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).

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)	0.42 (0.023)
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]	Mfr. Control No.	Date Received	Age	Sex	AE	COSTART Term	Daily Dose	Duration of Drug	Outcome
1	MOS	0372236A	04/06/95	8 mo	Female	Cellulitis Anemia	Cellulitis. Anemia	Unknown	Unknown	Hospitalization
2	CMS	0724826A	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	0867864A[2]	09/23/97	11 mo	Male	Renal failure	Kidney failure	10 mg/kg per dose	Unknown	Hospitalization[2]
4	MOS	0313900A	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	0356256A	02/23/95	1 yr	Female	Dehydration	Dehydration	Unknown	Unknown	Hospitalization
6	MOS	0356314A	02/23/95	1 yr	Male	Cellulitis face Bilateral otitis media	Cellulitis Otitis media	Unknown	Unknown	Hospitalization
7	MOS	0356366A	02/23/95	1 yr	Female	Infection	Infection	Unknown	Unknown	Hospitalization
8	CMS	0526725A	02/09/96	15 mo	Male	Hemoglobin and hematocrit decreased	Hypochromic anemia	10mg/kg, q8h	8 days	Hospitalization
9	MOS	0356831A	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.

Children's Motrin Ibuprofen Drops 50mg per 1.25mL
NDA 20-603
Supplemental New Drug Application
McNeil Consumer Products Company

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	10
Burning of the throat	1
Cough increased	1
Dyspnea	3
Epistaxis	3
Pharyngitis	1
Rhinitis	1
Skin and appendages	71
Erythema multiforme	1
Pruritus	4
Rash	46
Skin discolor	1
Sweat	3
Urticaria	16
Urogenital system	5
Oliguria	1
Urine abnormality	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.

Table 8-42. **Body System Summary for AE Reports with Serious Outcomes in Patients Less Than Two Years of Age. FDA Spontaneous Reporting System from November 1993 through August 1997, for Ibuprofen Products (Excluding AE Reports Received by McNeil CPC Presented in Section 8.6.5.1)**

Body System Adverse event	Number
Body as a whole	**19**
Allergic reaction	1
Congenital anomaly	1
Asthenia	1
Fever	2
Flu syndrome	1
Infection	3
Necrosis	1
No drug effect	1
Overdose	2
Accidental Overdose	2
Perinatal disorder	2
Sepsis	2
Cardiovascular system	**2**
Heart arrest	2
Digestive system	**5**
Diarrhea	1
Hepatitis	1
Nausea and vomiting	1
Stomach ulcer hemorrhage	1
Vomiting	1
Hemic and lymphatic system	**2**
Hemolytic anemia	1
Purpura	1
Metabolic and nutritive disorder	**4**
Creatinine increased	1
Dehydration	1
Edema	1
Hyperkalemia	1
Musculoskeletal system	**6**
Pyogenic arthritis	1
Tendinous contracture	2
Myositis	1
Osteomyelitis	2
Nervous system	**2**
Grand mal convulsion	1
Meningitis	1
Respiratory system	**2**
Lung hemorrhage	1
Aspiration pneumonia	1
Skin and appendages	**3**
Epidermal necrolysis	1
Erythema multiforme	1
Rash	1
Urogenital system	**5**
Bacterial infection	3
Acute kidney failure	3
Total for all body systems	51

Table 8-43. Reports of Adverse Events with Serious Outcomes in Patients Less Than Two Years Old from FDA Spontaneous Reporting System from November 1993 through August 1997, for Ibuprofen Products (Excluding Children's Motrin® Data Presented in Section 8.6.5.1).

