

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-128

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

**DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND
OPHTHALMIC DRUG PRODUCTS - HFD-550**

NDA 21-128

Children's MOTRIN Cold® Suspension

Submission date (letter): September 30, 1999
Submission type: NDA
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Drug generic name: Ibuprofen and Pseudoephedrine

Applicant: McNeil Consumer Healthcare

Pharmacologic category: Combination of NSAID (ibuprofen) and
sympathomimetic amine (pseudoephedrine)

Proposed indications: Temporary relief of symptoms associated with the
common cold, flu or sinusitis

Dosage form and route: 100 mg/5mL Ibuprofen and 15mg/5mL
Pseudoephedrine, Oral suspension

Related Reviews: Linda Hu / Marina Chang / Bettie Rylands (OTC)
Abi Adebawae (Biopharm)

/S/

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1.0 Materials Utilized In Review

Original submission: Volumes 1.1 and 1.15 to 1.22. Amendments submitted 11/5/99, 2/4/00 (Safety Update), 4/27/00 and 5/1/00.

2.0 Background

Children's Motrin® Cold Suspension (CMCS), a combination of ibuprofen (100 mg/ 5 mL) and pseudoephedrine HCl (15 mg/ 5 mL), has been developed by Ortho McNeil as an over the counter (OTC) medication for children 2 to 11 years old.

2.1 Indication

The proposed indication is "To temporarily relieve symptoms associated with the common cold, flu or sinusitis including nasal and sinus congestion, stuffy nose, headache, sore throat, body aches and pains and to temporarily reduce fever".

2.2 Related products

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), has been marketed as an over the counter (OTC) pediatric product for over four years for the temporary reduction of fever and relief of minor aches and pains due to the common cold, flu, sore throat, headaches and toothaches. Pseudoephedrine, a sympathomimetic amine, has been marketed for 23 years as an OTC pediatric nasal decongestant for the temporary relief of nasal congestion due to the common cold, hay fever, or other respiratory allergies and nasal congestion associated with sinusitis. McNeil's OTC combination product for adults and children 12 years of age and older (NDA 19-899, Motrin IB sinus) was approved by FDA in 1992.

2.3 Administrative History

The clinical development program for ibuprofen/pseudoephedrine in the pediatric population < 12 years of age was discussed with FDA at meetings held on July 30, 1997 and May 10, 1998. The Agency was concerned about the potential interaction in the PK of ibuprofen and/or pseudoephedrine by concurrent administration of both drugs in the combination suspension. An official Written Request for two pediatric studies was sent to McNeil on September 7, 1999.

2.4 Proposed Directions

The proposed dosing regimen for CMCS (Table 1) is based on the currently approved regimen for OTC pediatric ibuprofen, which uses the standard age and weight groupings described in the "Pediatric Dosing Information for OTC Human Drugs". The proposed dose of pseudoephedrine, which is usually given with a different schedule than that of ibuprofen, is based on the final Monograph for OTC Nasal Decongestants. The dosing

schedule for CMCS is supposed to maintain dosing within established safe and effective ranges for each ingredient.

Table 1. Children's Motrin Cold Suspension dose regimen used in the NDA ¹

Age (years)	Weight		CMCS ¹ Dose (teaspoon)	Ibuprofen		Pseudoephedrine	
	(lbs)	(kgs)		Dose (mg)	Range (mg/k)	Dose (mg)	Range (mg/kg)
2-3	24 to 35	10.9--15.9	1	100		15	
4-5	36 to 47	16.4--21.4	1 ½	150		22.5	
6-8	48 to 59	21.8--26.8	2	200		30	
9-10	60 to 71	27.3--32.3	2 ½	250		37.5	
11	72 to 95	32.7--43.2	3	300		45	

¹ To be measured with measuring cup provided with the product; 100 mg of ibuprofen and 15 mg of pseudoephedrine for each 5mL teaspoon to be given every 6 to 8 hours, not to exceed 4 times a day.

2.5 Foreign Marketing

No pediatric OTC or prescription ibuprofen/pseudoephedrine combination is currently marketed in the U.S. or non-U.S. country.

2.6 Financial Disclosure.

In Accordance with Certification and Disclosure Requirements (21 CFR 54.4), the applicant must submit a list of all clinical investigators who conducted "covered" clinical studies. Covered studies are any study of a drug or device submitted in a marketing application to support that the product is effective. This would in general not include phase 1 studies or pharmacokinetic studies, most clinical pharmacology studies and large open safety studies conducted at multiple sites.

Investigators and sub-investigators of study 99-086 (the large safety study), signed form 3454 - Certification of Financial Interest and Arrangements of Clinical Investigators - stating that they had no financial interests.

3.0 Chemistry, manufacturing and Controls

The formulation for Children's MOTRIN Cold Suspension has been developed in two flavors: Berry (Formula C-822-4) and Grape (Formula C-846-3). Stability data are provided on 6 batches of finished product including 3 of each flavor. No major chemistry issues were identified.

4.0 Animal Pharmacology

The nonclinical safety of ibuprofen and pseudoephedrine as single entities is well established. The nonclinical safety for the combination product was established with toxicology studies submitted to NDA 19-899, for Motrin IB Sinus caplets. There are no new animal pharmacology data in this NDA.

5.0 Description of Clinical Data sources

5.1 Primary Source Data (Development Program).

5.1.1 Study Type and Design

A summary of the studies is presented in Table 2. The NDA includes two pharmacokinetic studies (one in children with CMCS and one in adults with CMCS and the adult formulation) and one safety study.

Table 2. NDA 21-128. Children's Motrin Cold Suspension. Clinical studies.

Study	Design/length	Treatment	N	Measurements
98-057	OL, multiple dose, one-day PK study	Ibuprofen/pseudoephedrine ¹ suspension q 6 hours x 5	24 healthy children age 4-11	PK: ibuprofen and pseudoephedrine concentrations, safety, routine labs.
99-086	OL, multiple dose, 3-day safety study	Ibuprofen/pseudoephedrine ² suspension q 6 hours	124 children with common cold, flu, stuffy nose, age 2 - 11.	Safety (no laboratory data)
97-024	OL/R, single dose, crossover, bioequivalence study	A. Ibuprofen/pseudoephedrine ¹ suspension B. Children Motrin suspension ³ C. Children's Sudafed liquid ⁴	24 healthy adults age 20-47	PK: ibuprofen and pseudoephedrine concentrations by HPLC.

¹ Each dose of ibuprofen/pseudoephedrine combination was approximately 7.5 mg/kg ibuprofen and 1.125 mg/kg pseudoephedrine. ² Dosing based on age and weight as per Table 1. ³ Ibuprofen 7.5 mg/kg. ⁴ Pseudoephedrine hydrochloride 1.125 mg/kg.

