CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-604

MEDICAL REVIEW

Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL

NDA 21-604

Medical Officer Addendum Review

Submission Date:	November 20, 2003
Reviewer Received Date:	November 25, 2003
Review Completed:	December 19, 2003
Drug Name:	Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL
Applicant:	Taro Pharmaceuticals USA, Inc.
Pharmacologic Category:	Non-steroidal Anti-inflammatory
Proposed Indication:	Antipyretic and Analgesic for Children.
Dosage Form and Route:	100mg/5ml, Oral Suspension
Submission type:	Amendment submission
Materials Reviewed:	Primary documents: -Amendment AZ N-000 -Medical Officer Review of NDA 21-604 (HFD-550) -AE Letter (October 30, 2003)

Orig NDA # 21-604
HFD-550/Div File
HFD-550/PM/Dean
HFD-550/Pharm/Chen
HFD-550/Chem/Bhavnagri
HFD-550/Biopharm/Bashaw
HFD-550/Statistics/Lin
HFD-550/MO/Yao/Witter

(Michael Yao, M.D., Medical Officer)

Resume:

Taro Pharmaceuticals U.S.A., Inc. filed NDA21-604 as a 505(b) (2) New Drug Application for Children's ElixSure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL (CIB) on December 31, 2002. In this NDA, the Sponsor proposed a liquid delivery system that resists spilling from a spoon that is different from the other approved ibuprofen suspensions currently marketed.

The Sponsor proposed that CIB was indicated as antipyretic and analgesic for children ages 2 to 11 years.

The Original NDA submission was reviewed by both the Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (HFD-550, Michael Yao, October 30, 2003) and the Division of Over-the-Counter Drug Products (HFD-560, Rosemarie Neuner for safety review and Ida Yoder for labeling review, October 30, 2003). Upon completion of review, an approvable letter was sent (October 30, 2003), which discussed the language in the label relating to the studies that addressed the use of feeding tubes.

This brief review discusses the November 20, 2003 response by the Sponsor submitted to address the label deficiencies listed in the approvable letter.

Review of November 20, 2003 Sponsor response:

As noted upon review of feeding tube studies in the original NDA (see page 56-58 of MO review, HFD-550), problems were noted that were associated with the administration of this product via various feeding tubes as noted below (Yes = passed tube, No = did not pass tube, N/A = information not available):

Tube Type/Size	Un-diluted/One Hand Method	Un-diluted/Two Hand Method	Diluted/One Hand Method	Diluted/Two Hand Method
NG Tube/8 French	No	No	No	Yes
NG Tube/12 French	No	No	Yes	N/A
G Tube/14 French	Yes	N/A	N/A	N/A
J Tube/9/18 French	No	No	No	Yes

Since there are a variety of feeding tubes that have been studied and appear to have problems, the Division recommends that the Sponsor should change the currently proposed labeling indicating that includes the bullet [redacted] in the "Do not use" subsection of the Warnings On November 20, 2003.

Conclusion:

As noted in Medical Officer Review of the original NDA submission and approval letter for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL the Sponsor submitted a bullet in the "Do not use" subsection of the Warnings in the labeling for users who may administrate this product via feeding tubes. Owing to the concerns that this product may block a variety of feeding-type tubes as noted above, the Sponsor should

create the bullet as "with feeding tubes" instead of [redacted] in the "Do not use" subsection of the Warnings in the revised label.

Required Regulatory Action:

NDA 21-604 should be approved with language to address as "with feeding tubes" in the "Do not use" subsection of the Warnings in the revised label, rather than the currently proposed language of [redacted]

Michael Yi Yao, M.D.
Medical Officer, DAAODP

James Witter, M.D., Ph.D.
Team Leader, DAAODP

Cc:
IND
HFD-550/Division files
HFD-550/Reviewers
HFD-550/TL
HFD-550/CSO

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/s/

Michael Yao
12/18/03 05:19:12 PM
MEDICAL OFFICER

James Witter
12/19/03 12:34:07 PM
MEDICAL OFFICER
Concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL OFFICER REVIEW

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

NDA 21-604

Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL

NDA# 21-604

IND # 62,832

Medical Officer:	Michael Yao, M.D.
Submission Date:	December 31, 2002
Reviewer Received Date:	January 13, 2003
Review Completed:	August 18, 2003
Drug Name:	Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL
Applicant:	Taro Pharmaceuticals USA, Inc.
Pharmacologic Category:	Non-steroidal Analgesic
Proposed Indication:	Antipyretic and Analgesic for Children.
Dosage Form and Route:	100mg/5ml, Oral Suspension
Submission type:	Original NDA

Medical Review of the NDA# 21-604

Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL

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Executive Summary

Significant Issues

Taro Pharmaceuticals U.S.A., Inc. filed NDA21-604 as a 505(b) (2) New Drug Application for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL on December 31, 2002. In this NDA, the Sponsor proposed a liquid delivery system that resists spilling from a spoon that is different from the other approved ibuprofen suspensions currently marketed.

The Sponsor proposes that Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL is indicated as antipyretic and analgesic for children ages 2 to 11 years.

Since the active ingredient in Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL is ibuprofen, its efficacy and safety profiles are well established as mentioned above.

In support of this NDA submission, the Sponsor has submitted clinical safety data summarized from 3 biopharmaceutical studies, 1 fluoroscopic esophageal transit study, 1 open-label swallowing study in patient with dysphagia and feeding tube study with different types of feeding tubes. Also, a study utilizing radioactive labeling of material to evaluate swallow process of Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL will be as a phase IV trial.

In addition, the Sponsor summarized clinical trial efficacy data that was previously reviewed in support of NDA 19-842 for Children's Motrin 100 mg/5mL Oral Suspension sponsored by McNeil Consumer Products Company. In the meantime, the Sponsor also summarized results of an updated worldwide literature review in support of ibuprofen's global efficacy and safety profile in the hope of obtaining OTC marketing approval for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL for the temporary relief of fever and pain.

Conclusion

As mentioned above, the efficacy and safety profiles of ibuprofen are well established. To support the efficacy and safety of Children's Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL in treating fever and sore throat and/or ear pain in children, the Sponsor summarized and submitted clinical efficacy and safety data of oral ibuprofen suspension from different references. Review of these data is acceptable.

No new or unexpected adverse events associated with the use of this proposed formulation of ibuprofen were identified on review of the clinical safety data in this NDA submission. However, since the swallowing study (protocol No. IBU

036) involved only 7 patients, there is not sufficient evidence to rule out the possibility that some patients with dyphagia may have problems with aspiration.

To help complete the swallowing assessment, the Sponsor should submit data of a phase IV study utilizing radioactive labeling of material to evaluate swallow process of Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL to the Division when available. These phase IV study data will not effect approvability for Children's Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL.

Recommendation for Regulatory Action

Review of the global efficacy and safety data submitted by the sponsor in support of Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL was consistent with what is already known about ibuprofen. Based on the information and data reviewed in this NDA, there are no efficacy or safety issues for this ibuprofen suspension.

No significant efficacy or safety deficiencies were found for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL in this NDA submission. Therefore, the proposed indications for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL are appropriate.

Recommendation

The Sponsor should reflect in the labeling the feeding tube study results, which demonstrate that Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL can not be used in patients with 8/12 French NG feeding tubes and 9/18/French J tubes because they become blocked with this suspension.

Both the Division and the Sponsor agree that the data from the swallowing study in patients with dysphagia (protocol No. IBU 036) is a preliminary safety data, and the Sponsor will not impact the labeling.

Regulatory Action

NDA 21-604 should be approved with language to address the NG and J tubes as noted above.

Overview

The active ingredient in ElixSure™ IB suspension is ibuprofen, which is a member of the propionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). It is a white to off-white crystalline powder, with a melting point of [redacted] It is practically insoluble in water (<0.1 mg/mL), but readily soluble in organic solvents such as ethanol and acetone. Ibuprofen has a pKa of 4.43±0.03 and an n-octanol/water partition coefficient of 11.7 at pH 7.4. The chemical name for ibuprofen is (±)-2-(p-isobutylphenyl) propionic acid. The molecular weight of ibuprofen is 206.28 and its molecular formula is $C_{13}H_{18}O_2$.

Ibuprofen is of analgesic and antipyretic properties and mechanism of action is generally believed to be related to the inhibition of prostaglandin synthesis. In children aged 6 months and older, ibuprofen is indicated for the reduction of fever, relief of mild to moderate pain, and relief of signs and symptoms of juvenile arthritis. In adults, it is indicated for the relief of mild to moderate pain, treatment of primary dysmenorrhea and relief of signs and symptoms of rheumatoid arthritis, osteoarthritis.

In 1989, Ibuprofen suspension 100mg/5ml was approved by the FDA as a prescription antipyretic for use in children aged 6 months and older. That product was switched to non-prescription status in the United States in 1995, with both antipyretic and analgesic indications for children ages 2 to 11 years.

The Sponsor has developed an oral spill resistant, liquid delivery system. The resulting product, ElixSure™ IB (Ibuprofen NonSpil™ Suspension) pours like thick syrup and resists spilling from a spoon. The Sponsor has developed a liquid delivery system that resists spilling from a spoon. According to its character, this special delivery vehicle system should increase the ease and reliability of dosing with liquid medication and is a rapidly reversible shear thinning gel system made entirely of GRAS ingredients. "Shear thinning" simply describes the characteristic of changing viscosity or flow properties with a shear force. With just a little bit of pressure, or shear, its viscosity changes and it becomes " almost a liquid", As it settles, it rapidly becomes more viscous. Then, as soon as the spoon is place in the mouth and it exposed to the mild shear forces of the tongue and cheeks, it again liquefies, spreads over the buccal membrane like a liquid and then is swallowed. Based on these properties, the Sponsor proposed that this delivery system is good for pediatric, elderly patients and individuals with fine motor impairment.

Toxicity studies of ibuprofen have been conducted by using a variety of species, including mice, rats, rabbits, guinea pigs and beagle dogs. Single dose acute

toxicity studies indicate that ibuprofen in lethal doses depresses the CNS of rodents and that large doses are ulcerogenic in both rodents and nonrodents. Ulcerogenesis may occur with both parenteral and oral administration. Prior studies noted LD50 values of 800 mg/kg orally and 320 mg/kg intraperitoneally in the mouse and 1600 mg/kg orally and 1300 mg/kg subcutaneously in rats.

In other studies, the UD50 (ulcerogenic dose in 50%) were 70 mg/kg orally and 210 mg/kg with intravenous administrations. In dogs, no ill effects were seen following doses of 20 or 50 mg/kg. Oral doses of 125 mg/kg, or greater produced emesis, scouring, albuminuria, fecal blood loss and erosions in the gastric antrum and pylorus. Chronic toxicity studies in dogs demonstrated no gross or clinical signs of toxicity at 4, 8, or 16 mg/kg/day for 30 days.

A study to evaluate the potential carcinogenic activity of ibuprofen involved administration of a minimum of 100 mg/kg/day to mice for 80 weeks and 60 mg/kg/day to rats for 2 years.

The studies confirm that ibuprofen dose not induce tumors of the liver or other organs in the rats and mouse.

Teratogenicity studies of ibuprofen have been conducted in rabbits and rats. Results of studies indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits nor is there embryotoxic or teratogenic activity in pregnant rats even when administered in ulcerogenic doses. Effects of ibuprofen on circular strip of fetal lamb ductus arterious indicate that exposure may produce contraction of the ductus.

The type of adverse event occurring most frequently with ibuprofen is gastrointestinal toxicity. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range),

sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Also, anaphylactoid reactions may occur even in patients without prior exposure to ibuprofen.

As with other NSAIDs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Important Milestones in Product Development

1. The Sponsor submitted the pre-IND application to the Division on March 27, 2003.

2. An pre-IND meeting was held with the Sponsor on May 7, 2002. As per the FDA meeting minutes, the comments from the Division are as following:

   -A summary of the Pharmacology and Toxicology with a list of key references of Ibuprofen would be sufficient.

   -All of the specifications are acceptable for an IND submission. However, it is noted that 1) the viscosity values decrease with storage and 2) the largest particle size decreases from the initial time point to the two-month time point and then increases at the three-month time point. Attention needs to be paid to these two parameters to determine if these are real or artifacts.

   -A bracketing or a matrixing protocol is used when a large number of stability samples need to be analyzed. In the case of an IND, this number is relatively small. Therefore, bracketing or matrixing cannot be permitted.

   -In the latter stages of drug development, a bracketing/matrixing protocol may be allowed. However, such a protocol should be reviewed by the Division before it is used for stability studies.

   -The Division will provide the sponsor with the appropriate contacts in the FDA [redacted] *who can answer these two questions.*

-The storage conditions in the submitted label are those for a commercial product. An IND label should indicate that this is for investigational purposes only. The exact wording that should go on the label from the CMC standpoint is in 21 CFR 312.6. The proposed label will be reviewed in the context of the indication (i.e., OTC or prescription) being sought by the sponsor.

Additional Comments:

1) Please give the unit formulation, i.e., the components and composition per 5mL of the suspension.

2) Please indicate what the masking agent is.

3) Is the container closure of any special design or is the pouring/gelling effect purely a function of the formulation? If the container closure is of a special design, then this should be described in some detail in the IND.

4) It is recommended that the sponsor conduct a Food-effect study with the to-be-marketed formulation in adults.

5) Considering the formulation is unique, it is also recommended that the sponsor conduct a pharmacokinetic study in the pediatric patient.

6) Information on any safety issues with use of the ingredients that compose the spill resistant character of this formulation needs to be addressed.

7) The sponsor needs to demonstrate that accurate delivery of drug is possible from the spoon supplied and other sources (i.e., calibrated caps).

8) The Division is concerned about the potential for esophageal toxicity due to the possibility that the characteristics of the ingredients contained in this spill resistant formulation may not allow the ibuprofen dose to pass completely into the stomach. The sponsor needs to address this concern.

3. The Sponsor submitted IND application (IND 62,823) to the Division on August 2, 2002. The regulated action has been made by the Division as follows:

-There are no clinical hold issues at this time, the study should be allowed to proceed.

-The Sponsor should consider the following studies with the aim of completing this IND application.

1) A food-effect study in adult group.

2) A study of administration of Ibuprofen NonSpil ™ Oral Suspension to NG-tube, G-tube and J-tube in order to rule out the possibility of obstructing these tubes.

3) Swallowing studies in both healthy subjects and patients with dysphagia to rule out the possibility of aspiration.

4) Based on the pre-IND meeting on May 7, 2002, Sponsor should address a concern, which the potential for esophageal toxicity due to this spill resistant delivery system may not allow the ibuprofen dose to pass completely into the stomach.

5) The sponsor needs to clarify that accurate delivery of drug is possible from the spoon supplied and other sources (calibrated caps).