Case	Date	Age[1]	Sex[2]	Mfr Control	Manufacturer	Drug	Dosage[3]	Duration	COSTART	Outcome	Concomitant Drugs
1	Jun 94	M01	F	463617463	Upjohn	Motrin	800. Mg	10 Days	Perinatal disorder Stomach ulcer hemorrhage	Hospitalized Required Intervention Life-Threatening Other	
2	Jul 94	M01	F	IBU9410013	Boots	IBU	600. Mg	12 Days	Edema Lung hemorrhage Perinatal disorder Purpura	Died Required Intervention Life-Threatening	
3	Feb 95	M01	M	95001	Wyeth ------	Effexor Ibuprofen	37.5 Mg -----	---- ----	Congenital anomaly	Congenital Anomaly	Amitriptyline Cefadroxil Methadone
4	Aug 94	M08	F	SEPTRA2106	Whitehall BW	Advil Septra	----- 5. Ml	---- 8 Days	Diarrhea Fever No Drug Effect Rash	Hospitalized	Amoxicillin
5	Mar 95	M12	F	895073005A	Parke-Davis Wyeth	Benadryl Ibuprofen	----- -----	---- ----	Infection	Hospitalized	
6	Apr 95	M12	F	35622	Parke-Davis ------	Benadryl Ibuprofen	----- -----	---- ----	Infection	Hospitalized	
7	Oct 95	M12	M	895289002A	Wyeth	Children's Advil	400. Mg	55 Days	Hemolytic anemia	Hospitalized Life-Threatening Recovered	
8	Mar 95	M13	F	35334	Parke-Davis Wyeth McNeil	Benadryl Children's Advil Pediaprofen	----- 75. Mg 100. Mg	---- 2 Days 6 Days	Tendinous contracture Bacterial infection Necrosis	Hospitalized	
9	Mar 95	M13	F	895060001A	Parke-Davis Wyeth McNeil	Benadryl Children's Advil Pediaprofen	----- 75. Mg 100. Mg	---- 2 Days 6 Days	Fever Tendinous contracture Bacterial infection Myositis	Hospitalized Required Intervention Recovered	
10	Mar 95	M14	M	895032011A	------ Wyeth	Calamine Children's Advil	----- -----	---- ----	Infection Osteomyelitis	Hospitalized Required Intervention Recovered	

Table 8-43. Reports of Adverse Events with Serious Outcomes in Patients Less Than Two Years Old from FDA Spontaneous Reporting System from November 1993 through August 1997, for Ibuprofen Products (Excluding Children's Motrin® Data Presented in Section 8.6.5.1).

Case	Date	Age[1]	Sex[2]	Mfr Control	Manufacturer	Drug	Dosage[3]	Duration	COSTART	Outcome	Concomitant Drugs
11	Mar 95	M14	M	34903	Parke-Davis ------ ------	Benadryl Calamine Ibuprofen	----- ----- -----	---- ---- ----	Pyogenic arthritis Bacterial infection Osteomyelitis	Hospitalized	
12	Oct 95	M16	M	895139003A	Wyeth	Children's Advil	-----	1 Day	Acute kidney failure	Hospitalized	
13	Oct 95	M16	M	895139003A	Whitehall	Advil	-----	1 Day	Dehydration Flu Syndrome Acute kidney failure Nausea and vomiting	Hospitalized	
14	Mar 96	M16	F	--------	------	Ibuprofen	-----	11 Day	Allergic reaction Epidermal necrolysis Erythema Multiforme Hepatitis	Hospitalized Required Intervention Life-Threatening	Ativan Fentanyl Proventil Tylenol
15	Mar 94	M17	M	894061001L	Wyeth	Children's Advil	1. Tp	3 Day	Asthenia Creatinine increased Heart Arrest Sepsis	Died	Zantac
16	Jul 95	M17	M	94055	Whitehall	Advil	27-28 Tb		Accidental Overdose	Hospitalized Required Intervention	
17	Mar 95	M18	M	895073003A	Wyeth McNeil	Ibuprofen Tylenol	----- -----	---- ----	Heart Arrest Bacterial Infection Meningitis Sepsis	Died Hospitalized	
18	May 97	M21	M	515517463	Upjohn	Ibuprofen	8 Gm	----	Grand mal convulsion Hyperkalemia Acute kidney failure Accidental Overdose	Hospitalized Required Intervention Other	
19	Jun 97	M23	F	970170176	Whitehall	Children's Advil	2. Tp	1 dose	Overdose Aspiration pneumonia	Died	Cortef Desmopressin Acet Levoxyl
20	Feb 97	M23	F	897009001S	Whitehall	Advil	2. Tp	1 dose	Overdose Vomiting	Died Other	Cortef Desmopressin Acet Levoxyl

[1] Age in months (preceded by 'M'); [2] M = male, F = female; [3] Tb = tablets, Tp = teaspoon

Table 8-44. **Body System Summary for AE Reports with Non-Serious Outcomes. FDA Spontaneous Reporting System from November 1993 through August 1997, for Ibuprofen Product (Excluding McNeil CPC Data Presented in Section 8.6.5.1) in Patients Less Than Two Years of Age**