5.1.2 Demographics

Study 98-057 (the PK study) included 24 healthy subjects ages 4 to 11 years; eight of the 24 subjects (1/3) were younger than 7 years. Study 99-086 (the safety study) included 114 children of ages 2 to 11 with signs and symptoms of cold, flu or nasal congestion. Study 98-057 involved 24 healthy volunteers ages 18 to 42.

Table 3. NDA 21-128. Demographic characteristics in pediatric studies.

	Study 97-024 (n=24)	Study 99-086 (n= 114)
Sex (boys/girls)	16/8	61 / 53
Weight (lb)	64.9 ± 19.4	49.2 ± 18.9
Race (C/B/O) ¹	17 / 7 / 0	75 / 9 / 30
Age (years)	8.4 ± 2.3	5.8 ± 2.7
Age distribution (years)	4-11	2 to 11
2-3	none	38 (33%)
4-5	4 (17 %)	28 (25%)
6-8	4 (17 %)	28 (25 %)
9-11	16 (66 %)	19 (17 %)

1. C/B/O: Caucasian, Black, other.

As seen in Table 3, the PK study included more boys than girls, but the safety study included comparable numbers of boys and girls. The mean weight was higher in the PK study than in the safety study (64.9 +- 19.4 vs. 49.2 +- 18.9 Lbs) reflecting the older age of the children in the PK study. Of note, the Pediatric Written Request had requested that children 2 to 11 years be included in both studies.

5.1.3 Extent of Exposure

Study 024 enrolled 24 patients who would receive Children's Motrin Cold Suspension, one dose every 6 hours, for a total of five doses. All patients completed five doses as scheduled.

Study 086 enrolled 114 patients who would receive Children's Motrin Cold Suspension, one dose every 6 to 8 hours, for up to 3 days (a maximum of 9 to 12 doses). Only 15 % (18 patients) actually received 9 doses or more. The median number of total doses taken was seven. Seventy four percent of patients took three or more doses on day 1; 75 % took two or more doses on day 2 and 82% took one or more doses on day 3. Therefore 18% of patients did not receive any treatment on day 3. Of those who had ≥ 2 days of treatment, 25% took one dose or less on day 2. (Appendix 1)

Table 4. NDA 21-128. Exposure in pediatric studies. Cumulative number of doses.

Study 97-024 (n=24) ¹		Study 99-086 (n= 124) ²			
≥ 1		≥ 1	114	≥ 7	58
≥ 2		≥ 2	112	≥ 8	44
≥ 3		≥ 3	111	≥ 9	18
≥ 4		≥ 4	96	≥ 10	6
≥ 5	24	≥ 5	86	≥ 11	4
≥ 6		≥ 6	77		

¹ Treatment: One dose q 6 hours x 5. ² Treatment: One dose q 6-8 hours for up to 3 days.

Reviewer's comment: this pattern of exposure probably reflects the use of the product in real life, where most children taking OTC fever reducer products for non-serious conditions would rarely require to continue a q 6 h regimen for three days.

5.2 Secondary source data: Post-marketing Surveillance data.

The original submission included safety data for the OTC adult ibuprofen-pseudoephedrine combination product from the FDA Spontaneous Reporting System available through Freedom of Information and from McNeil's Spontaneous Reporting System, from January 1, 1994 through December 31, 1998, as previously agreed by the Agency. At the reviewers' request, additional post-marketing information for the individual products in the pediatric population was submitted on 4/27/00 (Amendment #3).

5.3 Comment on the Adequacy of Clinical Experience and Data Quality.

Study 98-057, the PK study, included 24 healthy subjects age 4 to 11 years. Study 99-086, the safety study, included 114 patients age 2 to 11 years of whom 38 were younger than 4 years.

In support of the PK study, the applicant provided PK data of the individual products available from published literature. Data on ibuprofen PK involved children down to 2 years of age, but for pseudoephedrine, only down to 4 years of age.

The submitted studies in addition to extensive post-marketing experience with the OTC individual products in the pediatric population and the OTC combination product in adults appear adequate to make a judgement regarding the potential safety of the combination in the pediatric population age 2 to 11 years.

Data are somewhat limited to address the safety of the product in children < 4 years, since there are no available PK data for the combination product or for pseudoephedrine alone in children of this age. However, pseudoephedrine is indicated in children \geq 2 years in the Monograph for Nasal Decongestants. Additionally, 38 pediatric patients age 2 and 3 years were exposed to ibuprofen/pseudoephedrine for up to 3 days in study 98-086.

6.0 **Pharmacokinetics**

6.1 Human PK considerations

6.1.1 Ibuprofen

Ibuprofen, a NSAID with analgesic and antipyretic properties, is a racemic mixture of (-)R- and (+)S-isomers. The (+)S-isomer is responsible for clinical activity. The (-)R form, is slowly and incompletely interconverted into the active species in adults. The degree of interconversion in children is unknown, but is thought to be similar to adults. The R(-)-isomer serves as a circulating reservoir.

Bioavailability studies indicate that ibuprofen is well absorbed orally from the various pediatric dosage forms, with peak plasma concentrations one to two hours after administration. The difference in T_{max} (time to reach peak concentration) between the ibuprofen suspension and chewable tablets was shown to have no effect on the onset of fever reduction in children (NDA 20-135) and the onset of analgesia in young adults with surgical dental pain (NDA 20-601).

Ibuprofen undergoes hepatic metabolism, with less than 1 % being excreted in the urine unchanged. It has a biphasic elimination-time curve with a plasma half-life of about two hours in both children and adults. Ibuprofen is given every 6 to 8 hours.

6.1.2 Pseudoephedrine

Pseudoephedrine is a sympathomimetic amine stereoisomer of ephedrine, without the potent central nervous system stimulatory effect of ephedrine. The mechanism of actions as a decongestant is thought to be due to stimulation of alpha adrenergic receptors and vasoconstriction of blood vessels of the nose and sinusoid vessels, with decrease in mucosal edema.

In adults, pseudoephedrine is well absorbed. Most of the drug is eliminated unchanged by renal excretion. Less than 1 % is demethylated in the liver to norpseudoephedrine. The clearance of pseudoephedrine is highly dependent upon urine pH. At urine pH values above 7.0, more drug is reabsorbed in the renal tubules resulting in decreased clearance. In clinical studies where urine pH was not controlled, mean $t_{1/2}$ (half life) in adults ranged from 4 to 7 hours, while in children ranged from 3 to 5 hours. The Monograph for OTC Nasal Decongestants recommends that pseudoephedrine be given every 4 to 6 hours.

The Agency raised the concern of potential interactions in the PK of ibuprofen and/or pseudoephedrine by the combined use of both drugs in children younger than age 12, particularly below age 6, which led to the conduct of the pediatric studies included in this NDA.

Since ibuprofen is recommended q 6 to 8 hours and pseudoephedrine is recommended q 6 to 8 hours, the schedule recommendation for the combination product should be q 6 hours.