4. The Sponsor submitted NDA (NDA 21-604) to the Division on December 31, 2003.

5. The Sponsor submitted a swallow study data in Normal subject on January 6, 2003

6. The Division issued a filing letter to the Sponsor on March 13, 2003. At that time, the Division have identified the following potential review issues:

1. The tradename needs to be clarified. The cover letter refers to the product as "Children's ElixSure TMIB (Ibuprofen) Oral Suspension". However, the proposed labeling of the product does not include the "IB" designation.

2. The submission notes that the product may have "nonspill" or "gel" characteristics. However, the teaspoon depiction, and the reference to "Ibuprofen Oral Suspension" on the PDP and other labeling does not convey that the product is any different from a traditional suspension. The labeling should be revised to differentiate this product from a traditional suspension.

3. You must submit drug facts specifications (font size, etc.).

4. You should submit a section on investigational formulations that were developed for this NDA.

5. Justification for the acceptance criteria of the drug product should be submitted.

6. Also, you should submit a statistical analysis justifying the proposed expiration period of the drug product, or submit a justification why such an analysis was not feasible.

7. Please submit the additional missing safety data requested by the Division, such as swallowing studies and the esophageal toxicity study in patients with dysphagia (stroke, CP, TBI, or other neurological disorders) within the review period after starting the review clock.

8. Please identify the components of the container/closure system that come in contact with the drug product. Please provide Letters of Authorization from the DMF holders of the container closure systems, indicating exactly where the pertinent

information is located. If possible, also request the DMF holders to include a statement in the LOA that it is safe for the component of the container closure system to come in contact with food and give the relevant CFR citations.

7. The Sponsor submitted swallow study protocol in patients with dysphgia to the Division on May 29, 2003 and re-submitted revised protocol to the Division on July 28, 2003.

8. In August 13, 2003, Biopharmcology team issued a comment regarding PK study in children in this NDA submission as follows:

   In support of a 505 (b) (2) application for the ibuprofen Nonspill (Children's Elixsure IB) product, the sponsor has conducted single dose bioequivalence (BE) studies in healthy adults and the product is bioequivalent to the reference product (Children's Motrin oral suspension) under both fast and fed conditions. In addition, the sponsor has conducted a bioequivalence study in children (3-12 yr) under fast condition, but their product is not bioequivalent to the reference product in children. In discussion with our management regarding this issue, it is felt that adult BE data would take precedence. Because historically, the 90% confidence interval criteria for bioequivalence are derived from adult data, and its utility in pediatric subjects is questionable in regulation sense. Historically for a similar product, the sponsor would conduct BE studies in adult subjects under fast and fed conditions, and just conduct a bioavailability (BA) study for the pediatric patients. In conclusion, the finding of non-bioequivalence in the pediatric subjects for this product is not considered an approvability issue.

Description of Clinical Data and Sources

Overall Clinical Study Data

Ibuprofen is a nonsteroidal anti-inflammatory agent (NSAID) known to possess analgesic and antipyretic properties. It has been marketed by prescription since 1969 in the United Kingdom and since 1974 in the United States, and as an over-the-counter drug in the United States since 1984. In 1989, Ibuprofen suspension 100mg/5ml was approved by the FDA as a prescription antipyretic for use in children aged 6 months and older. That product was switched to non-prescription status in the United States in 1995, with both antipyretic and analgesic indications for children ages 2 to 11 years.

Ibuprofen is available in various dosage forms: liquid suspension, chewable tablets, and film-coated, capsule-shaped tablets in current market.

Ibuprofen has been used in the treatment of pain, inflammation, and fever. Its mechanism of action is generally believed to be related to the inhibition of prostaglandin synthesis. In children aged 6 months and older, ibuprofen is indicated for the reduction of fever, relief of mild to moderate pain, and relief of

signs and symptoms of juvenile arthritis. In adults, it is indicated for the relief of mild to moderate pain, treatment of primary dysmenorrhea, and relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

The type of adverse reaction occurring most frequently with ibuprofen is gastrointestinal. In controlled clinical trials, 4% to 16% of adult patients reported one or more gastrointestinal complaints. When compared with equally effective doses of aspirin and indomethacin, the overall incidence of gastrointestinal complaints in ibuprofen-treated adults was half that of either of the other two agents.

The active ingredient in ElixSure™ IB is ibuprofen, and it has a well-established safety and efficacy profile in both adult and pediatric patients based upon previous clinical studies and post marketing data. The Sponsor presents relevant clinical information (with emphasis on the suspension formulation for pediatric patients) taken from the vast body of published data on ibuprofen, unpublished data from submissions to regulatory agencies in the United States and Canada as efficacy data in this NDA. The Sponsor also presents additional supportive safety data and clinical pharmacology data from safety studies and clinical pharmacology studies conducted by the Sponsor.

Clinical Pharmacology Study

Commercially available ibuprofen is a racemic mixture of two optical isomers: S-(+)-enantiomer and R-(-)-enantiomer. The racemic mixture is recognized in the U.S. Pharmacopeia (U.S.P.). After absorption of the racemic ibuprofen, the R-(-)-enantiomer slowly and incompletely (60%) undergoes inter-conversion to the S-(+)-form in adults, with similar interconversion believed to occur in children.[1]

The S- (+)-enantiomer possesses the majority of the pharmacological activity. As with other NSAIDs, ibuprofen exhibits marked enantio-selectivity in its action and disposition.

The mechanism of the gastrointestinal adverse effects of NSAIDs is not known, but there is evidence that the R- (-)-enantiomer may contribute to these effects. NSAIDs are reversible inhibitors of cyclooxygenase (COX), and this pharmacodynamic property may contribute to their clinical effects. In accordance with a theory proposed by J. Vane in 1971, it is generally believed that the mode of action of ibuprofen and other NSAIDs is via inhibition of the COX-mediated transformation of arachidonic acid to thromboxane and the various prostaglandins. Most of the clinical effects of NSAIDs can be explained by reduced prostaglandin production: prostaglandins are mediators of pain, inflammation, and platelet aggregation, and are gastric protectants and regulators of renal perfusion. This theory is supported by the finding that R-enantiomers of chiral NSAIDs do not inhibit prostaglandin synthesis and lack anti-inflammatory

efficacy. Other studies have suggested that these agents have modes of action for some of their biologic effects that are independent of COX-inhibition.

Pharmacodynamics

Absorption

Absorption of orally administered ibuprofen is rapid and complete, with peak plasma levels usually occurring within 1 to 2 hours. Studies of ibuprofen in febrile children have demonstrated the dose-proportionality of 5- and 10-mg/kg doses. All formulations (suspension, drops, caplets, and chewable tablets) are equally bioavailable in terms of peak plasma levels (Cmax) and extent of absorption (AUC). Time-to-peak-concentration (Tmax) differs among formulations, but there is no apparent effect on onset of effect or peak fever reduction in children. In adults, pharmacokinetic differences among the formulations are attributed to differences in the rate of absorption of ibuprofen from the dosage form.

Administration of ibuprofen with food affects the rate, but not extent, of absorption. Tmax is delayed by 30 to 60 minutes, and peaks levels are reduced by approximately 30 to 50%.

Administration of ibuprofen concomitantly with an antacid containing both aluminum hydroxide and magnesium hydroxide has no effect on the absorption of ibuprofen.

Distribution

Ibuprofen binds extensively to plasma albumin (>90% bound at 20 μg/mL) Protein binding is saturable and at concentrations >20 μg/mL, binding is non-linear. There is an age- or fever-related change in volume of distribution: febrile children older than 11 years have a volume of approximately 0.2 L/kg, whereas adults have a volume of approximately 0.12 L/kg.

Substantial concentrations of ibuprofen have been detected in synovial fluid. A study in children with juvenile rheumatoid arthritis given 40 mg/kg/day of ibuprofen (in 3 divided doses), showed peak concentrations in synovial fluid 5-6 hours after administration. Thereafter the synovial fluid concentrations were higher than in serum.

Metabolism

Following an oral dose, the majority of the drug was recovered in urine within 24 hours as the metabolites hydroxy- (25%) and carboxypropyl- (37%) phenylpropionic acid. Free (1%) and conjugated (14%) ibuprofen were found in

urine. The remainder of the drug was found in the stool as metabolites and unabsorbed drug.

Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all the oxidative metabolites of ibuprofen [both R- (-) and S- (+)]. The hydroxy and carboxy metabolites have no known pharmacological activity.

Elimination

Less than 1% of the dose is excreted unchanged in urine and excretion is virtually complete 24 hours after a dose. The plasma half-life is approximately 2 hours, with a biphasic elimination time curve. No differences between children and adults have been observed with regard to terminal elimination rate or half-life; however, there is an age- or fever-related change in total clearance, possibly due to changes in volume of distribution.

Pharmacokinetics in Various Patient Populations

Elderly

The pharmacokinetics of a single 600-mg dose of ibuprofen was compared in males and in females, aged 22-24 years and 60-88 years. T_{max} and C_{max} values were similar in each group; $t_{½}$ and volume of distribution were not significantly different when corrected for bodyweight; free fraction of ibuprofen in plasma appeared not to be affected by age. There were no apparent differences between young and elderly females, but the elderly men had lower clearance than the younger men (0.0576 vs. 0.0618 L/h•kg).

Another study comparing the pharmacokinetics of ibuprofen in males aged 65-78 years vs. 22-35 years showed no statistically significant difference in any parameter, suggesting that advanced age has only minimal influence on the pharmacokinetics of ibuprofen and dose adjustment is unnecessary.

Children

Studies in children have demonstrated no significant alterations in ibuprofen pharmacokinetics.

Doses of 5-10 mg/kg of ibuprofen administered to children 3 to 10 years old demonstrated no effect on ibuprofen pharmacokinetic parameters.

The relative proportion of ibuprofen in synovial fluid in children appeared to be slightly higher after repeated doses compared to adults given a single dose. The C_{max} in synovial fluid in children was about 40 % of the maximal concentration in serum, compared to about one-third in adults.

Intravenous ibuprofen has been given to newborn infants for the prevention of intra ventricular hemorrhage and closure of patent ductus arteriosus. It was found that gestational age and birth weight were unrelated to drug elimination. The percentage of protein-bound ibuprofen was significantly lower in full term cord plasma (98.4%) than in adult plasma (98.73%). Neonates, compared with adults and older children, have prolonged ibuprofen elimination and slightly lower protein binding.

Hepatic Impairment

Studies of ibuprofen pharmacokinetics in patients with alcoholic liver disease with fair to poor hepatic function have shown no substantial alterations in pharmacokinetic parameters. This finding is despite the fact that the liver is the primary organ of ibuprofen metabolism.

Renal Impairment

Renal impairment may influence the elimination of ibuprofen, which may be dependent upon the urinary excretion of conjugated metabolites. Single doses of ibuprofen given to patients with chronic renal insufficiency receiving hemodialysis had lower serum drug concentration compared with controls. Ibuprofen was less extensively bound to serum protein in renally impaired patients (mean free fraction was 3.08% compared with 1.07% in controls). The volume of distribution of unbound ibuprofen was lower and peak serum concentrations higher in the renal impaired patients.

Clinical Trials

To support the safety and efficacy of Elixsure ^{TM} IB (ibuprofen) Oral Suspension, 100mg/5mL 10mg/5ml for approval, the Sponsor summarized and submitted clinical study data of oral ibuprofen suspension from different references, which is acceptable at this time. As required by the Division, the Sponsor also submitted PK studies and safety studies conducted by the Sponsor.

Table 1 and 2 below identify the safety and efficacy studies, experimental design, and patient population.

To provide for the data of safety and efficacy of ibuprofen pediatric oral suspension (80 mg/5 mL), McNeil Consumer Products Company submitted data in their NDA 19-842 (12/27/88) from 3 U.S. studies sponsored by McNeil (Table 1) and 8 foreign studies (Table 2) in children with fever. Additionally, 7 bioavailability/bioequivalence studies were submitted in NDA 19-842.

Table 1. U.S. Trials in Children with Pyrexia Sponsored by McNeil Consumer Products Company Submitted in NDA #19-842 (12/27/88)

Study	Design	Drug/Dose (mg/kg)	Range of Age	No. Of Subjects Enrolled (No. of Evaluated)
No. 5-535	Single-dose, randomized, parallel, double blind study in febrile children	Ibuprofen/5-7.5 Acetminophen/10 -15	6 mo-6 years of age	50 (49)
No. 6-639	Single-dose, randomized, parallel, partial blind study in febrile children	Ibuprofen/3, 6, or 9 Acetminophen/12	6 mo-6 years of age	129 (126)
No. 6-640	Multiple-dose (up to 4/day and up to 4 days), parallel, single-blind, randomized study in febrile children	Ibuprofen/5-7 Acetminophen/10 -15	6 mo-11 years of age	413 (386)

Table 2. Foreign Trials* in Children with Pyrexia Submitted in NDA #19-842

Study	Design	Drug/Dose (mg/kg)	Range of Age	Total No. of Patients
S. Simila 1976	Open, comparative	Ibuprofen/0.5, 6 Aspirin/10 Acetaminophen/12.5 Aminophenazone/5 Indomethacin/0.5	3 mo-13 years of age	79
Keinanen-Kiukaaneimi 1980, Finland	Open, comparative	Ibuprofen/6 Ketoprofen/0.5, 1 Fenoprofen/10 Naproxen/1, 2	3 mo-14 years of age	64
Kandoth 1984, India	Open, single-dose, cross-over	Ibuprofen/7 Aspirin/15	1-12 years of age	28
Amdekar and Desai 1985, India	Open, parallel-group, single dose	Ibuprofen/7 Acetaminophen/8	2-12 years of age	39
Kotob 1985, Egypt	2-day study of 2 dose levels with qid dosing	Ibuprofen/5 or 7.5 qid	2-12 years of age	50 (44)
Wilson 1984, Portugal	Open, parallel group; dosed by age	Ibuprofen/50-200 mg Acetaminophen suppositories/125-500 mg	2 mo-10 years of age	35
Sheth 1980, India	Open, single-dose, comparative, syrup formulation	Ibuprofen Acetaminophen Doses calculated on basis of optimal adult doses (400 & 300 mg, respectively)	2-8 years of age	22

*One of the 8 studies is omitted from this table because a legible copy of the complete data is not available. (The study was conducted in India in 1985 in 45 patients, 2-10 years old.)

McNeil Consumer Products Company submitted data on 4 pivotal clinical trials in their Supplemental New Drug Submission (SNDS) to Health Canada/Health Protection Branch (file #9427-MO570-48, 10/7/97) to support the safety and efficacy of ibuprofen pediatric oral suspension, 100 mg/5 m (Table 3). One of these trails 9study No. 6-640) was also submitted in NDA 19-842.