Body System Adverse Event	Number
Body as a whole	**44**
Abdomen enlarged	2
Allergic reaction	1
Anaphylactoid reaction	1
Congenital anomaly	1
Chills	1
Chills fever	1
Edema face	4
Fever	3
Flu syndrome	1
Hypothermia	1
Infection	1
No drug effect	6
Overdose	1
Accidental Overdose	17
Pain	1
Perinatal disorder	1
Reaction unevaluable	1
Cardiovascular system	**4**
Hypotension	1
Vasodilation	3
Digestive system	**20**
Anomaly tooth	1
Constipation	1
Diarrhea	3
Dysphagia	1
Flatulence	1
Gastrointestinal hemorrhage	1
Liver function abnormal	2
Abnormal stools	1
Vomiting	9
Hemic and lymphatic system	**2**
Cyanosis	1
Leukopenia	1
Metabolic and nutritive disorder	**6**
Acidosis	1
Peripheral edema	2
Hypoglycemia	1
Alkaline phosphatase increased	2
Nervous system	**38**
Agitation	1
Chronic brain syndrome	1
Coma	1
Convulsion	2
Dizziness	2
Emotional lability	1
Hostility	1
Hyperkinesia	5
Insomnia	6
Manic react	1
Nervousness	6
Screaming syndrome	2

Table 8-44. **Body System Summary for AE Reports with Non-Serious Outcomes. FDA Spontaneous Reporting System from November 1993 through August 1997, for Ibuprofen Product (Excluding McNeil CPC Data Presented in Section 8.6.5.1) in Patients Less Than Two Years of Age**

Body System Adverse Event	Number
Nervous system (continued)	
Somnolence	5
Stupor	1
Tremor	2
Twitch	1
Respiratory system	**3**
Apnea	1
Dyspnea	1
Hypoventilation	1
Skin and appendages	**27**
Alopecia	1
Erythema multiforme	1
Pruritus	1
Rash	15
Maculopapular rash	2
Skin dry	1
Urticaria	6
	1
Urogenital system	
Hematuria	1
Total for all body systems	**145**

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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.

Table 8-46. Moderate or Major Outcomes with Single-Ingredient Ibuprofen Exposure In Children Less Than Two Years of Age from AAPCC TESS[1] Database, 1994 through 1996

Case	Date Rec'd	Age[2]	Sex	AAPCC Serial No	IBU Form[3]	Reason for Exposure	Clinical Effect	Outcome
1	12/27/94	25 d	M	090-34621	P	Adverse Drug Reaction	Erythema/flushed Diaphoresis Hypothermia	Moderate
2	3/23/96	5 m	F	036-2922990	A/U	Accidental: Therapeutic Error	Vomiting Acidosis Bleeding	Moderate
3	2/20/95	7 m	M	007-18561567	A/U	Accidental: Therapeutic Error	Vomiting Electrolyte abnormality	Moderate
4	9/03/94	1 y	F	072-18204590	A/U	Accidental: General	Vomiting Drowsiness/lethargy	Moderate
5	10/29/96	1 y	M	005-48762	P	Accidental: General	Vomiting ADR to treatment Other	Moderate
6	8/03/96	12 m	F	040-30080175	A/U	Accidental: General	Hypotension Coma Drowsiness/lethargy Miosis	Major
7	10/23/95	13 m	M	083-94031093	A/U	Accidental: General	Other	Moderate
8	12/01/95	13 m	M	091-141435	P	Accidental: General	Vomiting Drowsiness/lethargy Other	Moderate
9	4/06/96	13 m	Unk	040-30055849	A/U	Accidental: General	Vomiting Drowsiness/lethargy Acidosis	Moderate
10	4/21/95	14 m	F	030-1174497	A/U	Accidental: General	Drowsiness/lethargy	Moderate

[1]American Association of Poison Control Centers Toxic Exposure Surveillance System
[2]Patient age in days (d), months (m), or years (y)
[3]Ibuprofen formulation - pediatric (P) or adult/unknown (A/U)

Table 8-46. Moderate or Major Outcomes with Single-Ingredient Ibuprofen Exposure in Children Less Than Two Years of Age from AAPCC TESS[1] Database, 1994 through 1996