6.2 Individual PK studies (for a more detailed review the reader is referred to Dr. Adebowale's review).

6.2.1 Study 97-024 – Pharmacokinetics in children receiving the ibuprofen/pseudoephedrine combination product.

6.2.1.1. Study design/ treatment/ measurements

Study 97-024 was an open label, multiple dose study in twenty-four healthy children age 4 to 11 years, to assess the potential for a drug-drug pharmacokinetic interaction of the combination product, by comparing the results with those from previous single-ingredient studies in children. (Comparative data were available for children down to 2 years of age for ibuprofen and down to 4 years of age for pseudoephedrine). Medical history and physical examination were done at screening. Subject had normal laboratory tests within two weeks before the first dose. Demographic characteristics of the subjects have been described in section 5.1.2.

The treatment consisted of one dose of the pediatric suspension (7.5 mg/kg of ibuprofen and 1.125 mg/kg pseudoephedrine) every six hours, for five doses.

Blood samples were drawn for PK determinations just before the final dose and at 0.5, 1, 1.5, 2, 3, 4 and 6 hours after dosing. Urine was collected before and at five hours after the final dose, for pH measurements.

6.2.1.2 Results

Steady-state pharmacokinetics indicate that neither drug accumulated substantially after five doses. Neither drug affected the other's clearance, half-life or distribution volume in children 4 to 11 years of age.

When C_{max} and T_{max} of the combination suspension were estimated for comparison with published single ingredient data in children, there were no apparent differences in

pharmacokinetic parameters of ibuprofen/pseudoephedrine combination and those of the individual products. However, no PK data for pseudoephedrine (alone or in combination with ibuprofen) exist in children younger than 4 years of age.

As per the Agency's Pediatric Written Request, the study should have included 2 and 3-year-old children. The sponsor's rationale for not including these children was as follows:

1. The protocol involved invasive procedures that provided risk and no health benefit to the children.
2. Need for verbal assent to be given to a member of the clinical team in the absence of the parent or guardian.
3. Children of 2 and 3 years of age were not believed to be sufficiently cooperative to fulfill the high level of compliance needed for this study.
4. PK of both ibuprofen and pseudoephedrine for ages 4 to 11 years was expected to be comparable with and "extrapolable" to two- and three-year-old children.

[Reviewer's comment: Review of the submitted data by Dr. Adebowale shows that PK parameters were comparable for the ibuprofen/pseudoephedrine combination product and the individual components in children down to age 4. However, since the linear regression analysis showed no linear relationship between age and PK parameters, the data submitted can not be extrapolated down to the 2 and 3 year-olds.]

Of note, the adult PK study suggested a faster rate of absorption (an earlier peak and higher C max) for pseudoephedrine with the combination product compared to the individual product, however, the difference was within acceptable limits of bioequivalence. Adults also had a 50% decreased clearance compared to the children.]

6.2.2 Study 98-057 – Children's Motrin Cold Suspension. Bioequivalence study in adults.

6.2.2.1 Study design/ treatment/ measurements.

This was an open label, randomized, single dose, three-treatment crossover design (separated by one-week washout periods) in 24 healthy subjects (10 men, 14 women), ages 20 to 47 years.

Treatment consisted of:

Treatment A: One dose of ibuprofen-pseudoephedrine (7.5 mg/kg of ibuprofen and 1.125 mg/kg of pseudoephedrine HCl).

Treatment B: One dose of Children's Motrin® Ibuprofen Suspension (7.5 mg/kg of ibuprofen).

Treatment C: One dose of Children's Sudafed® Nasal Decongestant Liquid (1.125 mg/kg of pseudoephedrine HCl).

After each dose, 14 blood samples were collected over 14 hours. Plasma was analyzed for ibuprofen and pseudoephedrine concentrations using validated high performance (HPLC).

6.2.2.2 Results.

The study suggests that pseudoephedrine absorption rate was higher from the combination suspension than for the individual product as manifested by an earlier Tmax (approximately 1 hour earlier). The geometric mean ratios and the corresponding 90% CI for AUC (area under the curve) (100.1 (95.3 – 105.1) %), and Cmax (118.0, (113.3 – 122.8) %) for the comparison of the combination suspension and Sudafed® liquid were within the 80 to 125 % range acceptable for bioequivalence. There seem to be no significant gender differences in PK parameters.

Tmax and Cmax were within the range of other published and McNeil-sponsored studies for immediate-release, pseudoephedrine products in adults. The increased absorption observed with the suspension formulation of the combination was not seen with a prior ibuprofen-pseudoephedrine tablet formulation.

7.0 Efficacy Review

Since the efficacy of the two individual components (ibuprofen and pseudoephedrine) and the efficacy of the combination have already been substantiated in adults, the current pediatric studies did not particularly address the efficacy of the combination in children. The PK study involved healthy asymptomatic children. The safety study involved 114 children with symptoms of common cold, flu, upper respiratory infections and nasal congestion but there were no efficacy assessments.

8.0 Integrated Review of Safety

8.1 Background

As mentioned above, this NDA included three studies. Two PK studies - Study 97-024 (children) and 98-057-(adults) - were described in section 6.0. Study 99-086 will be described in this section, followed by an integrated review of safety from the three studies.

8.2 Study 99-086: Children's Motrin Cold Suspension Safety in children age 2-11 years

8.2.1 Study design/ treatment/ measurements

Study 99-086 was a multicenter (16 centers) open-label study of the safety of the ibuprofen/ pseudoephedrine combination in children age 2 to 11 years, weighing 24 to 95

pounds, with symptoms of the common cold, the flu or sinusitis who would potentially benefit from the use of the proposed pediatric product. Patients who had uncontrolled heart disease, high blood pressure, thyroid disease or diabetes, were excluded from the study.

Treatment consisted of ibuprofen/pseudoephedrine HCl 100mg/15 mg per 5 mL, dosed according to Table 1 (page 5). Study personnel gave the initial dose of study medication at the time of the initial clinic visit. For the next three days, medication was given "as needed for the symptoms of the common cold, the flu or sinusitis", and recorded in the subject's diary. The follow up visit was conducted within 48 hours of taking the last dose of study medication.

Safety measurements included baseline physical examination, vital signs and body weight. Vital signs were repeated at the end of the study. Adverse events were monitored. Laboratory measurements were not performed.

8.2.2 Results

One hundred and fourteen children 2 to 11 years of age were enrolled in this study. Overall, one third of patients were ≤ 3 years of age. Subjects were approximately evenly distributed in the younger age groups. There were 38 patients younger than age 4 years (23 children were 2.0 to 2.9 years old and 15 were 3.0 to 3.9 years old)

Most patients had symptoms of common cold. Five patients had low-grade fever. Several patients had concurrent diagnosis of otitis; one patient had a concurrent diagnosis of sinusitis. Ten patients had a prior history of asthma. Concomitant medications included systemic antibiotics (n=20), anti-histaminics (n=2), corticosteroid (n=3) and beta-2-adrenoreceptor agonists (n=6).

The combination product was well tolerated. The median number of doses taken was seven. However, only 18 patients had ≥ 9 doses and only 4 had ≥ 11 doses over a 3-day period.