Table 3. **U.S. Trials in Children with Pyrexia and/or Pain Sponsored by McNeil Consumer Products Company, Submitted in SNDS File #9427-MO570-48 (10/7/97)**

Study	Design*	Drug/Dose (mg/kg)	Range of Age	No. Of Subjects Enrolled (No. of Evaluated)
No. 89-949/ 90-001	Single-dose, randomized, double blind, placebo-controlled study in children with sore throat pain	Ibuprofen/5, 10 Acetminophen/12.5	8-12 years of age 5-7 years of age	260 (247)
No. 90-002/ 90-003	Single-dose, randomized, double blind, placebo-controlled study in children with ear pain	Ibuprofen/5, 10 Acetminophen/12.5	8-12 years of age 5-7 years of age	158 (153)
No. 94-437	Single-dose, randomized, investigator blind study in febrile children	Ibuprofen/7.5 Acetminophen/12.5	2-11 years of age	111 (108)
No. 6-640	Multiple-dose (up to 4/day; up to 4 days), single-blind, randomized study in febrile children	Ibuprofen/5-7 Acetminophen/10-15	6 mo-11 years of age	413 (386)

*All are multi-centered, parallel trials

The sponsor conducted 4 clinical Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL.are as follows: 1 studies of Children's comparative pharmacokinetics study, 2 comparative bioavailability studies, and 1 esophageal transit study using fluoroscopic imaging (Table 4) in current NDA submission.

Table 4. Studies of Ibuprofen Suspension Sponsored by Taro Pharmaceuticals Inc.

Study	Design	Drug	Range of Age	No. Of subjects enrolled (No. evaluated)
No. IUE-P1-262	Single 200-mg dose crossover comparative bioavailability in fasted subjects	Ibuprofen (Taro) 100 mg/5 mL oral suspension Children's Motrin 100 mg/5 mL oral suspension Children's Motrin 50 mg chewable tablets	23-49 (mean: 38)	27 (25)
No. IUE-P2-134	Single 200-mg dose crossover comparative bioavailability and pharmacokinetic profile in fed and fasted states	Ibuprofen (Taro) 100 mg/5 mL oral suspension Children's Motrin 100 mg/5 mL oral suspension	20-50 (mean: 37)	30 (28)
No. 02212	Randomized, open label, 1-way parallel, comparative pharmacokinetics after 10 mg/kg oral doses in children	Ibuprofen (Taro)/ 100 mg/5 mL oral suspension Children's Motrin/ 100 mg/5 mL oral suspension	3-12 (mean: 9)	40 (38)
No. IBU-0210	Esophageal transit of a single 30-mL dose using fluoroscopic imaging	10% barium sulfate in Children's Ibuprofen NonSpil Suspension 100 mg/5 mL	21-24 (mean: 22)	6 (6)

Reviewer's Comments:

Ibuprofen is an active ingredient in Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL. Its efficacy and safety profiles were well established as mentioned above. The pivotal studies of efficacy and safety for Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL in this NDA should be waived at this time. However, the Sponsor is conducting some additional safety studies specifically for this product such as swallowing study in normal subjects and patients with dysphagia due to neurological impairments and esophageal toxicity study by utilizing radioactive labeling of material (a phase IV study) as the division required.

Summary of Efficacy Studies

Data Supporting FDA Proposed Rule (21 CFR Parts 201 and 343)

Overall, that reports of 23 clinical trials demonstrated the effectiveness of ibuprofen for various pain and fever models were submitted to and reviewed by the FDA to support the proposed amendment to include ibuprofen as a generally recognized safe and effective analgesic/antipyretic active ingredient for over-the-counter use. The trials, which were reported in the literature between 1983 and 1996, compared over-the-counter doses of ibuprofen (tablets, caplets, and capsules) to aspirin, acetaminophen, and/or codeine-containing analgesic compounds in patients with dental pain, pain of arthritis, dysmenorrhea, episiotomy, headache, sore throat, and fever.

In 19 of the trials which were placebo-controlled, it was concluded that ibuprofen at the doses studied, was a more effective analgesic agent than placebo. In these and 3 active-controlled trials, ibuprofen at the doses studied was reported to be either comparable to or more effective than aspirin, acetaminophen, and various strengths of codeine-containing analgesics or other NSAIDs.

Two randomized, double-blind, parallel trials comparing the antipyretic effectiveness of ibuprofen and aspirin in adults demonstrated the effectiveness of ibuprofen at both 200- and 400-mg doses.

Based upon evaluation of the trial results, the FDA approved the effectiveness of ibuprofen as an over-the-counter drug product for a variety of pain and fever. The over-the-counter doses of ibuprofen were recommended at a minimum dose of 200 mg every 4 to 6 hours.

Reviewer's Comments:

In this NDA submission, the sponsor proposed target population is children. The Sponsor should specifically describe dosage and administration for this product in the labeling.

Literature Reports of Trials in Febrile Children

A report of a literature search (Medline 1966 to 1998) for trials comparing antipyretic effectiveness of ibuprofen and acetaminophen (paracetamol) in febrile children yielded 15 reports that were considered to be acceptable as supporting references.

Children as young as 2 months were included in one of these trials, and up to 14 years in another. The author concluded that both ibuprofen and acetaminophen were effective antipyretics in children and that ibuprofen appeared to produce a more rapid and prolonged decrease in temperature in children with fever.

Data on Pediatric Trials of Ibuprofen (From McNeil Submissions)

McNeil Consumer Products Co. NDA Summary Basis of Approval

The 3 trials sponsored by McNeil Consumer Products Company for their NDA (#19-842, submitted 12/27/88) for Ibuprofen Pediatric Suspension are summarized in the Summary Basis of Approval. Table 1 lists these 3 safety and efficacy trials conducted in children with pyrexia, aged 6 months to 11 years, comparing ibuprofen solution or suspension to acetaminophen elixir (Children's Tylenol® Elixir).

Study No. 5-535

Description of Protocol

This was a multi-center, double-blind, randomized, parallel, single-dose study comparing ibuprofen solution 5-7.5 mg/kg and acetaminophen elixir 10-15 mg/kg in the treatment of pyrexia in children aged 6 months to 6 years with rectal temperatures of 101.0°-104.9°F. No antibiotics were permitted up to 24 hours prior to study entry and no other medication or therapy was permitted during the study (except for treatment failure or temperature >105°F). The patients were divided into 5 groups according to their weight and were given incrementally higher doses within the stated dose range. Temperatures were recorded at baseline and at scheduled times up to 8 hours post-dose. Clinical response, defined as an assessment of the patient's overall well being, was recorded.

Results

Of the 50 children enrolled, 49 evaluated for efficacy; 24 received ibuprofen and 26 received acetaminophen. Mean baseline temperatures were 101.73°F and 101.99°F, respectively.

There was 1 adverse event (rash in an ibuprofen-treated patient), but it was judged to be unrelated to the treatment.

Re-medication (presumably because of treatment failure) was required in 8 patients in the ibuprofen group (in 6 of the 8, between 7 and 8 hours) and 15 patients in the acetaminophen group (in 9 of the 15, between 5 and 7 hours and in 5, between 7 and 8 hours). This suggests that ibuprofen may be more effective or have a longer duration of action between 5 and 7 hours. However, there were a larger number of patients in the acetaminophen group (6 patients) with higher baseline temperatures than in the ibuprofen group (3 patients).

There were no significant differences between the 2 treatment groups with respect to the primary efficacy parameters nor with respect to analyses made after

stratifying the patients into high and low temperature groups. Efficacy comparisons of the 2 drugs could not be clearly made because of the absence of a fixed dose.

It was concluded that ibuprofen solution in a single dose of 5-7.5 mg/kg might be comparable to acetaminophen elixir in a single dose of 10-15 mg/kg in treating pyrexia.

Study No. 6-639

Description of Protocol

This was a multi-center, partially-blind, randomized, parallel, single-dose study comparing ibuprofen suspension 3, 6, or 9 mg/kg and acetaminophen elixir 12 mg/kg in the treatment of pyrexia in children aged 6 months to 6 years. Baseline temperatures were 101.0°-103.9°F orally (ages 4-6 years old) and 102.0°-104.9°F rectally (ages 6 mo-3 years old). The patients were divided into 8 groups according to their weight and, within each group, were randomly assigned to 1 of the 4 treatments. Temperatures were recorded at scheduled times for up to 6 hours, or optionally, up to 8 hours. Clinical response (patient's overall well being and comfort relative to baseline) was assessed up to 6 hours.

Results

Of the total of 129 children enrolled at 3 study sites, 126 were evaluated for efficacy. Of the 129 patients, 32 received ibuprofen 3 mg/kg, 30 received ibuprofen 6 mg/kg, 34 received ibuprofen 9 mg/kg, and 33 received acetaminophen 12 mg/kg.

In 9 patients, temperatures were measured by the axillary route and adjusted by 1° or 2° (for oral or rectal measurement substitution, respectively). Although there were no significant demographic differences among patients at the 3 study sites, there were substantial mean differences between onset of fever and drug administration (5.1 hr vs 20.9 hr) among the sites. Study site enrollments were not well balanced, varying from 6 patients per site to 100 per site.

There were no serious or severe adverse events reported. One patient in each group reported adverse events.

There were no significant differences between treatment groups with regard to the time to re-medication or time to maximum temperature reduction. A separate analysis was performed after dividing the patients in each group into a low temperature group (103 patients) and a high temperature group (23 patients). In the low temperature group, the 4 treatments did not differ significantly, but in high temperature group, ibuprofen 9 mg/kg was more effective than acetaminophen 12 mg/kg.

It was concluded that ibuprofen in single doses of 3, 6, or 9 mg/kg was effective in reducing fever in this patient population.

Study No. 6-640

Description of Protocol

This was a multi-center, multiple dose, randomized, parallel, investigator-blind study comparing the safety and antipyretic efficacy of ibuprofen suspension 5-7 mg/kg and acetaminophen elixir 10-15 mg/kg in febrile children aged 6 months to 11 years under routine, home conditions. Baseline temperatures were 101.0°-103.9°F orally (ages 4-11 years old) and 102.0°-104.9°F rectally (ages 6 mo-3 years old). The patients were randomly assigned in a 3:1 ratio to ibuprofen or acetaminophen. The dosing volumes for the 2 treatment groups were based on the patient's age (not weight, as in the other trials). Dosing was at 4- to 6-hour intervals, as needed, for temperatures >101.0°F, to a maximum of 4 doses per day for up to 4 days. Temperatures were recorded at 2, 4, 6, and 8 hours after the first dose and at least every 8 hours thereafter. Clinical response and global effect of treatment (compared to baseline) were assessed each night by the parent/guardian. Concomitant antibiotics were permitted.

Results

Of the total of 413 children enrolled at 9 study sites, 386 evaluated for efficacy; 292 received ibuprofen and 94, acetaminophen. The mean ages were 3.7 years and 3.5 years, respectively. The average dose of ibuprofen used was 6 mg/kg.

Of the 409 patients analyzed for safety, adverse events occurred in 11% (35) of the patients receiving ibuprofen and 15% (15) of the patients receiving acetaminophen.

None of the events were serious or unexpected, although 6 events in ibuprofen-treated patients were judged by the investigator to be "marked." Adverse events in ibuprofen-treated patients were reported more frequently in younger patients (15%) than in older patients (6%), which was a statistically significant difference. The most frequently reported events with ibuprofen were diarrhea (13 reports) and vomiting (9 reports).

Both drugs were effective in reducing fever, with no significant differences with respect to the number of doses given per day or the total number of doses given over 4 days. The mean number of total doses given was 5.2 for ibuprofen and 5.6 for acetaminophen. Antibiotic usage rates were not significantly different between the 2 groups. Global ratings were significantly superior for ibuprofen for days 1 and 2, but there were no differences between the treatments on days 3 and

4. Clinical response assessments showed no significant differences between the treatments for any day.

It was concluded that ibuprofen suspension at 5-7.5 mg/kg and acetaminophen at 10-15 mg/kg, each given in multiple doses every 4 to 6 hours, were comparable in reducing fever in this patient population. Age was not a significant factor in the antipyretic effect of ibuprofen, nor did the use of antibiotics interfere with its action.

Reviewer's Comments:

In three clinical trials sponsored by McNeil Consumer Products Company, the data demonstrated that ibuprofen solution in a single dose and/or multiple doses is comparable to acetaminophen elixir in a single dose and/or multiple doses in treating pyrexia in children.

In study No.5-535, the data demonstrated that ibuprofen solution in a single dose of 5-7.5 mg/kg is comparable to acetaminophen elixir in a single dose of 10-15mg/kg in treating pyrexia. Also, this study suggests that ibuprofen may be more effective or have a longer duration of action between 5 and 7 hours compared to treatment group with acetaminophen elixir.

In study No. 6-639, it was concluded that ibuprofen in a single dose of 9 mg/kg was more effective than acetaminophen in a single dose of 12 mg/kg in high temperature group.

The study No. 6-604 was a multi-center, multiple dose, randomized, parallel, investigator-blind study comparing the safety and antipyretic efficacy of ibuprofen suspension 5-7 mg/kg and acetaminophen elixir 10-15 mg/kg in febrile children aged 6 months to 11 years under routine, home conditions. In this study, antibiotics were allowed in both study groups and antibiotic usage rates were not significantly different between the 2 groups. The data showed that ibuprofen suspension at 5-7.5 mg/kg and acetaminophen at 10-15 mg/kg, each given in multiple doses every 4 to 6 hours, were comparable in reducing fever in this patient population. Age was not a significant factor in the antipyretic effect of ibuprofen, nor did the use of antibiotics interfere with its action.

Published Reports of Foreign Trials

The 8 reports of foreign trials submitted by McNeil Consumer Products Company in their NDA (#19-842, submitted 12/27/88) for Ibuprofen Pediatric Suspension are summarized in the Summary Basis of Approval. Table 2 lists these 8 safety and efficacy trials, which were conducted in children with pyrexia, aged 2 months to 14 years, treated with ibuprofen for up to 5 days. The conclusions of these supportive studies are summarized as follows:

- The antipyretic effect of ibuprofen at 6-7 mg/kg is probably comparable to aspirin at 10-15 mg/kg, indomethacin at 1/2 mg/kg, acetaminophen at 8-12.5 mg/kg, ketoprofen at 1 mg/kg, fenoprofen at 10 mg/kg, naproxen at 2 mg/kg, or aminophenazone at 5 mg/kg.
- The antipyretic effect of ibuprofen is probably not significantly different when used concomitantly with or without antibiotics.
- The underlying cause of pyrexia (e.g., upper respiratory tract infection, and viral infection) probably has no effect on the antipyretic efficacy of ibuprofen or other drugs.
- The onset of action, extent of antipyretic efficacy, or duration of action of ibuprofen compared with other agents showed inconsistent results across studies.
- With one exception (cutaneous allergy), adverse drug reactions were not reported in these studies.
- Ibuprofen suspension (single doses of 6-7 mg/kg or divided doses of 20-30 mg/kg/day) is an effective antipyretic agent in children.