Case	Date Rec'd	Age[2]	Sex	AAPCC Serial No	IBU Form[3]	Reason for Exposure	Clinical Effect	Outcome
11	10/31/95	14 m	F	047-77931	A/U	Accidental: General	Coma	Moderate
12	2/17/96	14 m	M	031-581263	A/U	Accidental: General	Dehydration Agitation/irritable	Moderate
13	9/19/94	15 m	M	011-17732282	A/U	Accidental: General	Other	Moderate
14	10/24/94	15 m	M	006-17917397	A/U	Accidental: General	Drowsiness/lethargy Acidosis	Moderate
15	1/04/96	15 m	M	022-591800	A/U	Accidental: General	Other LFT abnormality	Moderate
16	11/20/94	16 m	F	009-17413922	A/U	Accidental: General	Ataxia Drowsiness/lethargy	Moderate
17	11/13/96	16 m	M	084-220194	A/U	Accidental: General	Drowsiness/lethargy Acidosis Hypoglycemia	Moderate
18	6/30/94	17 m	M	027-18761159	P	Adverse Drug Reaction	Hypothermia	Moderate
19	7/03/94	17 m	F	007-18396169	A/U	Accidental: General	Vomiting Coma Increased creatinine Acidosis	Major
20	5/01/94	18 m	M	025-18230392	A/U	Accidental: General	Coma Drowsiness/lethargy Acidosis	Major
21	6/20/94	18 m	F	008-17642442	A/U	Accidental: General	Ataxia Drowsiness/ lethargy Acidosis	Moderate

[1]American Association of Poison Control Centers Toxic Exposure Surveillance System
[2]Patient age in days (d), months (m), or years (y)
[3]Ibuprofen formulation - pediatric (P) or adult/unknown (A/U)

Table 8-46. Moderate or Major Outcomes with Single-Ingredient Ibuprofen Exposure in Children Less Than Two Years of Age from AAPCC TESS[1] Database, 1994 through 1996

Case	Date Rec'd	Age[2]	Sex	AAPCC Serial No	IBU Form[3]	Reason for Exposure	Clinical Effect	Outcome
22	11/10/95	18 m	F	027-2687703	A/U	Accidental: General	Bradycardia Hypertension Drowsiness/lethargy Acidosis Hypothermia	Moderate
23	11/05/96	18 m	M	009-38152	A/U	Accidental: Therapeutic Error	Hypotension Electrolyte abnormality Hyperglycemia Other	Moderate
24	3/31/94	19 m	M	010-17556117	A/U	Accidental: General	Dizziness/vertigo	Moderate
25	6/26/94	20 m	M	003-20104700	A/U	Unknown	Dysphagia Dystonia	Moderate
26	9/28/95	21 m	M	011-2616142	A/U	Accidental: General	Diarrhea	Moderate
27	10/05/96	22 m	F	027-376272	A/U	Accidental: General	Acidosis	Moderate
28	5/02/96	22 m	F	031-575945	P	Adverse Drug Reaction	Dyspnea	Moderate
29	3/09/96	22 m	F	011-2647872	A/U	Accidental: General	Tachycardia Drowsiness/lethargy Acidosis	Major

[1]American Association of Poison Control Centers Toxic Exposure Surveillance System
[2]Patient age in days (d), months (m), or years (y)
[3]Ibuprofen formulation - pediatric (P) or adult/unknown (A/U)

Table 8-47. Ibuprofen Overdoses with Serious Outcomes In Children Less Than Two Years of Age: FDA Spontaneous Reporting System from November 1993 Through August 1997

Case	Date	Age[1]	Sex[2]	Mfr Control	Manuf	Drug	Dosage[3]	Duration	COSTART	Outcome	Concomitant Drugs
1	Jul 95	M17	M	94055	Whitehall	Advil	27-28 Tb	- - - -	Accidental overdose	Hospitalized Required Intervention	- - -
2	May 97	M21	M	515517463	Upjohn	Ibuprofen	8 Gm	- - - -	Grand mal convulsion Hyperkalemia Acute kidney failure Accidental overdose	Hospitalized Required Intervention Other	- - -
3	Jun 97	M23	F	970170176	Whitehall	Children's Advil	2 Tp	1 dose	Overdose Aspiration pneumonia	Died	Cortef Desmopressin Acet Levoxyl
4	Feb 97	M23	F	897009001S	Whitehall	Advil	2 Tp	1 dose	Overdose Vomiting	Died Other	Cortef Desmopressin Acet Levoxyl

[1]Age in months (preceded by 'M')
[2]M = male, F = female
[3]Tb = tablets, Tp = teaspoon

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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.

/S/

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

/S/

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

3/29/99 —
The sponsor may want to consider modifying the name of the concentrated suspension (drops) to denote a product commensurate with the intended age group targeted for treatment. Thus, consideration could be given to modifying the product's name to "Baby" "Pediatric" or "Infant" Motrin ibuprofen oral suspension) drops.

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