Reviewer's comment: this amount of exposure is probably consistent with the way the product will be used in and OTC setting, for non-serious conditions. Labeling should recommend not using the product for more than 3 days.

8.3 Significant or potentially significant events in this NDA.

8.3.1 Deaths and significant adverse events.

There were no deaths. There were no serious adverse events. There were no cases of asthma exacerbation, anaphylactoid reactions, or severe neurologic, cardiovascular or hemodynamic effects.

8.3.2 Adverse events leading to discontinuation.

There were 2 cases of adverse events leading to discontinuation: two patients in study 086 (one for urticaria and one for abdominal pain, both of them in children older than age 4 years). There were no discontinuations in studies 024 and 057.

- Patient #30028 (086) was a four-year old girl with history of eczema and allergic rhinitis who developed urticaria over the arms, chest and abdomen and associated edema of the right eye, four hours after taking the third dose of study medication. The episode was considered by the investigator to be moderate in intensity and possibly related to study medication. The urticaria was treated with oral Benadryl and resolved within 3 hours.
- Patient #110101 (086) was an eight-year-old boy who developed abdominal pain approximately one hour after taking the third dose of study medication. The episode was considered moderate in intensity. It resolved within two hours without specific treatment. This patient also complained of insomnia.

8.4 Overdosage exposure. There were no cases of overdosage.

8.5 Common adverse events in the NDA.

As seen in Table 5, there were few adverse events. The most common adverse event was somnolence seen in eight patients in study 086 of whom five were in the <6 year-old age group (7.6%) and three in the ≥ 6 year-old age group (6.3%).

Table 5. NDA 21-128. Adverse Events with the ibuprofen/pseudoephedrine combination.

	Study 97-024 (n=24 children)	Study 99-086 (n=114 children)	Study 98-057 (n=24 adults)
Any adverse event	6	21	2**
Body as a whole			
Abdominal pain	3	2 (1*)	
Fever		1	
Infection		1	
Pain		1	
Digestive			
Diarrhea			1
Nausea		1	
Musculoskeletal			
Myalgia		1	
Nervous			
Hyperkinesia		1	
Insomnia		2	
Nervousness		1	
Somnolence		8	1
Respiratory			
Nasal drip	1		
Cough increased		1	
Skin and appendages			
Urticaria		2 (1*)	
Antecubital bruises	1		
Antecubital irritation	1		

1* one patient required discontinuation. ** Additionally, one patient had dizziness with pseudoephedrine alone and one had an infection with ibuprofen alone.

There was no difference in the incidence of adverse events among the different age and weight groups.

8.6 Laboratory Findings

There were no changes from baseline in mean laboratory values including sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, bilirubin, total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and uric acid in study 98-024. Study 99-086 did not include laboratory measurements.

8.7 Vital Signs

There were no changes in blood pressure and heart rate from baseline in study 98-024. There were no significant differences from baseline in blood pressure, heart rate, temperature and respiration in study 99-086. Because changes were not expected, weight was measured at entry but not at the end of the studies.

8.8 Post-marketing experience

Ibuprofen has been marketed as a prescription pediatric product for approximately 10 years and as an OTC pediatric product for over four years. Pseudoephedrine has been marketed as a prescription pediatric nasal decongestant for 39 years and as an OTC pediatric nasal decongestant for 23 years. Pseudoephedrine is recognized in the final Monograph for OTC Nasal Decongestants as a safe and effective pediatric decongestant (59 FR 43386, August 1994).

Adult OTC ibuprofen/pseudoephedrine combination products are marketed in the U.S. and in foreign countries. McNeil's adult OTC combination product was approved by FDA on December 31, 1992 (Motrin IB sinus). One adult prescription combination product (Roveril) is currently marketed in Argentina.

No pediatric OTC or prescription ibuprofen/pseudoephedrine combination is currently marketed in the U.S. or non-U.S. country.

8.8.1 Post-marketing experience with ibuprofen/pseudoephedrine combination in adults.

The applicant estimates that approximately [redacted] dosage unit equivalents of OTC adult ibuprofen-pseudoephedrine combination products were sold in the U.S. from January 1, 1994 through December 31, 1998.

Of note, only 135 adverse events involving this combination (including McNeil and non-McNeil reports from the U.S. and other countries submitted to the FDA and published literature) were reported during this period, of which twelve were considered to be serious by the reporting subject (Table 6).

Table 6. Adverse events with serious outcomes for OTC adult ibuprofen/pseudoephedrine combination products (1/94-12/98)*.

Age/sex	Origin of report	Reaction	Dose/duration
1. 21/ F	Foreign	Generalized macular rash	2.0 days
2. 21/ F	US	Allergic reaction. Edema larynx	1 dose
3. 32/ F	US	Thrombocytopenic purpura, eosinoph.	10 days
4. 35/ F	Foreign	Palpitations, rash, allergic reaction	1 dose
5. 38/ F	Foreign	Angioedema, syncope, hypotension	1 dose
6. 48/ F	US	Thrombocytopenia, hemorrhage	10 days
7. 49/ F	Foreign	Asthma	1 dose
8. 52/ M	Foreign	Angina pectoris	Unknown
9. 73/ M	US	Nausea, vomiting, urticaria, allergic reaction	1 dose
10. ?/ F	US	Anaphylactoid reaction, paresthesia, dyspnea	1 dose
11. ?/ F	Foreign	Coma	1 dose
12. ?/ M	Foreign	Hemiplegia, vasculitis, arteriospasm	5 days

* From FDA Spontaneous Reports System and McNeil's Drug Safety Reporting System. COSTART terms.

All twelve serious reports required hospitalization (one to five days) but none of them had a fatal outcome. Six of the twelve involved allergic reactions, including anaphylactoid reactions and angioedema, after a single dose of the combination product.

Of the non-serious events, the most common were described under the "Body as a whole" body system (n=92) including "no drug effect" (n=55) and allergic reactions (n=6). The "Nervous system" category (n=47) included 8 cases of insomnia and 6 of dizziness. The "Respiratory system" (n=14) included 6 cases of dyspnea and one case of asthma. Review of the list of serious and non-serious post-marketing adverse events in adults receiving OTC ibuprofen/pseudoephedrine combination products supports the safe use of the combination product in the adult population.

8.8.2 Adverse events associated with pediatric use of the adult combination product.

Only one report was found with pediatric use of an adult ibuprofen-pseudoephedrine combination product: an 11-year old who presented with abdominal pain after use of one tablet. This adverse event had a non-serious outcome.

8.8.3 Post-marketing experience with pseudoephedrine individual product in the pediatric population.

It is estimated that pediatric dosage unit equivalents of OTC pediatric single ingredient non-generic products have been sold in the U.S. during the four-year period January 1, 1996 to December 31, 1999.