McNeil Consumer Products Co. Supplemental New Drug Submission

McNeil Consumer Products Company submitted four pivotal clinical trials in their Supplemental New Drug Submission (SNDS) to Health Canada/Health Protection Branch (file #9427-MO570-48) for ibuprofen pediatric oral suspension, 100 mg/5 mL[13] in 1997.

Table 3 lists the 4 pivotal safety and efficacy trials conducted in children with pyrexia, sore throat pain, or ear pain which were submitted in McNeil's SNDA. One of these studies (No.6-640) was also submitted in McNeil's NDA. The other 3 are summarized below.

Study No. 90-001/89-949

Description of Protocol

This was a multi-center, single-dose, randomized, double-blind, placebo-controlled study comparing the safety and analgesic efficacy of ibuprofen suspension 5 mg/kg and acetaminophen elixir 12.5 mg/kg to placebo in the treatment of children aged 5 to 12 years with sore throat pain. Study No. 90-001 included ages 5 to 7 years and Study No. 89-949 included ages 8 to 12 years. Both protocols were identical except for one additional scale used to assess pain in the older children. Both ran concurrently with the same investigators.

The patients presented with acute illness in which a sore or painful throat was a prominent symptom, present for at least 6 hours prior to study entry, and rated at least 5 on a 10-point scale and at least moderate on a scale of mild, moderate, or severe. Antibiotics were not permitted within 24 hours prior to study entry or

during the study period. The patients assessed pain up to 6 hours after dosing, using 3 different measurement scales, plus a fourth scale for the older children. The scales were age-appropriate and used with the aid of a study nurse.

Results

A total of 260 patients were enrolled at 6 centers: 147 in Study No. 89-949 and 113 in Study No. 90-001. Of the 260 patients randomly assigned to the 4 treatment groups, 247 evaluated for efficacy. Ibuprofen 10 mg/kg was administered to 67 patients and 5 mg/kg, to 66 patients. Acetaminophen 12.5 mg/kg was administered to 63 patients and placebo to 64 patients.

There were no serious or unexpected adverse events. Events were reported in 3 patients each in the ibuprofen 5 mg/kg group and placebo group, in 1 patient in the ibuprofen 10 mg/kg group, and 2 patients in the acetaminophen group.

Pairwise comparisons of the treatments within age categories demonstrated that ibuprofen at either dose was significantly superior to placebo in both age groups. Acetaminophen was significantly superior to placebo only in the older group. Ibuprofen at either dose was significantly superior to acetaminophen in the younger age group.

It was concluded that ibuprofen suspension at doses of 5 mg/kg and 10 mg/kg are safe and effective in the relief of sore throat pain for up to 6 hours in children.

Study No. 90-002/90-003

Description of Protocol

This was a multi-center, single-dose, randomized, double-blind, placebo-controlled study comparing the safety and analgesic efficacy of ibuprofen suspension 5 mg/kg and acetaminophen elixir 12.5 mg/kg to placebo in the treatment of children aged 5 to 12 years with ear pain believed to be due to acute otitis media. Study No. 90-002 included ages 5 to 7 years and Study No. 90-003 included ages 8 to 12 years. Both protocols were identical except for one additional scale used to assess pain in the older children. Both ran concurrently with the same investigators.

The patients presented with acute illness in which a sore or painful ear was a prominent symptom, present for at least 6 hours and not more than 72 hours prior to study entry. Ear pain or soreness was rated at least 5 on a 10-point "hurt" scale and at least moderate on a scale of none, mild, moderate, or severe. Antibiotics were not permitted within 24 hours prior to study entry or during the study period. The patients assessed pain for 6 hours after dosing using 3 different measurement scales, plus a fourth scale for the older children. The scales were age-appropriate and used with the aid of a study nurse.

Results

A total of 158 patients were enrolled at 6 centers: 81 in Study No. 90-002 and 77 in Study No. 90-003. Of the 158 patients randomly assigned to the 4 treatment groups, 153 were evaluated for efficacy. Ibuprofen 10 mg/kg was administered to 35 patients and 5 mg/kg, to 40 patients. Acetaminophen 12.5 mg/kg was administered to 40 patients and placebo to 43 patients.

There were no serious or unexpected adverse events. Somnolence, reported in 2 patients in the ibuprofen 10 mg/kg group, was the only adverse event.

Interaction of age with treatment was found not to be significant for any measure on any scale. Pairwise comparisons of the treatments demonstrated that ibuprofen 10 mg/kg at was significantly superior to placebo in on all but one scale, where the significance was borderline. Ibuprofen 5 mg/kg was significantly superior to placebo on 2 scales, borderline on 1, and not significantly superior on 1. Acetaminophen was borderline superior to placebo on 2 scales. Ibuprofen 5 mg/kg was significantly superior to placebo from 3-4 hours post-dose to 6 hours. With a few isolated exceptions, there were essentially no significant differences between the other treatment groups at any of the measurement intervals.

It was concluded that ibuprofen suspension at doses of 5 mg/kg and 10 mg/kg are safe and effective in the relief of ear pain for up to 6 hours in children.

Study No. 94-437

Description of Protocol

This was a multi-center, single-dose, randomized, parallel, investigator-blind study comparing the safety and antipyretic efficacy of ibuprofen suspension 7.5 mg/kg with acetaminophen suspension 12.5 mg/kg in children aged 2 to 11 years. Baseline temperatures were 101.0°-104.5°F orally or 102.0°-105.5°F rectally. The patients were randomized to 1 of the 2 treatments within a low fever and a high fever group: low fever was 101.0°-102.5°F orally or 102.0°-103.5°F rectally, and high fever was 102.6°-104.5°F orally or 103.6°-105.5°F rectally. Temperature was measured at specified times up to 8 hours post-dose. Antibiotics were not permitted within 8 hours prior to study entry.

Results

A total of 111 patients were enrolled at 6 centers. Of the 111 patients, 108 were evaluated for efficacy. Of the 108 patients, ibuprofen 7.5 mg/kg was administered to 27 in the low fever group and 26 in the high fever group, and acetaminophen 12.5 mg/kg was administered to 30 in the low fever group and 25 in the high fever group.
There were no serious or unexpected adverse events. Three ibuprofen-treated patients and 4 acetaminophen-treated patients reported adverse events. Vomiting

was the most frequent event (5 of 8 reports in the 7 patients who had adverse events).

The results for each of the treatments was analyzed in a combined fever group, low fever group, and high fever group.

In the combined fever group, ibuprofen-treated patients had significantly greater temperature reduction (and percent temperature reduction) than acetaminophen-treated patients from 1 to 7 hours.

In the low fever group, ibuprofen-treated patients had significantly greater temperature reduction than acetaminophen-treated patients at 2 hours. At 1 hour, temperature reduction in ibuprofen-treated patients was marginally significantly better. Percent temperature reduction was significantly greater for ibuprofen at 1, 2, 6, and 7 hours.

In the high fever group, ibuprofen-treated patients had significantly greater temperature reduction than acetaminophen-treated patients from 3 to 8 hours. Percent temperature reduction was significantly greater for ibuprofen from 3 to 6 hours.

The area-under-the-temperature-reduction-curve over the entire 8-hour study period (sum of temperature differences from baseline) was significantly greater for ibuprofen compared to acetaminophen.

It was concluded that a single 7.5 mg/kg dose of ibuprofen suspension provides significantly greater fever reduction over 8 hours (and beginning 1 hour after dosing) than acetaminophen suspension in a single 12.5 mg/kg dose.

Reviewer's Comments:

In above three clinical trials sponsored by McNeil Consumer Products Company, the data demonstrated that ibuprofen solution in a single dose and/or multiple doses is comparable to acetaminophen elixir in a single dose and/or multiple doses in treating with sore throat pain in children.

The Study No. 90-001/89-949 was a multi-center, single-dose, randomized, double-blind, placebo-controlled study comparing the safety and analgesic efficacy of ibuprofen suspension 5 mg/kg and acetaminophen elixir 12.5 mg/kg to placebo in the treatment of children aged 5 to 12 years with sore throat pain. There were no serious or unexpected adverse events in this study.

The data demonstrated that acetaminophen was significantly superior to placebo only in the older group. Ibuprofen at either dose of 5 mg/kg and 10 mg/kg was significantly superior to acetaminophen in the younger age group. It was concluded that ibuprofen suspension at doses of 5 mg/kg and 10 mg/kg are safe and effective in the relief of sore throat pain for up to 6 hours in children.

The Study No. 90-002/90-003 was a multi-center, single-dose, and randomized, double blind, placebo-controlled study. It compared the safety and analgesic efficacy of ibuprofen suspension 5 mg/kg and acetaminophen elixir 12.5 mg/kg to placebo in the treatment of children aged 5 to 12 years with ear pain due to acute otitis media. Antibiotics were not permitted within 24 hours prior to study entry or during the study period. There were no serious or unexpected adverse events. The data demonstrated that ibuprofen suspension at doses of 5 mg/kg and 10 mg/kg are safe and effective in the relief of ear pain for up to 6 hours in children.

The Study No. 94-437 was a multi-center, single-dose, randomized, parallel, investigator-blind study comparing the safety and antipyretic efficacy of ibuprofen suspension 7.5 mg/kg with acetaminophen suspension 12.5 mg/kg in children aged 2 to 11 years. It was concluded that a single 7.5 mg/kg dose of ibuprofen suspension provides significantly greater fever reduction over 8 hours (and beginning 1 hour after dosing) than acetaminophen suspension in a single 12.5 mg/kg dose.

Motrin Product Monograph

The McNeil Consumer Healthcare Product Monograph for Children's Motrin Suspension, Children's Motrin Suspension Drops, and Junior Strength Motrin Caplets provides a summary of efficacy data. The Product Monograph documents the studies and pain models that demonstrate the efficacy of ibuprofen as an analgesic and antipyretic in patients with dental pain, sore throat or ear pain (pediatric models), dysmenorrhea, osteoarthritis pain, headache, soft tissue injury, and fever (adults and children).

Sore Throat or Ear Pain

Controlled clinical trials have been conducted in children aged 5-12 years with sore throat pain believed due to infection or ear pain believed due to acute otitis media. Ibuprofen 5 or 10 mg/kg or acetaminophen 12.5 mg/kg all provided significant pain relief compared with placebo within 1-2 hours of administration and had a duration of action of up to 6 hours. Ibuprofen 5 mg/kg demonstrated pain relief comparable to acetaminophen 12.5 mg/kg. Ibuprofen 10 mg/kg demonstrated greater pain relief than acetaminophen 12.5 mg/kg from 3-6 hours after administration.

Fever

Controlled clinical trials have been conducted in children aged 6 months to12 years with fever due primarily to viral illness. Ibuprofen 5 to 10 mg/kg or acetaminophen 10 mg/kg to 15 mg/kg reduced fever in the first hour and provided maximum fever reduction between 2 and 4 hours. There was some evidence that the higher dosage range of ibuprofen (10 mg/kg) resulted in a longer duration of effect (6-8 hours) and that it was more effective for children with higher baseline temperatures (>102.5°F), but the numbers of patients were inadequate to draw definitive conclusions. Ibuprofen at 5 mg/kg to 10 mg/kg or acetaminophen at 10 mg/kg to 15 mg/kg was equally effective in children with baseline temperatures at or below102.5°F.

One controlled, single-dose trial comparing ibuprofen 7.5 mg/kg with acetaminophen 12.5 mg/kg demonstrated the superiority of ibuprofen over an 8-hour period.

Reviewer's Comments:

Overall, all of clinical studies above mentioned demonstrated that ibuprofen solution in a single dose and/or multiple doses are effective and safe in treating fever and sore throat or ear pain in children.

Due to ibuprofen is an active ingredient in Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL. Its efficacy profiles were well established as noted above. The pivotal studies of efficacy for Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL in this NDA should be waived in this NDA submission.

To support the efficacy of Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL safe in treating fever and sore throat and/or ear pain in children, that the Sponsor summarized and submitted clinical efficacy data of oral ibuprofen suspension from different references for approval is acceptable at this time.

Summary of Safety Studies

Adverse Events

Ibuprofen Labeling

The Sponsor lists adverse reactions and incidences reported with the prescription use of ibuprofen in Table 5 from "Product Monograph, Children's Motrin Suspension, Children's Motrin Suspenion Drops, and Junior Strength Motrin Caplets: Analgesic, Antipyretic Agent-for Children". (McNeil Consumer Healthcare, Guelph, Canada. 12/12/96 (revised 7/8/99)) and also sated "Those listed under "unknown causal relationship" are those events, reported rarely, where a relationship to ibuprofen could not be established, but also could not be excluded."

Table 5. Adverse Reactions Reported with Ibuprofen

Body System	Incidence, %	Adverse Reaction
Gastro-intestinal	3-9	Nausea, epigastric pain, heartburn
	1-3	Diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps and pain , fullness of GI tract (bloating or flatulence)
	< 1	Gastric or duodenal ulcer with bleeding and/or perforation, GI hemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin, alkaline phosphatase) (Generally modest elevations of serum transaminase activity observed are usually without clinical sequelae, but severe, potentially fatal toxic hepatitis can occur)
Central Nervous System	3-9	Dizziness
	1-3	Headache, nervousness
	< 1	Depression, insomnia
	Unknown causal relationship: parasthesias, hallucinations, dream abnormalities; aseptic meningitis in patients with systemic lupus erythematosus or other connective tissue disease; aseptic meningitis and meningioencephalitis and (1 case) eosinophilia in cerebrospinal fluids (in patients without connective tissue disease); cognitive dysfunction in elderly patients.	
Skin	3-9	Rash (including maculopapular type)
	1-3	pruritis
	< 1	Vesiculobullous eruptions, urticaria, erythema multiforme
	Unknown causal relationship: alopecia, Stevens-Johnson Syndrome	
Special Senses	1-3	Tinnitus
	< 1	Amblyopia (blurred and/or diminished vision, scotoma and/or changes in color vision)
	Unknown causal relationship: conjunctivits, diplopia, optic neuritis	
Metabolic	1-3	Decreased appetite, edema, fluid retention

...continued...

