the subjects underlying febrile illnesses (febrile seizures, discomfort, exanthem, nausea, vomiting, etc . . .). Although some events such as the GI complaints, epistaxis, and rash could be drug-related and are known to occur with this product they could also be due to the subjects' underlying illnesses. Since the sponsor did not submitted the case forms for these studies, it is impossible for this medical reviewer to draw any conclusions regarding ibuprofen's safety profile in the pediatric populations that participated in these studies.

6. Overdose Data: (a.) AAPCC TESS ibuprofen data from the years 1994 through 1996 for children ≤ 2-years of age. (The 1997 report was not yet available.) (b.) Reports from the FDA's Spontaneous Reporting System. (c.)Reports from McNeil's CPC Drug Safety Reporting System.

The American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) collected a total of 2,726,446 reports of possible human poisonings due to therapeutic drugs during the time period of 1994-1996. The sponsor has provided in this submission the data pertaining to ibuprofen overdoses. A total of

118,841 reports (4.4%) out of all of the reports collected for this time period were due to an ibuprofen containing product. In children < 2 years of age, there was a total of 17,635 reports of exposures to ibuprofen for this time period, out of which 17,173 (97.4%) were classified as non-toxic, minor, minimal or no effect reported. Of the remaining 462 case reports, 433 (2.3%) reported an unrelated effect or were lost to follow up. Although a total of 29 cases in this age group were classified as having resulted in a moderate (25 cases) or major (4 cases) outcome, none resulted in a death of a child. Only 24 out of these 29 cases with a moderate or major outcome involved either unknown pediatric formulations or an adult formulation of ibuprofen. Table 8-46, at the end of this section prepared by the sponsor lists these cases by increasing chronological age.

In addition, the sponsor obtained data from the FDA's Spontaneous Reporting System (SRS) for the time period November 1,1993 through August 25, 1997 and also queried its own data base for any case reports of ibuprofen overdoses in children < 2 years of age. This search of the SRS database yielded 22 reports, out of which 4 were listed as having serious outcomes. The following attached sponsor's table, Table 8-47, lists these 4 cases. Two of the 4 cases (MR 970170176 and MR 897009001S) which resulted in the death of a 23-month-old female child appear to be the same case. Review of the associated case reports reveals that this case was confounded by some underlying unspecified enzyme deficiencies as well as other congenital abnormalities in the child. The child reportedly suffocated on her vomitus while in bed after receiving an overdose of a competitor's ibuprofen suspension for the treatment of a fever. The other 2 cases involved a 17-month-old male who accidently ingested 27-28 tablets of an OTC adult formulation of ibuprofen. He was hospitalized for observation following emergency treatment for the drug overdose and survived without any reported sequelae. The last case was a report from worldwide literature about a 21-month-old male with a history of hypocalcemia and hypomagnesemia who was hospitalized for the treatment of a metabolic acidosis associated with drowsiness and tachypnea after an overdose of 8 grams of ibuprofen. He subsequently developed acute tonic-clonic seizures and renal failure, but reportedly recovered.

Medical Reviewer's Comments: Since little information is provided regarding whether the 24 cases of non-serious overdoses involved pediatric or unknown adult formulations of ibuprofen, this reviewer at best recommends that the indicated labeled age ranges for the pediatric formulations be modified to improve clarity. As such, it may be prudent to not have overlapping age ranges as one such attempt at minimizing dosing misadventures.

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The sponsor submitted reanalyses of data from clinical studies previously conducted. No new clinical trials were conducted in support of this efficacy supplement. Therefore, no debarment certification is required.

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HFD-560 ActingDir/Bowen
HFD-560 Dep Dir/Katz
HFD-560 Team Leader/Lumpkins
HFD-550 Team Leader/Hyde
HFD-560 MO/Neuner
HFD-560 PM/KRothschild

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ON ORIGINAL

Medical Reviewer's Overall Safety Comments: The sponsor has submitted an application in support of their request to lower the current approved age range from 2 to 3 years of age down to 2 months of age for their formulation of pediatric ibuprofen suspension. This product is currently available as a prescription drug for use in children 6 months to 2 years of age who are under a health care provider's care. Thus, the provider has made the determination as to the appropriateness of use of this product in this age group. This controlled access may account for the low incidence of reported post-marketing adverse events associated with ibuprofen suspension in children < 2 years of age. As noted above, most of the overdose safety data in the pediatric population was generated by inadvertent overdosing or accidental ingestion of adult ibuprofen products. At the September 18,1998 NDAC some of the committee members recommended that the age threshold for use of this product might be lowered down to 2 months based on the presentations of data at that meeting, but they also felt that additional warnings needed to appear on the label to safeguard against the use of the product in select populations where additional medical input was needed (i.e., preemies, children with significant fevers, fevers accompanied by lethargy, etc . . .) In face of the fact that the largest supporting source of safety data in a pediatric population < 6 months of age is heavily flawed, and the validity of some of its conclusions are questionable at best, this reviewer feels that there is insufficient safety data in the infant population < 6 months of age to support a lowering of the approved indicated age range to this level.

Recommendations: Based on the data contained in this submission Children's MOTRIN® (ibuprofen oral suspension) Drops, 50 mg/1.25 mL is safe to be used in an OTC pediatric population ≥ 6 months of age. There is insufficient data to currently support an age range lower than the above. Due to the possible threat of dosing misadventures due to consumer confusion, an overlap in dosing age ranges should be avoided for this product and its sister product, Children's MOTRIN® (ibuprofen) Suspension, 100 mg/5 mL. Thus, the concentrated drops should be labeled for use in children ≤ 2 years of age, and the less concentrated solution should be labeled for use in children ≥ 2 years of age. To further help prevent these incidents from happening in the future, the sponsor needs to re-label this product as "concentrate" as follows: Children's MOTRIN® (ibuprofen) Concentrated Drops, 50 mg/1.25 mL.