Post-marketing information was obtained from the following databases:

- McNeil Drug Safety Reporting system (DSRS) from 1/1/92 to 1/31/00 for McNeil pseudoephedrine pediatric product (PediaCare®).
- FDA Spontaneous Report System (SRS) from 1/1/92 to 10/31/97 and Adverse Event Reporting System (AERS) from 11/1/97 to 9/30/99 for non-McNeil pseudoephedrine pediatric products.
- American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS), from 1992 to 1998.
- Review of the literature.

During the eight-year period, there were 67 reports of adverse events associated with the use of pseudoephedrine in children younger than 11 years old, of which 65 were from McNeil's or FDA's safety reporting systems, two were from the AAPCC annual reports. Nine of them were associated with serious outcomes, including three deaths. Published literature reveals 306 children younger than age 12 exposed to pseudoephedrine (in clinical trials and case reports). Of these, only four presented adverse events with a serious outcome of whom only one was younger than 2 years.

8.8.3.1 Deaths and serious adverse events with pseudoephedrine

Deaths and serious adverse events associated with the use of pseudoephedrine are summarized in table 7 and 8.

Table 7. Post-marketing Data. Deaths associated with Pseudoephedrine*.

Deaths			
Source	Age/sex	Dose	Comments
1. FDA. Non-US.	3 y M	Unknown	Allergic reaction, liver failure, lung hemorrhage
2. AAPCC (1997)	2 ½ mo M	Unknown	Older child rolled over him. High blood levels of pseudoephedrine and phenylpropanolamine.
3. AAPCC (1993)	8 y F	Unknown	Found comatose in bath tub. Several cough medications present in the household.

* Post-marketing data from January 1992 to January 2000.

Of the three deaths reported in association with pseudoephedrine, one was apparently related to a severe allergic reaction and two were related to CNS depression in children who had taken an unknown dose of pseudoephedrine along with unknown doses of concomitant medications. Two of the deaths were in children younger than 4 years of age.

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Table 8. Post-marketing Data. Serious adverse events associated with pediatric pseudoephedrine. *

Source	Age/sex	Dose	Comments
1. McNeil. US.	6 mo M	Unknown	Convulsions, lab test abnormality.
2. FDA's SRS US.	3 mo F	0.4 mL	Vomiting, emotional lability, nervousness
3. FDA's AERs. US.	2 mo M	One dose 150mg PO	Concomitant ibuprofen, one dose of 200 mg PO. Mental impairment, hospitalization.
4. Mc Neil. US.	? M	Unknown	Dyspnea. Hospitalization.
5. FDA' SRS. Non-US.	5 y M	30 mg	Allergic reaction. Arthralgia, rash, meningitis. Concomitant use of ibuprofen.
6. FDA's SRS. US.	? F	Unknown	Anaphylaxis
7. Literature	3 y F	20 mg/kg	Hallucinations.
8. Literature	10 y F	15 mgPRN	History of asthma. Concomitant use of prednisone 5 mg/d, azithromycin and albuterol x 2 days. Hallucinations, irritability, confusion.
9. Literature	10 y M	Unknown	Hypersensitivity skin reaction
10. Literature	Fetus	Unknown	Fetal tachycardia while mother taking pseudoephedrine.

* Post-marketing data from January 1992 to January 2000. y: years. M: male. F: female.

Of the serious adverse events, three were coded as allergic reactions and three involved CNS effects. Case #5, was the only post-marketing report that includes concomitant use of pseudoephedrine and ibuprofen in children age 2 to 11 years. It is conceivable that this patient did not have an allergic reaction but the arthralgia, rash and meningitis were part of the underlying disease for which he was given ibuprofen and pseudoephedrine.

Of the serious events reported with pseudoephedrine, three were in children younger than one year (to whom pseudoephedrine should not have been given), one was in a 3 year old, three were in children older than age 4 years, one was in a fetus and two were of in children of unknown age.

8.8.3.2 Non-serious outcomes associated with pseudoephedrine

In children <2 years there were 36 cases, all from McNeil's DSRS. The most frequently reported adverse events were "no drug effect" (16), insomnia (6) and screaming syndrome (4). There were also six hypersensitivity reactions: urticaria (2), edema of the face (1), pruritus (1), rash (1), maculopapular rash (1).

In children 2-11 years of age there were 22 cases of non-serious adverse events: fifteen from McNeil's Safety Reporting System, 7 from FDA's SRS. Most common events were "no drug effect" (8), nausea (2), nervousness (2) and vomiting (2).

8.8.3.3 Literature reports associated with pseudoephedrine

The sponsor conducted a search of the MEDLINE and EMBASE databases, involving the terms clinical trials, pseudoephedrine, ephedrine, safety, efficacy, adverse effects, poisoning and toxicity in children younger than 12 years of age. The search found seven controlled clinical trials (that involved at least 103 children of age 2 to 11 years), two

case-controlled studies and one case series. None of these articles reported adverse events with a serious outcome. In a case series of 140 children age <6 years who had acute ingestion of 180 mg of pseudoephedrine there were no serious adverse events (mean exposure of 11 mg/kg). Four case reports reported adverse events with serious outcome: two cases with hallucination, one allergic skin reaction and one fetal tachycardia.

8.8.3.4. Conclusions from the use of pseudoephedrine

The review of post-marketing reports and published literature from January 1992 to December 1999 supports the safety of pseudoephedrine in the pediatric population. Potentially serious adverse events include allergic reactions and CNS effects: hallucinations and CNS depression. There was one report of a child receiving concomitant ibuprofen and pseudoephedrine who developed an allergic reaction, arthralgia, meningitis and rash. It is likely that the meningitis preceded the use of the products, however, labeling for an ibuprofen/pseudoephedrine combination product should emphasize that children need to be evaluated by a physician if symptoms do not improve or get worse within 24 hours.

8.8.4 Post-marketing experience with ibuprofen individual product in the pediatric population.

It is estimated that over [] pediatric dosage units equivalents (ibuprofen 50 mg) of prescription and OTC single-ingredient pediatric ibuprofen products have been dispensed or sold in the U.S. during the five year period January 1, 1994 to December 3, 1998.

Pediatric ibuprofen data included:

- McNeil Drug Safety Reporting System (DSRS) from 11/1/93 to 1/1/00. (The last McNeil's submission for a pediatric ibuprofen product for this age group: Children's Motrin Ibuprofen Oral Suspension 100 mg/5mL was November 1993).
- FDA SRS/AERS from November 1, 1993 to September 30, 1999.
- AAPCC (1992-1998).
- Literature review.

8.8.4.1 Deaths associated with the use of with ibuprofen.

Deaths with ibuprofen are presented in Table 12.

Of the 23 deaths, 11 were in children <2 years of age and 12 in children age 2 to 11 years. Of note, two of the 23 children died of gastrointestinal complications, two had renal failure, and at least four (all of them in the >2 to 11 years group) seem to have had an anaphylactoid reaction.

There were several cases of death associated with serious infections, (including two cases of meningitis). It is likely that the serious infection preceded the use of ibuprofen. Ibuprofen could mask the signs of serious underlying infections. If symptoms do not improve or persist after 24 hours, children should be evaluated by a health care provider.