Table 5. Adverse Reactions Reported with Ibuprofen (continued)

Hematologic	< 1	Leukopenia, decreases in hemoglobin and hematocrit
	Unknown causal relationship: hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes (purpura, epistaxis, hematuria, menorrhagia); autoimmune hematologic anemia; fatal aplastic anemia	
Cardio-vascular	< 1	Congestive heart failure in patients with marginal cardiac function, elevated blood pressure
	Unknown causal relationship: arrhythmias (sinus tachycardia, sinus bradycardia, palpitations)	
Allergy	< 1	Anaphylaxis
	Unknown causal relationship: fever, serum sickness, lupus erythematosus syndrome	
Endocrine	--	Gynecomastia, hypoglycemia, menstrual delays, dysfunctional uterine bleeding
Renal	*Unknown causal relationship:* decreased creatinine clearance, polyuria, azotemia, decrease in renal blood flow glomerular filtration rate (in patients with mild renal impairment); renal papillary necrosis	

Reviewer's Comments:

According to FDA-approved labeling for ibuprofen suspension (Motrin), the most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%. The Sponsor needs to identify incidence rates of GI adverse reaction in Table 5.
Adverse reactions observed during controlled clinical trials in adults at an incidence greater than 1% are as follows:

Cardiovascular system: *Edema, Fluid retention (generally responds promptly to drug discontinuation).*

Digestive system: *Nausea, Epigastric Pain, Heartburn, Diarrhea, Abdominal Distress, Nausea and Vomiting, Indigestion, Constipation, Abdominal Cramps or Pain, Fullness of GI Tract (bloating and flatulence).*

Nervous system: *Dizziness, Headache, and Nervousness.*

Skin and appendages: *Rash (including maculopapular type), Pruritus*

Special senses: *Tinnitus.*

Above reactions listed under the heading "Incidence Greater than 1% (but less than 3%) Probable Causal Relationship," encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Occurring less frequently than 1 in 100, were reported in controlled clinical trials and from postmarketing experience. These reactions have been divided into two categories: "Incidence less than 1%--Probable Causal Relationships," lists reactions with Ibuprofen therapy for which the probability of a causal relationship exists; this category was completed over time with postmarketing serious adverse reactions. "Incidence less than 1% --Causal Relationship Unknown," lists reactions with ibuprofen therapy for which a causal relationship has not been established, but are presented as alerting information for physicians.

The following adverse reactions were reported in clinical trials at an incidence of less than 1%, or were reported from postmarketing or foreign experience. The probability exists between the drug and these adverse reactions.

Body as a whole: *Anaphylaxis and anaphylactoid reactions.*

Cardiovascular system: *Cerebrovascular accident, hypotension, congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations.*

Digestive system: *Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, pancreatitis, melena, gastritis, duodenitis, esophagitis, hematemesis, hepatorenal syndrome, liver necrosis, liver failure, hepatitis, jaundice, abnormal liver tests.*

Hematologic system: *Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decrease in hemoglobin and hematocrit, pancytopenia.*

Nervous system: *Depression, insomia, confusion, emotional liability, somnolence, convulsions, and aseptic meningitis with fever and coma*

Respiratory: *Bronchospasm, dyspnea, and apnea.*

Skin and appendages: *Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia, exfoliative dermatitis, Lyell's syndrome (toxic epidermal necrolysis), and photosensitivity reactions.*

Special senses: *Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision)*

Urogenital system: *Acute renal failure in patients with pre-existing significantly impaired renal function, renal papillary necrosis, tubular necrosis, glomerulitis, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria.*

Miscellaneous: *Dry eyes and mouth, gingival ulcer, rhinitis.*

The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested by marketing experience under circumstances where a causal relationship could not be definitely established. They are listed as alerting information for the physician.

Allergic: *Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, and angioedema.*

Cardivascular system: *Arrhythmias (sinus tachycardia, sinus bradycardia).*

Hematologic system: *Bleeding episodes (e.g., epistaxis, and menorrhagia).*

Metabolic/endocrine: *Gynecomastia, hypoglycemic reaction, and acidosis.*

Nervous system: *Paresthesias, hallucinations, dream abnormalities, pseudo-tumor cerebri.*

Special senses: *Conjunctivitis, diplopia, optic neuritis, and cataracts.*
Therefore, the Sponsor's statement under adverse reactions section in this NDA submission such as "Those listed under "unknown causal relationship" are those events, reported rarely, where a relationship to ibuprofen could not be established, but also could not be excluded." are incomplete and unclear.

Reports in the Literature

A overview survey of the global literature (through 1996) on adverse reactions to ibuprofen reported in clinical trials using over-the-counter dosages showed a favorable safety profile compared with other NSAIDs published by Rainsford, etc. (Of the 730 publications yielded by the search, 111 met the criteria to be included in the analysis.). The majority of adverse events were gastrointestinal, primarily dyspepsia, nausea or vomiting.

Table 6 shows the distribution of adverse event data on ibuprofen pooled from all the trials, including children and adults.

Table 6. **Overall Adverse Event (AE) Rates for Ibuprofen* Grouped by Duration of Dosing from Pooled Trial Data**

Days dosed	Total No. of patients	Overall % with AEs	Total No. of patients with AEs	Total No. of AEs
<1	2312	6	148	172
1	215	8	18	22
2-7	227	9	20	29
8-30	272	19	52	52
31-90	85	29	25	29
TOTAL	3111	8	263	304

* Maximum over-the-counter dosages: for adults, 400 mg single dose or 1200 mg/day; for children 1-12 years old, divided doses 20 mg/kg, or 1-2 years old, 50 mg single dose or 200 mg/day; 3-7 years old, 100 mg single dose or 400 mg/day; 8-12 years old, 200 mg single dose or 800 mg/day.

As shown in Table 6, the overall percentage of adverse events with ibuprofen was 8%, with a marked difference where the drug is being given for 8-30 days (19%) compared with 31-90 days (29%).

Table 7 shows the adverse event data on ibuprofen from 5 trials that included only children under 12 years of age. (The data from these trials are pooled in the data provided in Table 6.)

Table 7. **Adverse Event (AE) Rates for Ibuprofen* Reported in Five Pediatric Trials**

Days dosed	Age (years old)	Total No. of patients	Overall % with AEs	Total No. of patients with AEs	Total No. of AEs
<1	12	39	0	0	0
<1	12	20	0	0	0
<1	12	14	0	0	0
1	ns	93	1	1	1
1	4	34	18	6	6
TOTAL	-	200	3.5	7	7

* Maximum over-the-counter dosages: for children 1-12 years old, divided doses 20 mg/kg; or 1-2 years old, 50 mg single dose or 200 mg/day; 3-7 years old, 100 mg single dose or 400 mg/day; 8-12 years old, 200 mg single dose or 800 mg/day.
ns=not specified.

As shown in Table 7, the percentage of adverse events with ibuprofen was overall very low (0-1%), but was markedly higher (18%) in children 4 years of age or

under. Several of these events were febrile seizures, which the drug was taken to prevent. In the same study in children 4 years of age or under, comparable results were seen with acetaminophen (22% had adverse events).

Reviewer's Comments:

According to adverse event pooled data on ibuprofen from all the trials, a marked difference where the drug is being given for 8-30 days (19%) compared with 31-90 days (29%) in both children and adults. Also, the overall percentage of adverse events with ibuprofen was 8% in Rainsford's study.

Furthermore, the percentage of adverse events with ibuprofen was overall very low (0-1%), but was markedly higher (18%) in children 4 years of age or under from 5 clinical trials that included only children under 12 years of age. As an Agency, the Division would like to follow up and monitor overall postmarketing adverse event data on ibuprofen. Also, the Division suggests the sponsor should collect and follow up postmarketing adverse event data on this product closely.

Studies from Taro Pharmaceuticals Inc.

Clinical Pharmacology

Pharmacodynamics

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that possesses anti-inflammatory, analgesic and antipyretic activity. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition. After absorption of the racemic ibuprofen, the [-]R-enantiomer undergoes interconversion to the [+]S-form. The biological activities of ibuprofen are associated with the [+]S-enantiomer.

In clinical studies in adult patients with rheumatoid arthritis and osteoarthritis, ibuprofen has been shown to be comparable to aspirin in controlling pain and inflammation, though causing fewer of the mild gastrointestinal side. MOTRIN may be well tolerated in some patients who have had gastrointestinal side effects with aspirin, but these patients, when treated with MOTRIN, should be carefully followed for signs and symptoms of gastrointestinal ulceration and bleeding. Although it is not definitely known whether ibuprofen causes less peptic ulceration than aspirin, in one study involving 885 adult patients with rheumatoid arthritis treated for up to one year (438 patients on ibuprofen and 447 patients on aspirin), there were no reports of gastric ulceration with ibuprofen whereas frank ulceration was reported in 13 patients in the aspirin group (statistically significant $p<.001$).

Gastroscopic studies at varying doses of ibuprofen showed an increased tendency toward endoscopic lesions at higher doses. However, at clinically comparable

doses (2,400 mg of ibuprofen vs. 3,600 mg of aspirin), endoscopic lesions were approximately half that seen with aspirin. Studies using ^{51}Cr-tagged red cells indicate that fecal blood loss associated with ibuprofen in doses up to 2400 mg daily did not exceed the range of normal, and was significantly less than that seen in aspirin-treated patients. The clinical significance of these findings is unknown.

Pharmacokinetics

As noted above, ibuprofen is a racemic mixture of [-] R-and [+] S-isomers. *In vivo* and *in vitro* studies indicate that the [+]S-isomer is responsible for clinial activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (60%) interconverted into the active [+]S species in adults. The degree of interconversion in children is unknown, but is thought to be similar. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. Ibuprofen is well absorbed orally, with less than 1% being excreted in the urine unchanged. It has a biphasic elimination time curve with a plasma half-life of approximately 2 hours. Studies in febrile children have established the dose-proportionality of 5 and 10 mg/kg doses of ibuprofen. Studies in adults have established the dose-proportionality of ibuprofen as a single oral dose from 50 to 600 mg for total drug and up to 1200 mg for free drug.

Absorption

In vivo studies indicate that ibuprofen is well absorbed orally from the suspension, drops, caplet and chewable tablet formulations, with peak plasma levels usually occurring within 1 to 2 hours. The pharmacokinetic differences between the products in adults (see Table 1) are due to differences in the rate of absorption of ibuprofen from the various dosage forms. The observed differences in the table between adults and children, in terms of AUC and C_{max}, are due to both differences in dose per body weight and age-or fever-related change in volume of distribution (Vd/F). All of the formulations are equally bioavailable in terms of peak plasma levels (C_{max}) and extent of absorption (AUC), however, the time-to-peak (T_{max}) is different between the products. Clinically, this has been shown to have no effect on either onset or peak fever reduction in children.

Table A						
Pharmacokinetic Parameters of Ibuprofen Formulations						
[Mean Values (% coefficient of variation)]						
Dose	**200mg (=2.8 mg/kg) in Adults**				**10 mg/kg in Febrile Children**	
Formulation	**Suspension**	**Drops**	**Caplet**	**Chewable Tablet**	**Suspension**	**Chewable Tablet**
Number of Patients	24	24	25	24	18	18
AUCinf (µg•h/mL)	64	74	60	66	155	176
	(27%)	(19%)	(19%)	(22%)	(24%)	(25%)
Cmax (µg/mL)	19	24	20	15	55	43
	(22%)	(21%)	(18%)	(24%)	(23%)	(39%)
Tmax (h)	0.79	1.0	1.04	2.0	0.97	1.43
	(69%)	(60%)	(50%)	(56%)	(57%)	(69%)
Cl/F (mL/h/kg)	45.6	43.4	45.0	42.8	68.6	60.9
	(22%)	(18%)	(19%)	(18%)	(22%)	(27%)
Legend: AUCinf = Area-under-the-curve to infinity						
Tmax = Time-to-peak plasma concentration						
Cmax = Peak plasma concentration						
Cl/F = Clearance divided by fraction at drug absorbed						

Antacid-- A bioavailability study in adults has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Food Effects-- Absorption is most rapid when MOTRIN is given under fasting conditions. Administration of MOTRIN Suspension, MOTRIN Oral Drops, MOTRIN Chewable Tablets and MOTRIN Caplets with food affects the rate but not the extent of absorption. When taken with food, T_{max} is delayed by approximately 30 to 60 minutes and peak levels are reduced by approximately 30 to 50%.

Distribution

Ibuprofen, like most other drugs of its class, is highly protein bound (>99% bound at 20 µg/mL). Protein binding is saturable and at concentrations >20 µg/mL binding is non-linear. Based on oral dosing data there is an age-or fever-related change in volume of distribution for ibuprofen. Febrile children <11 years old have a volume of approximately 0.2 L/kg while adults have a volume of approximately 0.12 L/kg. The clinical significance of these findings is unknown.

Metabolism

Following oral administration, the majority of the dose was recovered in the urine within 24 hours as the hydroxy-(25%) and carboxypropyl-(37%) phenylpropionic acid metabolites. The percentages of free and conjugated ibuprofen found in the urine were approximately 1% and 14%, respectively. The remainder of the drug was found in the stool as both metabolites and unabsorbed drug.

Elimination

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. It has a biphasic plasma elimination time curve with a half-life of approximately 2.0 hours. There is no difference in the observed terminal elimination rate or half-life between children and adults, however, there is an age-or fever-related change in total clearance. This suggests that the observed change in clearance be due to changes in the volume of distribution of ibuprofen.

Clinical Studies

Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen suspension and 10-15 mg/kg of acetaminophen elixir have been conducted in children 6 months to 12 years of age with fever primarily do to viral illnesses. In these studies there were no differences between treatment in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours, children treated with ibuprofen 5mg/kg tended to have recurrence in fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

A comparison of MOTRIN Chewable Tablets and MOTRIN Suspension in febrile children showed similar antipyretic effects of the two formulations, lasting between 6 and 8 hours. No clinical studies of fever reduction in children have been performed with MOTRIN Caplets or MOTRIN Oral Drops.

Controlled single-dose clinical analgesia trials comparing doses of 5 and 10 mg/kg ibuprofen suspension with acetaminophen suspension 12.5 mg/kg and placebo, have been conducted in children 5 to 12 years of age, with sore throat pain due to an infectious agent, or ear pain due to acute otitis media. Onset of pain relief provided by ibuprofen was similar to that of acetaminophen, occurring within the first hour, usually around the half-hour mark. All active treatments showed significant pain relief verus placebo, and the 10 mg/kg dose of ibuprofen

had a duration of analgesic effect of 6 to 8 hours. Ibuprofen 10 mg/kg provided more overall pain relief than the 5 mg/kg dose.

Controlled studies have demonstrated that ibuprofen is a more effective analgesic than propoxyphene for the relief of episiotomy pain, pain following dental extraction procedures, and for the relief of the symptoms of primary dysmenorrhea.

In patients with primary dysmenorrhea, ibuprofen has been shown to reduce elevated levels of prostaglandin activity in the menstrual fluid and to reduce resting and active intrauterine pressure, as well as the frequency of uterine contractions. The probable mechanism of action is to inhibit prostaglandin synthesis rather than simply to provide analgesia.

In clinical studies in adult patients with rheumatoid arthritis, ibuprofen has been shown to be comparable to indomethacin in controlling the signs and symptoms of disease activity, with a lower incidence of milder gastrointestinal and CNS side effects than indomethacin.

MOTRIN may be used in combination with gold salts and/or corticosteroids.