Rosemarie Neuner, MD

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

Linda M. Katz, MD, MPH 3/29/99
Deputy Dir., HFD-560

CC: NDA 20-603 File
HFD-560 Div. File
HFD-550 Div. File

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

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

APR 15 1999

Re: Infant's Motrin Concentrated Drops
NDA 20-603/S-003
Revised Commitment Letter

Dear Dr. Bowen:

We acknowledge your fax of 4/15/99 (copy attached) regarding S-003/NDA 20-603. As requested, we agree to the following:

- Labeling described in your fax of 4/15/99 will serve as a basis of approval for S-003;

- Submit Final Printed Labeling consistent with the above.

We trust we have adequately responded to your request. Should you have any questions, please call me at (215) 273-7115.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Willie D. Pagsuyoin
Director, Regulatory Affairs

WDP:dtg
Attachment

cc: Kerry Rothschild (HFD-560)
p:\nda\corresp\bowen3.doc

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

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

APR 1 4 1999

Re: NDA 20-603/S-003
Children's MOTRIN® Oral Drops

Dear Dr. Bowen:

We acknowledge your fax of 4/14/99 (copy attached) regarding S-003/NDA 20-603. As requested, we commit to the following:

1. Labeling outlined in your fax will serve as a basis of approval for S-003/NDA 20-603. with the following revisions:

   Elimination of the word "OTC" from the instructions to not use the product if the child "has ever had an allergic reaction to any OTC pain reliever/fever reducer".

   Addition of the word "is" to the end of the following subheading: "Ask a doctor or pharmacist before use if the child"

   Under the above subheading, elimination of the word "OTC" in the phrase, "taking any other product that contains ibuprofen, or any other OTC pain reliever/fever reducer."

2. Final printed labeling identical to the labeling described herein will be submitted to FDA.

We trust we have adequately responded to your request.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Paula DeLuise For
Willie D. Pagsuyuin
Director, Regulatory Affairs

WDP:dtg
Attachment
p:\nda\corresp\bowen4.doc

cc: Kerry Rothschild (HFD-560)

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

APR 13 1999

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

Re: Children's Motrin Drops
NDA 20-603/S-003
Response to FDA Comments

Dear Dr. Bowen:

We refer to your fax of 4/12/99 (copy attached) which outlined FDA proposed changes to our draft labeling for Children's Motrin Drops. We agree to the changes outlined by FDA in your fax of 4/12/99, as modified below (changes in italics):

A. We acknowledge FDA's recommended alternate name, Baby Motrin Concentrated Drops; however, our preference is to market this product with our original proposed name of Infant's Motrin Concentrated Drops.

B. For clarity, we propose the following change under Important section:

From: **Read all product information before using. Keep this box for important information. This product is intended for use in ages 6 months to 23 months of age.**

To: **Read all product information before using. Keep this box for important information. This product is intended for use *in children* ages 6 months to 23 months.**

C. For clarity, we propose the following changes Under Warnings:

From: **Sore throat warning:** severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician.

To*: **Sore throat warning:** severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult *a doctor* promptly. Do not use more than 2 days or administer to children under 3 years of age *for sore throat* unless directed by a *doctor.*

*Please note that we have changed any reference from "physician" to "doctor".

From: **Ask a doctor before us if the child has**...not been drinking

To: **Ask a doctor before use if the child has**...not been drinking *fluids*

D. We have included the warning if stomach upset lasts or gets worse in the Stop use and ask a doctor section, as follows:

From: **Stop use and ask a doctor if**...stomach pain gets worse or lasts

To: **Stop use and ask a doctor if**...stomach pain *or upset* gets worse or lasts

E. For clarity, we propose the following changes Under Directions:

From: **Directions**...do not take more than directed

To: **Directions**...do not *give* more than directed

From: **Directions**...use only the enclosed dropper. Do not use any other dosing device. Fill to prescribed level.

To: **Directions**...use only *with* enclosed dropper. Fill to *dose* level. Do not use any other dosing device.

To emphasize the importance of using only the appropriate device to dose the product, we wish to include this information under Directions, as well as retain the current information following the dosing chart, i.e., **"Attention: Specifically designed for use with enclosed dropper. Use only enclosed dropper to dose this product. Do not use any other dosing device."**

F. To be consistent with the 3/17/99 Final Rule on OTC labeling requirements for human drugs, we propose moving information concerning action to take in the event of stomach upset with use of the product to the appropriate subheading:

"When using this product, give with food or milk if stomach upset occurs."

Therefore, this information is deleted from the Directions section (as last bullet: "if stomach upset occurs while taking this product; give with food or milk").

For your convenience, we have attached revised, draft labeling with the above changes. We trust we have adequately responded to your request. Should you have any questions, please call me at (215) 273-7115.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Willie D. Pagsuyuin
Director, Regulatory Affairs

WDP:dtg
Attachment

cc: Kerry Rothschild (HFD-560)

p:\nda\corresp\bowen3.doc

APPEARS THIS WAY
ON ORIGINAL

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
McNeil CONSUMER HEALTHCARE

DATE OF SUBMISSION
APR 13 1999

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

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) 20-603

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

PROPRIETARY NAME *(trade name)* IF ANY Children's MOTRIN Oral Drops

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

CODE NAME *(If any)*

DOSAGE FORM: Drops

STRENGTHS: 40mg/mL

ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: For the temporary relief of fever and minor aches and pains due to colds, flu, sore throat, headaches and toothaches

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

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
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
Corres: Response to FDA Comments

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

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)