Table 9. Post-marketing Data. Deaths associated with OTC pediatric ibuprofen.

Source	Age/sex	Dose	Comments
Deaths (23 reports)			
Deaths in children < 2 years of age (11)			
1.0103. McNeil. US.	1.5 y M	Unknown	Meningitis, sepsis, heart arrest
2.0107. McNeil. US.	3 mo F	1.5 ml PO	Fever, apnea. Concomitant ceftriaxone.
3.0105. McNeil. US.	11 mo F	10mg/k/dose	?doses. Kidney failure
4.036. FDA. US.	17 mo M	1 tp x 3day	Sepsis. Heart arrest
5.002. FDA. US.	1 mo F	600 mg	Perinatal disease. Purpura. Edema. Hem. lung
6.038. FDA. US.	18 mo M	Unknown	Sepsis. Meningitis. Heart arrest
7.046. FDA. US.	23 mo F	2 tp	Overdose. Vomiting
8.001. FDA. Non US.	1 mo M	Unknown	Hypothyroidism. Apnea. Acute renal failure
9.043. FDA. US.	22 mo F	2 tp	Aspiration pneumonia
10. 518. AAPCC, 1997	3 mo F	1.5 mL x 1	With ceftriaxone for ear infection.
11. 640. AAPCC, 1994	12 mo F	Unknown	45 tabs of iron sulfate. Blood levels of ibuprofen
Deaths in children 2-11 years of age (11 reports)			
12. 0101. McNeil. US.	3 y M	10 mg/k dose	Q4h x 5d. GI hemorrhage
13. 0102. McNeil. US.	8 y ?	Unknown	Infection
14. 0104. McNeil. US.	25 mo M	3 doses	Edema face. Anaphylactoid reaction. Apnea
15. 0106. McNeil. Fran	2.5 y M	once	Edema of the brain. ? anaphylactoid reaction
16. 095. FDA. US.	2 y M	Unknown	Edema face. Apnea
17. 269. FDA. US.	8 y ?	Unknown	Infection
18. 103. FDA. Foreign	2 y F	300mg ?days	Stomach ulcer, peritonitis, sepsis
19. 289. FDA. US.	9 y M	Unknown	Hemolytic anemia
20. 058. FDA. US.	? F	1 dose 1.5 ml	Pyrexia, crying, respiratory arrest
21. 016. FDA. US.	2 y M	Unknown	Cerebral edema
22. 015. FDA. Foreign	24 mo M	Unknown	Unknown cause of death
23. 331. AAPCC, 1997	2 y M	3 doses	History of prior facial swelling with ibuprofen

* Post-marketing data from November 1993 to January 2000.

8.8.4.2 Serious outcomes reported with ibuprofen

A summary of adverse events with serious outcomes associated with the use of ibuprofen is presented in Table 13. These events are supposed to be non-replicated events.

Most commonly listed serious events were infection (33, including bacterial and viral), fever/pyrexia (21), convulsions (17), kidney failure (17), creatinine increase (13) allergic reaction (14), rash (14), face edema (13) and hematemesis (14). There were also 6 cases of meningitis. Of note, these are events, not patients, therefore the same patient may be listed more than once (e.g. under kidney failure and under creatinine increase).

Some of the reported serious events are known to be associated with the use of ibuprofen in adults and were likely due to ibuprofen (e.g. kidney failure, allergic reaction, hematemesis). Others were most likely related to the underlying disease for which ibuprofen was indicated (e.g. fever/pyrexia, may be some of the cases of meningitis).

Table 10. Post-marketing Data. Serious adverse events reported with pediatric ibuprofen.*

Children <2 years of age				
McNeil reports (n= 20 reports, 53 events)	Convulsions	4	Edema of face	3
	Cellulitis	3	Vomiting	3
	Increase creatinine	3	Urticaria, allergic reaction	3
	Kidney failure	3	Hematemesis, GI hemorrhage	2
FDA reports (n=27 reports, 100 events)	Kidney failure	7	Lethargy	3
	Infection & bacterial infection	6	Dehydration	3
	Fever, pyrexia	6	Convulsion	2
	Allergic reaction, skin reaction	4	GI hemorrhage	2
	Anorexia	3	Irritability	2
Children 2-11 years of age				
McNeil reports (74 reports, 219 events)	Edema of the face	10	Kidney failure	5
	Hematemesis	10	Ulcer stomach	4
	Dyspnea	9	GI hemorrhage	4
	Rash	9	Meningitis	3
	Convulsions	7	Cough increased	3
	Vomit	7	Gastritis	3
	Allergic reaction	6	Anaphylaxis	2
	Cellulitis	6	Sepsis	2
	Infection	6	Confusion	2
	FDA Reports (97 reports, 408 events)	Infection bacterial	16	Allergic reaction
Myositis		10	Coma	3
Creatinine increased		10	Leukopenia	3
Fever, pyrexia		15	Meningitis	3
Cellulitis		8	Skin necrosis	3
Convulsions		6	Purpura	3
Infection viral		5	Dyspnea	2
Rash		5	Hematemesis	2
Shock		4	Hematuria	2
Dehydration		4	Herpes zoster	2
Hypotension		4	Kidney failure	2
Sepsis		4	Liver failure	2

- Post-marketing data from November 1993 to January 2000. Only adverse events for which there are at least two reports are listed.

Of note, reports of hypersensitivity reactions including face and tongue edema were not uncommon.

Review of the cases of convulsions suggest that most cases were likely related to febrile seizures, however, in some cases the etiology was unknown.

Of the 5 cases of meningitis reported in association with the use of ibuprofen, two were clear cases of bacterial meningitis (one case of Group A Streptococcus bacteriemia with meningitis and one meningococcal meningitis). The three cases in which the reporter considered the event as potential aseptic meningitis are as follows:

- Case #1. A third-year medical student reported that an 8 year-old male was taking erythromycin and an unknown dose of Children's Motrin suspension for an upper respiratory infection for 7 days prior to hospitalization. The day of admission the patient presented to the

ER with somnolence and neck rigidity. According to the medical student, the patient was diagnosed with aseptic meningitis and was being treated in the ICU.

- Case #2. A 7 year-old male presented to a physician with 2-weeks history of fever and sore throat and was prescribed amoxicillin. Five days later the patient became afebrile but developed unilateral headache. The child received Motrin 2.25 teaspoons every 8 hours as needed. No improvement was noted after a few days. Cefzil® was prescribed for sinusitis. Patient did not improve and was hospitalized for further evaluation of headache and treated empirically with intravenous Claforan®. Motrin® was continued during the first three days of hospitalization. The day after Motrin® was discontinued the patient had a temperature spike of 102.7 F and a lumbar puncture showed WBC 83, protein 60, glucose and cell smears within normal limits; all cultures were negative. According to the physician, the preliminary diagnosis was aseptic meningitis. On follow up, the physician reported that one week after discontinuation of Motrin® the child had recovered completely.
- Case #3. A nurse reported that a 2-month-old male infant was hospitalized for aseptic meningitis after use of Children's Motrin oral drops to reduce fever. A physician follow-up report indicated that the final diagnosis was probable viral meningitis. He stated that during rounds the possibility of ibuprofen etiology had been raised. The infant had been on ibuprofen 10 mg/kg every 6 hours for 2 ½ days. Ultimately, it was felt that ibuprofen did not play any causative role.