Bioavailability and Pharmacokinetic Profile Study No. IUE-P1-262

Study Title:

Single Dose Crossover Comparative Bioavailability Study of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL vs. Children's Motrin® Oral Suspension (McNeil) and Children's Motrin® Chewable Tablets (McNeil) in Healthy Male Volunteers Following a 200 mg Administration under Fasting State.

This study was a randomized, single oral dose (200 mg), cross-over study designed to evaluate the pharmacokinetic profile and estimate the bioequivalence of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL compared to two reference formulations, Children's Motrin® oral suspension (McNeil) (reference 1: 100mg/5 mL) and Children's Motrin® chewable tablets (McNeil) (reference 1: 50 mg) under fasting conditions.

Study No. (Date of Report):

IUE-P1-262 (July 29, 2002).

Objective:

To evaluate and compare the relative bioavailability and therefore the bioequivalence of three formulations of ibuprofen after a single oral dose under fasting conditions.

Subjects:

27 healthy, Caucasian males, aged 23 to 49 years old (mean ± S.D. of 38 ± 8 years old); body mass index within 19 to 30.

Of the twenty-seven healthy male subjects who were included in the study, 25 completed the three periods three sequence crossover study and were considered in the statistical analysis.

Study method:

The drug was administered, under fasting conditions, as a single 200mg oral dose of either one of the three formulations. Each study phase was separated by a 7 days washout period. The subjects fasted overnight for at least 10 hours pre-dose and until 4 hours post-dose. Blood samples were collected pre-dose and at scheduled times up to 16 hours post-dose. In each period 18blood samples were collected at the following time points: pre-dose, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 and 16.0 hours after drug administration.

The crossover study design of bioavailability and pharmacokinetic profile study No. IUE-P1-262 is as follows in Table 8:

Table 8. **The 3-period, 3-sequence crossover design of Study No. IUE-P1-262**

Sequence	N	Period 1	Period 2	Period 3
1	27	Test	Reference 1	Reference 2
2	27	Reference 1	Reference 2	Test
3	27	Reference 2	Test	Reference 1

Ibuprofen plasma concentrations were measured by using a validated HPLC/UV method with a limit of quantitation of 0.5ug/mL.

Study Result:

Results of the study indicated that the mean C_{max} of Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL, Children's Motrin 100mg/5ml oral suspension and Children's Motrin 50mg chewable tablets were 18.2ug/ml, 20.6ug/ml and 16.0ug/ml respectively. The mean AUC_{0-t} of Children's Elixsure

TM IB (ibuprofen) Oral Suspension, 100 mg/5mL, Children's Motrin 100mg/5ml oral suspension and Children's Motrin 50mg chewable tablets were 57.6ugh/ml, 59.4ugh/ml and 62.9ugh/ml respectively.

The mean T_{max} of Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL, Children's Motrin 100mg/5ml oral suspension and Children's Motrin 50mg chewable tablets were 1.00h, 1.00h and 1.50h respectively.

The 90% confidence interval of the relative geometric mean of the test formulation to he reference 1 and reference 2 formulations for C_{max}, AUC_T, and AUC_{inf} were all within the acceptance range of 80 to 125%.

Therefore, the test formulation, Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL, was judged to be bioequivalent to reference 1 formulation, Children's Motrin® oral suspension (McNeil), and to reference 2 formulation, Children's Motrin® chewable tablets (McNeil) on the basis of C_{max} and AUC parameters.

Safety Issues:

All 3 formulations of ibuprofen were well tolerated. Of the 27 subjects, 8 subjects reported adverse events and the maximal intensity ranged from mild to severe. Five of 6 reports of headache were considered to be possibly related to the study drugs. Reports of eye injury, headache, nasopharyngitis, and sore throat were assessed to be unlikely or not related to the study drugs.

The results of laboratory evaluations pre- and post-study showed 2 clinically significant changes assessed to be possibly related to the study drugs: one subject had an abnormal platelet count and one had an increased aspartate aminotransferase value.

There was an SAE filed for this study.

Reviewer's Comments:

Based upon data mentioned above, Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL (Taro) is bioequivalent to reference 1 formulation, Children's Motrin® oral suspension (McNeil), and to reference 2 formulation, Children's Motrin® chewable tablets (McNeil) on the basis of C_{max} and AUC parameters.

Also, all of three formulations of ibuprofen administrated during the study were well tolerated in subjects.

The Division recommends that the Sponsor should closely follow up severe adverse reaction profiles during postmarketing phase such as abnormal platelet count and aspartate aminotransferase value.

Bioavailability and Pharmacokinetic Profile Study No. IUE-P2-134

Study Title:

Single Dose Crossover Comparative Bioavailability Study of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL in Healthy Male Volunteers Following a 200 mg Administration under Fasting and Fed States.

This was a randomized, single dose, 4-period, 2-sequence, cross-over study designed to evaluate the pharmacokinetic profile and bioavailability of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL (test formulation) comparing with Children's Motrin ® oral suspension (McNeil) (reference formulation) in 30 healthy male subjects under fasting and fed conditions.

Study No. (Date of Report):

IUE-P2-134 (October 29, 2002).

Objective:

To evaluate and compare the relative bioavailability and therefore the bioequivalencen as well as to determine the effect of food on the bioavailability of two formulations of ibuprofen after a single oral dose under fasting and fed conditions.

Subjects:

27 healthy males; 25 Caucasoid, 4 Black, 1 Asian; aged 20 to 50 years (mean $\pm$ S.D. of 37 $\pm$ 9 years), body mass index within 19 to 30.

Totally, All of 30 subjects completed the study, but data from 28 were included in the statistical and pharmacokinetic analyses.

Study method:

In the first two periods, the drug was administered, under fasting conditions, as a single 200 mg oral dose of either formulation. In the last two periods, the drug was administered, under fed conditions.

Each study phase was separated by a 7-day washout period.

In two periods, the subjects fasted overnight for at least 10 hours pre-dose and until approximately 5 hours post-dose. In the other two periods, a single 200 mg dose was orally administered, thirty minutes after a high fat breakfast. Blood samples were collected pre-dose and at scheduled times up to 12 hours post-dose.

The crossover study design of bioavailability and pharmacokinetic profile study No. IUE-P2-134 is as follows in Table 9:

Table 9. The 4-period, 2-sequence crossover design of Study No. IUE-P2-134

Sequence	N	Period 1 FASTING	Period 2 FASTING	Period 3 FED	Period 4 FED
1	15	Test	Reference	Test	Reference
2	15	Reference	Test	Reference	Test

Ibuprofen plasma concentrations were measured by using a validated HPLC/UV method with a limit of quantitation of 0.5ug/mL.

Study Result:

The relative geometric mean of the test to the reference formulation ratios for C_{max} were 87% and 93% for fasting and fed conditions, respectively.

The 90% confidence interval of the relative geometric mean of the test to the reference formulation for AUC_T, and AUC_{inf} were within the acceptance range of 80 to 125% under both fasting and fed conditions.

Therefore, the standards for comparable bioavailability were met between the test formulation, Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL, and the reference formulation, Children's Motrin® oral suspension (McNeil), under both fasting and fed conditions.

In addition, the 90% confidence interval of the relative geometric mean of the test formulation to the reference formulation for C_{max}, AUC_T, and AUC_{inf} were all within the acceptance range of 80 to 125% under both fasting and fed conditions.

Therefore, under both fasting and fed conditions, the test formulation, Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL, was judged to be bioequivalent to the reference formulation, Children's Motrin® oral suspension (McNeil) on the basis of C_{max} and AUC parameters.

Safety Issues:

Both formulations of ibuprofen were well tolerated. Of the 30 subjects, 16 reported adverse events. The maximal intensity ranged from mild to severe. Of

the reported events, four were considered to be possibly treatment-related: flatulence, headache, nasal congestion, and rhinorrhoea. The other events were assessed to be unlikely or not related to the study drugs. These include: increased diastolic blood pressure, increased systolic blood pressure, chemical eye injury, diarrhoea, decreased heart rate, increased heart rate, nasopharyngitis, and skin lesion (right ankle).

The laboratory values at the beginning and at the end of the study were considered normal or not clinically significant except in four subjects where these events were assessed to be possibly related to the study drugs. One subject each had: increased blood alkaline phosphatase, decreased hemoglobin, increased alanine aminotransferase, and red blood cells in urine.

Reviewer's Comments:

Based upon data mentioned above, Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL (Taro) is bioequivalent to reference formulation, Children's Motrin® oral suspension (McNeil) on the basis of C_{max} and AUC parameters under both fasting and fed conditions.

Also, all of two formulations of ibuprofen administrated during the study were well tolerated in study subjects.

As mentioned before, the Division recommends that the Sponsor should closely follow up severe adverse reaction profiles during postmarketing phase such as increased blood alkaline phosphatase, decreased hemoglobin, increased alanine aminotransferase, and red blood cells in urine were positive.

Pediatric Absorption Study No. 02212

Study Title:

Randomized, Single Dose, One Way Parallel, Comparative Pharmacokinetic Study of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL at 10mg/kg in Healthy Children under Fasting State.

This study was a single-center, open-label, single dose, randomized, 1-period, parallel, comparative bioavailability study, to compare the rate and extent of absorption of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL versus Children's Motrin oral suspension, administered as a 1 x 10 mg/kg oral suspension under fasting conditions. Children age 3 to 12 years participated in the study.

Study No. (Date of Report):

02212 (December 13, 2002).

Objective:

To compare the rate and extent of absorption of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL to Children's Motrin (McNeil) 10 mg/kg oral suspension (reference formulation) as a 1x 10 mg/kg oral suspension under fasting condition.

Subjects:

40 children; aged 3 to 12 years (mean =9 years), 14 males, 26 females, 6 Black and 34 Hispanic.

Study Result:

Mean (CV%) pharmacokinetic parameters and ratios of geometric means (Taro/Motrin®) are summarized below:

Table 10. **The rate and extent of absorption of Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL versus Children's Motrin oral suspension under fasting conditions**

		Taro (n=19)		Motrin® (n=19)		Ratio (%)
AUC_{0-t}	(ng hr/mL)	163693	(29)	146677	(16)	112
AUC_{0-inf}	(ng hr/mL)	167290	(31)	149518	(16)	112
C_{max}	(ng/mL)	52000	(16)	60515	(10)	85

Based on the least-squares means ratios for AUC_{0-t}, AUC_{0-inf} and C_{max}, it can be concluded that a single dose of Taro's Ibuprofen oral suspension demonstrates a slightly higher extent of absorption and a slightly lower rate of absorption compared to a single dose of Children's Motrin, Ibuprofen, 10 mg/kg, oral suspension when administered to healthy children under fasting conditions.

Safety Issues:

Both formulations were well tolerated and no adverse events were reported in this study.

Reviewer's Comments:

In support of a 505(b) (2) application for Children's Elixsure TM IB (ibuprofen) Oral Suspension (100 mg/5mL), the sponsor has conducted single dose bioequivalence (BE) studies (Study No.IUE-P2-134) in healthy adults. The results demonstrated that Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL is bioequivalent to the reference product (Children's Motrin oral suspension) under both fast and fed conditions. In addition, the sponsor has conducted a bioequivalence study in children (3-12 yr) under fast condition, but their product is not bioequivalent to the reference product in children. In

discussion with biopharmcology team regarding this issue, it is felt that adult BE data would take precedence. Because historically, the 90% confidence interval criteria for bioequivalence are derived from adult data, and its utility in pediatric subjects is questionable in regulation sense. Historically for a similar product, the sponsor would conduct BE studies in adult subjects under fast and fed condition, and just conduct a bioavailability (BA) study for the pediatric patients.

In conclusion, the finding of non-bioequivalence in the pediatric subjects for this product is not considered an approvability issue.

Based upon mentioned above, the bioequivalent study in children (3-12years) conducted by the Sponsor is acceptable for approval at this time.

Also, all of two formulations of ibuprofen administrated during the study were well tolerated in children.

Although no adverse reactions reported in study No.IUE-P2-134, the Division still recommends that the Sponsor should closely follow up adverse reaction profiles during postmarketing phase.

Gastric Tolerability

Patients receiving chronic therapy with NSAIDs may develop serious gastrointestinal toxicity such as bleeding, ulceration, and perforation at any time, with or without warning symptoms [1]. Minor upper gastrointestinal problems, such as dyspepsia, usually develop early in therapy, while ulceration and bleeding may occur with chronic treatment. In clinical trials of several months to 2 years' duration, symptomatic upper gastrointestinal ulcers, gross bleeding, or perforation occurred in approximately 1% of the patients treated for 3 to 6 months, and 2% to 4% of the patients treated for one year. To date, there are no studies identifying any subset of patients not at risk of developing peptic ulceration and bleeding.

Reviewer's Comments:

According to FDA-approved Labeling, serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

As noted above, studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

The Division suggests the sponsor should collect and follow up postmarketing adverse event data on Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL closely, especially for gastrointestinal adverse reactions.

Drug Contraindications and Interactions

Contraindications

Ibuprofen is contraindicated in patients who have previously demonstrated hypersensitivity to it, or who have a history of allergic manifestations to aspirin or other NSAIDs [1,16]. Administration of ibuprofen is not recommended during pregnancy, labor, or delivery, or to nursing mothers. Safety and efficacy has not been established in infants below 6 months of age.

Children's Motrin ibuprofen is also contraindicated in patients with Systemic Lupus Erythematosus, acute peptic ulcer, or gastrointestinal bleeding [16]. Caution must be exercised when the risk of dehydration is present which might increase the risk of renal toxicity with ibuprofen [16].

Reviewer's Comments:

Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL should not be used in patients with previously demonstrated hypersensitivity to ibuprofen, or in individuals with a history of allergic manifestations to aspirin or other NSAIDs. Severe anaphylactic-like reactions to ibuprofen have been reported in such patients, some with fatal outcome.

Drug Interactions

Anti-Arthritics: Ibuprofen may be used in combination with gold salts and/or corticosteroids, but use in conjunction with aspirin cannot be recommended in the absence of controlled clinical trial data [1].

Anticoagulants: Short-term studies have failed to demonstrate any significant effect of ibuprofen on prothrombin times or various other clotting factors administered to individuals receiving coumarin-type anticoagulants [1]. However, caution is advised when ibuprofen is administered concomitantly with anticoagulants since NSAIDs are associated with gastrointestinal bleeding. It is recommended that the use of Children's Motrin ibuprofen be avoided by patients with intrinsic coagulation defects and by those on anticoagulant therapy [16].

Methotrexate: Ibuprofen and other NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices, which may indicate that they could enhance the toxicity of methotrexate [1]. Caution is therefore advised if ibuprofen is administered comcomitantly with methotrexate.

Histamine-2 Antagonists: Clinical trials of ibuprofen administered concomitantly with cimetidine or ranitidine have shown no substantive effect on ibuprofen serum concentrations [1].

Antihypertensives/Diuretics: Reports have suggested that ibuprofen and other NSAIDs diminish the antihypertensive effect of angiotensin converting enzyme inhibitors, which is an interaction that should be considered. Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients; a response attributed to the inhibition of renal prostaglandin synthesis. Patients receiving these drugs concomitantly should be observed for signs of renal failure and diuretic efficacy.

Lithium: Ibuprofen administered concomitantly with lithium elevated plasma lithium levels (15%) and reduced renal lithium clearance (19%) in a clinical trial in normal subjects [1]. The effect was attributed to the inhibition of renal prostaglandin synthesis by ibuprofen. Patients receiving concomitant therapy with these 2 agents should be observed for signs of lithium toxicity.

Reviewer's Comments:

Animal studies show that aspirin given with NSAIDs, including ibuprofen yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels.

Additional Studies from Taro Pharmaceuticals Inc.

1. **An Open Label Swallowing Study of Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL: IBU036**

2. **Study Utilizing Radioactive Labeling of Material**

3. **Feeding Tube Study in Different Feeding Tubes**

4. Esophageal Transit Study (IBU-0210)

Based upon T-con discussion with the Sponsor on June 28, 2003, the Sponsor have proposed two additional studies to evaluate swallowing process and esophageal toxicity profiles of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL:

-Clinical study: An Open Label Swallowing Study of Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL: IBU036).

-Study utilizing radioactive labeling of material.

An agreement had been made between the Division and the Sponsor, which the study utilizing radioactive labeling of material will be conducted as a phase IV study. The study protocol of study utilizing radioactive labeling of material and postmarketing commitment will be submitted in a separate correspondence.

In addition, the Sponsor conducted a esophageal transit Study using videofluoroscopy of 10% barium sulfate in Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL after single 30mL oral doses in fasting healthy adult male volunteers. The study report submitted to the Division on January 2, 2003.

As the Division requested, the Sponsor also assessed a feeding tube study to evaluate administration of Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL through various feeding tubes.

An Open Label Swallowing Study of Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL: IBU036

Study Title:

An open label study to assess ease of swallowing of Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL after single oral doses in adult patients with mild to moderate difficulty swallowing due to neurological impairment.

Study No. (Date of Report):

IBU036 (October 16, 2003)

Objective:

To evaluate the safety of Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL in patients with mild to moderate difficulty swallowing due to neurological conditions such as stroke, multiple sclerosis, etc. Patients will be chosen who can more easily swallow pureed and semisolid foods than simple liquids.

Subjects:

Ten subjects were enrolled into the study based on a history of an identifiable neurologic illness (ALS) associated with dysphagia. All individuals lived at home and maintained themselves exclusively on oral feedings. Following a swallowing evaluation by a certified speech pathologist, 7 of the 10 subjects were qualified. These 7 subjects developed either wet phonation or cough when attempting to swallow 20 cc or less of water but had no evidence of aspiration (i.e. did not develop cough or wet phonation) when swallowing 20 cc of pureed food, specifically applesauce.

The study subjects ranged in age from 44 to 76 years old at enrollment, with a mean of 62.1±11.9 years. Three of the 10 subjects (30%) were male; 9 of the 10 subjects (90%) were Caucasian.

Study method:

This study is open label, non-blinded, single period design. The ease of swallowing on Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL will be evaluated using a standardized "bedside" clinical evaluation of swallowing.

Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL will be test drug in this study. Patients will receive a single oral dose of up to 20 mL (400 mg) of Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mLduring the study.

Inclusion Criteria:

Patients to be included in the study are those who:

-Provide signed informed consent,
-Are willing to follow the study procedures and complete the study;
-Patients aged from 18 to 80 years;
-Able to eat reasonable quantities of soft food without coughing on a regular basis;
-Have difficulty swallowing a tablespoon of a liquid without occasionally experiencing coughing;
-Have adequate motor strength to sit comfortably in an upright position.

Exclusion Criteria:

Patients to be excluded from the study are those who:

-Have had recurrent aspiration pneumonia; significant history of hypersensitivity to ibuprofen or any related products as well as severe hypersensitivity reactions (like angioedema) to any drugs;
-Presence or history of significant gastrointestinal, liver or kidney disease;
-Presence or history of significant cardiovascular, pulmonary, hematologic, psychiatric, endocrine, immunologic or dermatologic disease;
-Significant history of asthma; presence or significant history of peptic ulcer or inflammatory disease of the gastrointestinal system;
-Presence or significant history of syndrome of nasal polyps; history of bronchospastic reactivity and angioedema to ASA, ibuprofen or other NSAIDs;
-Maintenance therapy with any drug, or significant history of drug dependency, alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic), or serious psychological disease;
-Any clinically significant illness in the previous 28 days before this study;
-Participation in another clinical trial in the previous 28 days before day 1 of this study.

Endpoints

Swallowing of the Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL will be compared to a selection of solid and liquid foods, including a routine liquid, pureed material and a softer solid. The ease of swallowing and evidence of aspiration (e.g. coughing) are noted and graded.

Study Result:

Ten (10) subjects with a history of long-standing dysphagia, who were living at home, were able to maintain themselves exclusively with oral feeding, and by history had more trouble swallowing water than pureed food. Of the enrolled subjects, 3 were excluded from the per protocol analysis: two (2) of the 10 subjects were excluded because they had no difficulty swallowing liquids and one (1) subject was excluded because he demonstrated signs of aspiration with both liquids and the pureed food (Table 12).

Seven (7) subjects were included in the per-protocol population. All of these subjects met the predefined inclusion criteria – they developed either wet phonation or cough when attempting to swallow 20 cc or less of water but had no clinical evidence of aspiration (i.e. did not develop cough or wet phonation) when swallowing 20 cc of pureed food, specifically applesauce.

The data showed that all 7 eligible subjects swallow Taro's Ibuprofen NonSpil™ Suspension without significant clinical aspiration.

Among the 7 subjects there were no failures with either Taro's Ibuprofen NonSpil™ Suspension or pureed food (p=1.00).

Table 12 Patient's Baseline Swallowing Characteristics and Swallowing Study Results

	History	Swallowing Difficulties				Study Results		
Subject		Dysphagia	Liquids	Purees	Solids	Water	Apple Sauce	Ibuprofen NonSpil
01	ALS	Yes	Caution	Normal	Caution	Cough	None	None
02	ALS	Yes	Caution	Normal	Caution	Wet Phonation	None	None
03	ALS	Yes	Caution	Caution	Caution	Cough & Wet Phonation	None	None
04*	ALS	Yes	Caution	Normal	Caution	None	None	None
05	ALS	Yes	Caution	Caution	Caution	Cough & Wet Phonation	None	None
06*	ALS	Yes	Caution	Normal	Caution	None	None	None
07	ALS	Yes	Caution	Normal	Caution	Wet Phonation	None	None
08**	ALS	Yes	Caution	Caution	Caution	Cough & Wet Phonation	Cough & Wet Phonation	Cough & Wet Phonation
09	ALS	Yes	Caution	Normal	Caution	Wet Phonation	None	None
10	ALS	Yes	Caution	Normal	Caution	cough	None	None

* Patients 04 and 06 were excluded because on swallowing study they could swallow liquids without difficulty
** Patient 08 was excluded because on swallowing study he could not swallow liquids or purees without aspiration

Reviewer's Comments:

Based upon above swallowing study data, patients who had a history of long-standing dysphagia with more trouble swallowing water than pureed food swallowed Taro's Ibuprofen NonSpil™ Suspension without significant clinical aspiration. The Division reminds the Sponsor that above study is a preliminary safety swallowing study, and the Sponsor can not conclude any statement regarding above swallowing study results in the labeling. However, clinicians should be cautious to use this product in patient with dysphagia.

Study Utilizing Radioactive Labeling of Material

This study will be a phase IV study. The study protocol is pending.

Esophageal Transit Study No. IBU-0210

Study Title:

Esophageal Transit Study Using Videofluoroscopy of 10% Barium Sulfate in Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL After Single 30mL Oral Doses in Fasting Healthy Adult Male Volunteers.

Study No. (Date of Report):

IBU-0210 (November 15, 2002).

Objective:

To examine the transit of Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL through the oropharynx and esophagus.

Subjects:

Six healthy male subjects were enrolled in this study, aged 21 to 24 years (mean =22 years), 4 Caucasian, 1 Middle-Eastern and 1 Black.

Study Methods:

Fasted healthy adult male volunteers were administered single 30-mL oral doses of 10% Barium Sulfate in Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL. Subjects were given the test product while in an upright position. Swallowing and esophageal images of the subject's esophagus were obtained prior to swallowing and for approximately 30 seconds after swallowing and again at approximately 1, 3 and 5 minutes after a single swallow of the test product.

Study Result:

Table 10. Esophageal Transit Study Using Videofluoroscopy of 10% Barium Sulfate in Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL After Single 30mL Oral Doses in Fasting Healthy Adult Male Volunteers

No. of Subjects	Test articles	Bolus volume	Results
#1	Elixsure plus 10% barium sulfate	30ml	No residue in oropharynx and esophagus
#2	Elixsure plus 10% barium sulfate	30ml	No residue in oropharynx and esophagus
#3	Elixsure plus 10% barium sulfate	30ml	No residue in oropharynx and esophagus
#4	Elixsure plus 10% barium sulfate	30ml	No residue in oropharynx and esophagus
#5	Elixsure plus 10% barium sulfate	30ml	No residue in oropharynx and esophagus
#6	Elixsure plus 10% barium sulfate	30ml	No residue in oropharynx and esophagus

Normal transit of the 10% Barium Sulfate in Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL through the oropharynx and esophagus occurred in all subjects without any obstruction. Each subject demonstrated normal swallowing of the test suspension, followed by normal peristalsis through

the esophagus. The bolus of the test drug was seen in the stomach 11 to 30 seconds after swallowing the test drug. Barium coating of the esophagus was undetectable after 2 to 3 minutes of swallowing the test material, indicating that the test material passed completely into the stomach in all subjects.

Safety Issues:

No adverse events were reported during this study. All final laboratory tests results were within normal limits or were judged to be not clinically significant by the Sub-Investigator.

Reviewer's Comments:

All subjects were well tolerated esophageal transit study using videofluoroscopy of 10% barium sulfate in Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL after single 30mL oral doses. The study results demonstrated that normal transit of the 10% Barium Sulfate in Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL through the oropharynx and esophagus occurred without any obstruction and aspiration in all subjects.

Feeding Tube Study in Different Feeding Tubes

Study Title:

To evaluate the feasibility of administrating a 30-50ml bolus of Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL, undiluted and in a 1:1 dilution with water, from a syringe through several different feeding tubes.

Objective:

To evaluate administration of the Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL through various feeding tubes.

Study Methods:

Each feeding tube was flushed with 30ml of water to document that the tube was open and that water flowed freely. Using a 2oz syringe, the investigator attempted to push 30ml of Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL through each tube. I addition a 1:1 dilution of Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL and water was pushed through the NG tube and the J/G tubes. The material pushed through the tube was collected in graduated cylinders and volume measured.

Study Result:

Table 11. To evaluate the feasibility of administrating a 30-50ml bolus of Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL, undiluted

and in a 1:1 dilution with water, from a syringe through several different feeding tubes

Tube Type/Size	Un-diluted/One Hand Method	Un-diluted/Two Hand Method	Diluted/One Hand Method	Diluted/Two Hand Method
NG Tube/8 French	No	No	No	Yes
NG Tube/12 French	No	No	Yes	N/A
G Tube/14 French	Yes	N/A	N/A	N/A
J Tube/9/18 French	No	No	No	Yes

Nasogastric (NG) Feeding Tube 8 French Study:

It was not possible to dispense un-diluted Ibuprofen NonSpil suspension through nasogastric (NG) feeding tube 8 French. Using one hand, it was very difficult to administer 50ml of the 1:1 dilution of Ibuprofen NonSpil suspension and water through the 8 French tube. Two hands were required to administer the product through the 8 Ftrench NG tubes.

Nasogastric (NG) Feeding Tube 12 French Study:

It was not possible to dispense un-diluted Ibuprofen NonSpil suspension through this NG tube. However, using only one hand, it was easy to administer 50ml of the 1:1 dilution of Ibuprofen NonSpil suspension and water through this 12 French NG tube.

Replacement Balloon Gastrostomy (G) Tube 14 French Study:

For administration through the G tubes, 30ml of Ibuprofen NonSpil suspension (un-diluted) passed without difficulty through the 14 French balloon G tubes using one hand.

Neojejunal (J) feeding Tube 9/18 French Study:
It was not possible to dispense un-diluted Ibuprofen NonSpil suspension through this J tube. Using one hand, it was difficult to administer 50ml of 1:1 diluted Ibuprofen NonSpil suspension with water through the 9/18 French tube with. Two hands were required to administer the product through the J tube.

Safety Issues:

Based upon tube study information, Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL can not be used in patients with 8/12 French NG tubes and 9/18/French J tubes.

Reviewer's Comments:

As mentioned above, Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL can not be used in patients with 8/12 French NG tubes and 9/18/French J tubes. The Sponsor should reflect above tube study information in the labeling for clinician's reference.

Foreign Marketing History

Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL is not approved for use in foreign markets.

Ibuprofen is a well-established molecule. Because of its record of efficacy and safety, ibuprofen was approved for sale as a nonprescription product in the United States in 1984. In 1989, ibuprofen suspension 100mg/5ml was approved by the FDA as a prescription antipyretic for use in children age 6 months and older. That product was switched to nonprescription status in the United States in 1995, with both antipyretic and analgesic indications for children ages 2 to 11 years.

Ibuprofen is currently marketed in the United States as a prescription and OTC product in a variety of strengths and dosage forms.

Labeling Issues

Children's Elixsure ™ IB (ibuprofen) Oral Suspension, 100 mg/5m will be marketed in 120ml bottle. The product will also be distributed as a physician sample in a 28 mL bottle.

The labeling for the 120 ml bottle will include a bottle label and carton label. The labeling for the 28 ml bottle will include a bottle label and an information leaflet.

Four draft copies of Taro's pharmaceuticals U.S.A. Inc.'s proposed labels and labeling for Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5m are provided in this NDA submission as follows:

-Carton and bottle label for 120 mL bottle
-Bottle label for 28 Ml bottle
-Information leaflet for 28 ml bottle

Reviewer's comments:

Please see OTC labeling review for details.

Summary of Review

Regulatory History

The Sponsor submitted the pre-IND application to the Division on March 27, 2003.

An pre-IND meeting was held with the Sponsor on May 7, 2002. As per the FDA meeting minutes, the comments from the Division are as following:

-A summary of the Pharmacology and Toxicology with a list of key references of Ibuprofen would be sufficient.