None of these potential cases of aseptic meningitis are very compelling. The first two involved antibiotic use and could have been cases of partially treated bacterial meningitis. The third case was ultimately considered viral meningitis, although there were no confirmatory studies. Aseptic meningitis is a well-known adverse event associated with the use of ibuprofen in adults, even at OTC doses. Therefore, it is still possible that ibuprofen may be associated to aseptic meningitis in children.

8.8.4.3 Adverse events with non-serious outcome reported with ibuprofen.

In children younger than 2 years:

McNeil's DSRS included 604 events with non-serious outcomes. Most common cases were allergic reactions (including face edema (150), rash/urticaria (120) and edema of the tongue (4)); accidental overdose (250); CNS adverse events (including insomnia (59), nervousness (60), hyperkinesia (20), somnolence (18)) and gastrointestinal adverse events (including glossitis/stomatitis (250), vomiting (45), abdominal pain (13), diarrhea (13), hematemesis (6), and melena (4)). There were only 3 non-serious reports reported to the FDA's safety reporting system.

In children 2 to 11 years of age:

McNeil's Drug Safety Reporting System included 2137 reports with non serious outcomes. Most common events were allergic reactions (including rash/urticaria (445) face edema (150), edema of tongue (3), and angioedema (2)); accidental overdose (274); no effect 133; CNS events (including hallucinations (20), hyperkinesia (36), insomnia (20) and somnolence (52)) and gastrointestinal events (including glossitis/stomatitis (480);

vomiting (130), dyspepsia (22), hematemesis/gastrointestinal bleeding/melena (9)). FDA reports included approximately 200 cases of adverse events with non-serious outcomes. The adverse events reported to FDA were similar to those reported to McNeil's DSRs.

8.8.4.4 Literature for ibuprofen

The sponsor conducted a MEDLINE and EMBASE search for clinical trial data on the efficacy and safety of ibuprofen in children younger than 12 years of age, from 1992 to January 2000. Seventy-two publications describing the results of 54 clinical trials were found. Only three adverse events with a serious outcome were reported: one case of gastrointestinal bleeding, one case of headache and one case of anemia. The age of the children who presented these serious outcomes was not stated.

8.8.4.5 Conclusions for the use of ibuprofen in the pediatric population.

The commercial marketing safety data supports the acceptable safety profile of single ingredient pediatric prescription and OTC ibuprofen products. The most concerning events seen with the individual products in the pediatric population were anaphylactoid reactions, gastrointestinal bleeding, kidney failure and liver failure (similar to the adult population). Of note, several children presented with convulsions. Most of these cases appeared to be related to febrile seizures.

8.8.5 Safety Update

The 4-month safety update submitted on February 9, 2000, contained post-marketing information for the ibuprofen/pseudoephedrine combination product in adults from January 1, 1999 to December 31, 1999. Of 25 post-marketing adverse events reported during this period, two were considered to be serious by the reporting subject, both of them related to severe allergic reactions within 2 days of starting the product. No new safety issues were identified during this period.

8.9 Summary of Key Adverse Findings

The ibuprofen/pseudoephedrine combination product was well tolerated in the NDA studies. There were no deaths or serious adverse events in the NDA database. There were no severe allergic reactions, episodes of asthma exacerbation, (an adverse event that had been requested to be specifically addressed in the Pediatric Written Request), neurologic, cardiovascular or adverse hemodynamic effects. There were no major changes in vital signs and no changes in mean laboratory values among the 24 patients who had laboratory measurements. The most common adverse event was somnolence, seen in 7% of patients in study 99-086.

The most concerning adverse events reported in post-marketing with both ibuprofen and pseudoephedrine were severe allergic reactions including anaphylaxis, sometimes after a single dose. Other serious events reported with pseudoephedrine were CNS depression

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and hallucinations. Serious events reported with ibuprofen were kidney failure, liver failure and gastrointestinal bleeding.

8.10 Comment on the Adequacy of the proposed dosing.

As seen in Table 1 (page 5), the dose of Children's Motrin Cold Suspension used in the safety study was based on a five-tiered dose regimen supposed to maintain dosing within established safe and effective ranges for each component. The dose used in the PK study (1 dose = 7.5 mg/kg ibuprofen and 1.125 mg/kg pseudoephedrine) correlated very closely with the five-tiered dose regimen.

This five-tiered regimen for the combination product maintained similar ranges (mg/kg per dose) of ibuprofen and pseudoephedrine compared with the individual products for the different age/weight groups.

As seen in Table 1, the dose and schedule of ibuprofen as part of CMCS is exactly the same as recommended for the individual product: 5 tiered regimen, given every 6 to 8 hours, while pseudoephedrine has a two-tiered regimen and is given every 4 to 6 hours (Table 11).

Table 11. NDA 21-128. Dosage recommendations for the individual products.

Ibuprofen ¹			Pseudoephedrine ²		
Average dose of 7.5 mg/kg may be repeated q. 6-8 hours not to exceed 30 mg/kg/day			Dose may be repeated q. 4-6 hours not to exceed 60 mg/day for children <6 years or 120 mg/day for children 6 to 11 years.		
Age (years)	Weight (kgs)	Dose	Age (years)	Weight not considered	Dose
< 6 months		Consult a doctor	<2 years		Consult a doctor
2-3	10.9--15.9	100 mg	2 to <6		15 mg
4-5	16.4--21.4	150 mg			
6-8	21.8--26.8	200 mg	6 to <12		30 mg
9-10	27.3--32.3	250 mg			
11	32.7--43.2	300 mg			

¹ As recommended in the Childrens Motrin Suspension label. 1 tsp contains 100 mg/5 ml

² As recommended in the Monograph for OTC Nasal Decongestants.

As seen in Table 12 the maximum daily doses of pseudoephedrine recommended for the 4 to 5 year olds and 9 to 11 year olds in the combination product are higher than the maximum recommended dose in the Monograph for OTC Nasal Decongestants, which is independent of weight. Of note, none of the OTC products containing pseudoephedrine currently recommend the use of doses higher than 60 mg and 120 mg in a 24-hour period for children ages <6 years and 6 to 12 years, respectively.

Table 12. NDA 21-128. Children's Motrin Cold Suspension dose regimen¹. Comparison with maximum recommended doses of individual products.

Age (years)	CMCS ¹ Dose ² (teaspoon)	Ibuprofen			Pseudoephedrine		
		Dose (mg)	Maximum daily dose recommended (mg/day)		Dose (mg)	Maximum daily dose recommended (mg/day)	
			As part of combination, q 6h regimen	For individual product ²		As part of combination, q 6h regimen	For individual product ³
2-3	1	100	400	327 - 477	15	60	60
4-5	1 ½	150	600	492 - 642	22.5	90	
6-8	2	200	800	654 - 804	30	120	120
9-10	2 ½	250	1000	819 - 969	37.5	150	
11	3	300	1200	990 - 1290	45	180	

¹ 100 mg of ibuprofen and 15 mg of pseudoephedrine for each 5mL teaspoon q 6 - 8 hours, not to exceed 4 times a day. ² Average Ibuprofen dose q 6 - 8 hours not to exceed 30 mg/kg/day. Calculated based on weight from Table 1. ³ As recommended in the Monograph for OTC Nasal Decongestants, not to exceed 60 mg/day in children <6 or 120 mg/day in children ages 6 to 11.

To avoid the use of pseudoephedrine at doses higher than the recommended in the Monograph, the applicant should consider the use of a two-tiered regimen (Table 13). This regimen might under-dose a little on the ibuprofen side, although, all patients would receive ibuprofen doses close to or above 5 mg/kg (minimum recommended dose for OTC). From a safety perspective, it would be preferable to under-dose with an NSAID than to overdose with pseudoephedrine. McNeil has conducted several studies to support the efficacy of the 5 mg/kg dose. Data from those studies indicates that while the peak effect is comparable for 5 and 10 mg/kg doses, there is a difference in the duration of effect. Since the product would be used q 6 hours, this would not be a problem. (See Memorandum from Dr. Adebowale, PK reviewer).

Table 13. Children's Motrin Cold Suspension (CMCS) two-tiered dose regimen¹.

Age (years)	Weight (kgs)	CMCS Dose	Ibuprofen ²		Pseudoephedrine ³	
			Dose	Maximum received in a q q 6h regimen	Dose	Maximum received in a q q 6h regimen
2-3	10.9--15.9	1 tsp.	100 mg	400mg/day	15 mg	60 mg/day
4-5	16.4--21.4					
6-8	21.8--26.8	2 tsp.	200 mg	800 mg/day	30 mg	120 mg/day
9-10	27.3--32.3					
11	32.7--43.2					

¹ 100 mg of ibuprofen and 15 mg of pseudoephedrine for each 5mL teaspoon q 6 hours, not to exceed 4 times a day. ² Ibuprofen dose: 5 to 10 mg/kg, q 6 - 8 hours not to exceed 30 mg/kg/day. ³ As recommended in the Monograph for OTC Nasal Decongestants, q 4 - 6 hours, not to exceed 60 mg/day in children <6, or 120 mg/day in children ages 6 to 11.

9.0 Labeling Review

9.1 Indication – Sinusitis.

The proposed indication of Childrens Motrin Cold Suspension is to temporarily relieve symptoms associated with the common cold, flu or sinusitis, including nasal and sinus congestion, stuffy nose, headache, sore throat, body aches and pains, and to temporarily reduce fever.

The efficacy of the product in children with sinusitis has not been appropriately studied. None of the individual products has this indication. Therefore, "sinusitis" should be removed from the label.

9.2 Dosing

A two-tiered regimen for a q 6 hours interval would prevent a maximum recommended dose of pseudoephedrine that exceeds the daily doses recommended in the Monograph for the 4-5, 8-9 and 10-11 year-old groups.

9.3 Safety

10.0 Conclusions

10.1 Pharmacokinetics of the combination product in children and adults

PK parameters showed no age-related changes for ages 4 – 11 years. No PK model was available for extrapolation of values to the 2-4 years of age population.

PK parameters in adults suggested a faster rate of absorption of the pseudoephedrine component in the combination product (in particular T_{max} and C_{max}) compared to the individual product. This difference, however, was within bioequivalence limits. In addition, children had a higher clearance than adults.

10.2 Safety of the product

CMCS was well tolerated in children ages 2 to 11 years. 138 children received at least one dose of the combination product. Forty-four of the 138 children received 8 doses or more over a three-day period. Only 4 patients received 11 doses or more over a three-day period.

Post-marketing data from the individual products support the safety of the individual products in the pediatric population down to age 2 years.

Post-marketing data from the ibuprofen/ pseudoephedrine combination in the adult population support the safety of the product in the pediatric population down to 4 years of age, taking into consideration that PK parameters in adults are comparable to those in children down to that age 4.

The available data did not allow for extrapolation of the PK data from 4 to 11 year-olds to 2 and 3 year-olds. However, safety data from 38 pediatric patients younger than 4 years included in the NDA suggest that the combination product does not behave differently in 4-11 year-olds compared to 2-4 year-olds.

10.3 Dosing and schedule

Although no serious adverse events were seen at the recommended doses that would provide up to 90 mg/day, 150 mg/day and 180 mg/day of pseudoephedrine in children age 4-5, 8 -9 and 10-11 years, respectively, the number of patients in the NDA was relatively small. The Monograph for Nasal Decongestants recommends the use of up to 60 mg/day for children below 6 years or 120 mg/day for children 8-11 years. Therefore, a two-tiered regimen is preferred to the five-tiered regimen.

Dosing interval for the individual components and PK studies conducted during the NDA support the q 6 hours interval, but not the q 8 hours interval.

11.0 **Recommendations**

This application should be Approvable, for children 2 to 11 years, with the two-tiered regimen, q 6 hours.



Table 3.8-9. Cumulative Distribution of the Number of Doses Taken by Day — McNeil Study 99-086

Day ^a	Number of Doses Taken by		Number of Subjects (N = 114)	Percentage of Subjects
	Day			
1	≥ 1		114	100.0
	≥ 2		107	93.9
	≥ 3		84	73.7
	≥ 4		34	29.8
	≥ 5		2	1.8
2	≥ 1		108	94.7
	≥ 2		85	74.6
	≥ 3		43	37.7
	≥ 4		6	5.3
3	≥ 1		93	81.6
	≥ 2		39	34.2
	≥ 3		9	7.9
	≥ 4		1	0.9
4	≥ 1		1	0.9

a: A day was defined as a 24-hour period measured from the time of the first dose.

Table 3.8-8. Distribution of Number of Days at Least One Ibuprofen-Pseudoephedrine Suspension Dose Was Taken — McNeil Study 99-086

Number of Days ^a at Least One Dose Was Taken	Number of Subjects	Percentage of Subjects
1	4	3.5
2	19	16.7
3	90	78.9
4	1	0.9

a: A day was defined as a 24-hour period measured from the time of the first dose.

Table 3.8-7. Median Number of Doses Taken by Age Group — McNeil Study 99-086

Age Group (y)	N	Median Number of Doses
2-3	38	7
4-5	28	7
6-8	28	6
9-10	18	6
11	2	8

5 *pages of revised draft
labeling have been
redacted from this portion
of the document.*