-All of the specifications are acceptable for an IND submission. However, it is noted that 1) the viscosity values decrease with storage and 2) the largest particle size decreases from the initial time point to the two-month time point and then increases at the three-month time point. Attention needs to be paid to these two parameters to determine if these are real or artifacts.

-A bracketing or a matrixing protocol is used when a large number of stability samples need to be analyzed. In the case of an IND, this number is relatively small. Therefore, bracketing or matrixing cannot be permitted.

-In the latter stages of drug development, a bracketing/matrixing protocol may be allowed. However, such a protocol should be reviewed by the Division before it is used for stability studies.

-The Division will provide the sponsor with the appropriate contacts in the FDA [redacted] *who can answer these two questions.*

-The storage conditions in the submitted label are those for a commercial product. An IND label should indicate that this is for investigational purposes only. The exact wording that should go on the label from the CMC standpoint is in 21 CFR 312.6. The proposed label will be reviewed in the context of the indication (i.e., OTC or prescription) being sought by the sponsor.

Additional Comments:

1) Please give the unit formulation, i.e., the components and composition per 5mL of the suspension.

2) Please indicate what the masking agent is.

3) Is the container closure of any special design or is the pouring/gelling effect purely a function of the formulation? If the container closure is of a special design, then this should be described in some detail in the IND.

4) It is recommended that the sponsor conduct a Food-effect study with the to-be-marketed formulation in adults.

5) Considering the formulation is unique, it is also recommended that the sponsor conduct a pharmacokinetic study in the pediatric patient.

6) Information on any safety issues with use of the ingredients that compose the spill resistant character of this formulation needs to be addressed.

7) The sponsor needs to demonstrate that accurate delivery of drug is possible from the spoon supplied and other sources (i.e., calibrated caps).

8) The Division is concerned about the potential for esophageal toxicity due to the possibility that the characteristics of the ingredients contained in this spill resistant formulation may not allow the ibuprofen dose to pass completely into the stomach. The sponsor needs to address this concern.

The Sponsor submitted IND application (IND 62,823) to the Division on August 2, 2002. The regulated action has been made by the Division as follows:

-There are no clinical hold issues at this time, the study should be allowed to proceed.

-The Sponsor should consider the following studies with the aim of completing this IND application.

1) A food-effect study in adult group.

2) A study of administration of Ibuprofen NonSpil TM Oral Suspension to NG-tube, G-tube and J-tube in order to rule out the possibility of obstructing these tubes.

3) Swallowing studies in both healthy subjects and patients with dysphagia to rule out the possibility of aspiration.

4) Based on the pre-IND meeting on May 7, 2002, Sponsor should address a concern, which the potential for esophageal toxicity due to this spill resistant delivery system may not allow the ibuprofen dose to pass completely into the stomach.

5) The sponsor needs to clarify that accurate delivery of drug is possible from the spoon supplied and other sources (calibrated caps).

The Sponsor submitted NDA (NDA 21-604) to the Division on December 31, 2003.

The Sponsor submitted esophageal transit study data (protocol IBU-0210) in Normal subject on January 6, 2003

The Division issued a filing letter to the Sponsor on March 13, 2003. At that time, the Division have identified the following potential review issues:

1. The tradename needs to be clarified. The cover letter refers to the product as "Children's ElixSure TM IB (Ibuprofen) Oral Suspension". However, the proposed labeling of the product does not include the "IB" designation.

2. The submission notes that the product may have "nonspill" or "gel" characteristics. However, the teaspoon depiction, and the reference to "Ibuprofen Oral Suspension" on the PDP and other labeling does not convey that the product is any different from a traditional suspension. The labeling should be revised to differentiate this product from a traditional suspension.

3. You must submit drug facts specifications (font size, etc.).

4. You should submit a section on investigational formulations that were developed for this NDA.

5. Justification for the acceptance criteria of the drug product should be submitted.

6. Also, you should submit a statistical analysis justifying the proposed expiration period of the drug product, or submit a justification why such an analysis was not feasible.

7. Please submit the additional missing safety data requested by the Division, such as swallowing studies and the esophageal toxicity study in patients with dysphagia (stroke, CP, TBI, or other neurological disorders) within the review period after starting the review clock.

8. Please identify the components of the container/closure system that come in contact with the drug product. Please provide Letters of Authorization from the DMF holders of the container closure systems, indicating exactly where the pertinent information is located. If possible, also request the DMF holders to include a statement in the LOA that it is safe for the component of the container closure system to come in contact with food and give the relevant CFR citations.

The Sponsor submitted swallow study protocol in patients with dysphgia to the Division on May 29, 2003 and re-submitted revised protocol to the Division on July 28, 2003.

On August 13, 2003, Biopharmcology team issued a comment regarding PK study in children in this NDA submission as follows:

In support of a 505 (b) (2) application for the ibuprofen Nonspill (Children's Elixsure IB) product, the sponsor has conducted single dose bioequivalence (BE) studies in healthy adults and the product is bioequivalent to the reference product (Children's Motrin oral suspension) under both fast and fed conditions. In addition, the sponsor has conducted a bioequivalence study in children (3-12 yr) under fast condition, but their product is not bioequivalent to the reference product in children. In discussion

with our management regarding this issue, it is felt that adult BE data would take precedence. Because historically, the 90% confidence interval criteria for bioequivalence are derived from adult data, and its utility in pediatric subjects is questionable in regulation sense. Historically for a similar product, the sponsor would conduct BE studies in adult subjects under fast and fed conditions, and just conduct a bioavailability (BA) study for the pediatric patients. In conclusion, the finding of non-bioequivalence in the pediatric subjects for this product is not considered an approvability issue.

On October 16, 2003, the Sponsor submitted data of swallowing study in patient with dysphagia to the Division (protocol IBU036).

Clinical Trials

Ibuprofen is an active ingredient in Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL. Its efficacy and safety profiles were well established as mentioned above. The pivotal studies of efficacy and safety for Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL in this NDA should be waived at this time. However, the Sponsor is conducting some additional safety studies specifically for this product such as swallowing study in normal subjects and patients with dysphagia due to neurological impairments and esophageal toxicity study by utilizing radioactive labeling of material (a phase IV study) as the Division required.

Efficacy issues

In this NDA submission, the sponsor proposed target population is children. The Sponsor should specifically describe dosage and administration for this product in the labeling.

In three clinical trials sponsored by McNeil Consumer Products Company, the data demonstrated that ibuprofen solution in a single dose and/or multiple doses is comparable to acetaminophen elixir in a single dose and/or multiple doses in treating pyrexia in children.

In study No.5-535, the data demonstrated that ibuprofen solution in a single dose of 5-7.5 mg/kg is comparable to acetaminophen elixir in a single dose of 10-15mg/kg in treating pyrexia. Also, this study suggests that ibuprofen may be more effective or have a longer duration of action between 5 and 7 hours compared to treatment group with acetaminophen elixir.

In study No. 6-639, it was concluded that ibuprofen in a single dose of 9 mg/kg was more effective than acetaminophen in a single dose of 12 mg/kg in high temperature group.

The study No. 6-604 was a multi-center, multiple dose, randomized, parallel, investigator-blind study comparing the safety and antipyretic efficacy of ibuprofen suspension 5-7 mg/kg and acetaminophen elixir 10-15 mg/kg in febrile children aged 6 months to 11 years under routine, home conditions. In this study, antibiotics were allowed in both study groups and antibiotic usage rates were not significantly different between the 2 groups. The data showed that ibuprofen suspension at 5-7.5 mg/kg and acetaminophen at 10-15 mg/kg, each given in multiple doses every 4 to 6 hours, were comparable in reducing fever in this patient population. Age was not a significant factor in the antipyretic effect of ibuprofen, nor did the use of antibiotics interfere with its action.

In three clinical trials sponsored by McNeil Consumer Products Company, the data demonstrated that ibuprofen solution in a single dose and/or multiple doses is comparable to acetaminophen elixir in a single dose and/or multiple doses in treating with sore throat pain in children.

The Study No. 90-001/89-949 was a multi-center, single-dose, randomized, double-blind, placebo-controlled study comparing the safety and analgesic efficacy of ibuprofen suspension 5 mg/kg and acetaminophen elixir 12.5 mg/kg to placebo in the treatment of children aged 5 to 12 years with sore throat pain. There were no serious or unexpected adverse events in this study. The data demonstrated that acetaminophen was significantly superior to placebo only in the older group. Ibuprofen at either dose of 5 mg/kg and 10 mg/kg was significantly superior to acetaminophen in the younger age group. It was concluded that ibuprofen suspension at doses of 5 mg/kg and 10 mg/kg are safe and effective in the relief of sore throat pain for up to 6 hours in children.

The Study No. 90-002/90-003 was a multi-center, single-dose, and randomized, double blind, placebo-controlled study. It compared the safety and analgesic efficacy of ibuprofen suspension 5 mg/kg and acetaminophen elixir 12.5 mg/kg to placebo in the treatment of children aged 5 to 12 years with ear pain due to acute otitis media. Antibiotics were not permitted within 24 hours prior to study entry or during the study period. There were no serious or unexpected adverse events. The data demonstrated that ibuprofen suspension at doses of 5 mg/kg and 10 mg/kg are safe and effective in the relief of ear pain for up to 6 hours in children.

The Study No. 94-437 was a multi-center, single-dose, randomized, parallel, investigator-blind study comparing the safety and antipyretic efficacy of ibuprofen suspension 7.5 mg/kg with acetaminophen suspension 12.5 mg/kg in children aged 2 to 11 years. It was concluded that a single 7.5 mg/kg dose of ibuprofen suspension provides significantly greater fever reduction over 8 hours (and beginning 1 hour after dosing) than acetaminophen suspension in a single 12.5 mg/kg dose.

Overall, all of clinical studies demonstrated that ibuprofen solution in a single dose and/or multiple doses are effective and safe in treating fever and sore throat or ear pain in children.

In summary, due to ibuprofen is an active ingredient in Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL. Its efficacy profiles were well established as noted above. The pivotal studies of efficacy for Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL in this NDA should be waived in this NDA submission.

To support the efficacy of Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL safe in treating fever and sore throat and/or ear pain in children, that the Sponsor summarized and submitted clinical efficacy data of oral ibuprofen suspension from different references for approval is acceptable at this time.

Safety Issues

According to FDA-approved labeling for ibuprofen suspension (Montrin), the most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%. The Sponsor needs to identify incidence rates of GI adverse reaction in Table 5. Adverse reactions observed during controlled clinical trials in adults at an incidence greater than 1% are as follows:

Cardiovascular system: Edema, Fluid retention (generally responds promptly to drug discontinuation).

Digestive system: Nausea, Epigastric Pain, Heartburn, Diarrhea, Abdominal Distress, Nausea and Vomiting, Indigestion, Constipation, Abdominal Cramps or Pain, Fullness of GI Tract (bloating and flatulence).

Nervous system: Dizziness, Headache, Nervousness.

Skin and appendages: Rash (including maculopapular type), Pruritus

Special senses: Tinnitus.

Above reactions listed under the heading "Incidence Greater than 1% (but less than 3%) Probable Causal Relationship," encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Occurring less frequently than 1 in 100, were reported in controlled clinical trials and from postmarketing experience. These reactions have been divided into two categories: "Incidence less than 1%--Probable Causal Relationships," lists

reactions with Ibuprofen therapy for which the probability of a causal relationship exists; this category was completed over time with postmarketing serious adverse reactions. "Incidence less than 1% --Causal Relationship Unknown," lists reactions with ibuprofen therapy for which a causal relationship has not been established, but are presented as alerting information for physicians.

The following adverse reactions were reported in clinical trials at an incidence of less than 1%, or were reported from postmarketing or foreign experience. The probability exists between the drug and these adverse reactions.

Body as a whole: Anaphylaxis and anaphylactoid reactions.

Cardiovascular system: Cerebrovascular accident, hypotension, congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations.

Digestive system: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, pancreatitis, melena, gastritis, duodenitis, esophagitis, hematemesis, hepatorenal syndrome, liver necrosis, liver failure, hepatitis, jaundice, abnormal liver tests.

Hematologic system: Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decrease in hemoglobin and hematocrit, pancytopenia.

Nervous system: Depression, insomia, confusion, emotional liability, somnolence, convulsions, aseptic meningitis with fever and coma

Respiratory: Bronchospasm, dyspnea, apnea.

Skin and appendages: Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia, exfoliative dermatitis, Lyell's syndrome (toxic epidermal necrolysis), photosensitivity reactions.

Special senses: Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision)

Urogenital system: Acute renal failure in patients with pre-existing significantly impaired renal function,renal papillary necrosis, tubular necrosis, glomerulitis, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria.

Miscellaneous: Dry eyes and mouth, gingival ulcer, rhinitis.
The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested by marketing experience under circumstances where a causal relationship could not be definitely established. They are listed as alerting information for the physician.

Allergic: Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema.

Cardivascular system: Arrhythmias (sinus tachycardia, sinus bradycardia).

Hematologic system: Bleeding episodes (e.g., epistaxis, menorrhagia).

Metabolic/endocrine: Gynecomastia, hypoglycemic reaction, acidosis.

Nervous system: Paresthesias, hallucinations, dream abnormalities, pseudo-tumor cerebri.

Special senses: Conjunctivitis, diplopia, optic neuritis, cataracts.
Therefore, the Sponsor's statement under adverse reactions section in this NDA submission such as "Those listed under "unknown causal relationship" are those events, reported rarely, where a relationship to ibuprofen could not be established, but also could not be excluded." are incomplete and unclear.

According to adverse event pooled data on ibuprofen from all the trials, a marked difference where the drug is being given for 8-30 days (19%) compared with 31-90 days (29%) in both children and adults. Also, the overall percentage of adverse events with ibuprofen was 8% in Rainsford's study.

Furthermore, the percentage of adverse events with ibuprofen was overall very low (0-1%), but was markedly higher (18%) in children 4 years of age or under from 5 clinical trials that included only children under 12 years of age. As an Agency, the Division would like to follow up and monitor overall postmarketing adverse event data on ibuprofen. Also, the Division suggests the sponsor should collect and follow up postmarketing adverse event data on this product closely.

According to FDA-approved labeling for ibuprofen suspension (Montrin), the most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%. The Sponsor needs to identify incidence rates of GI adverse reaction in Table 5. (NDA 21-604, page 17)

The Sponsor needs to clarify or correct that statement under adverse reactions section in this NDA submission such as "Those listed under "unknown causal relationship" are those events, reported rarely, where a relationship to ibuprofen could not be established, but also could not be excluded". (NDA 21-604, page 16)

Studies from Taro Pharmaceuticals Inc.

Study No. IUP-P1-262

Based upon data from study No. IUP-P1-262, Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL (Taro) is bioequivalent to reference 1 formulation, Children's Motrin® oral suspension (McNeil), and to reference 2 formulation, Children's Motrin® chewable tablets (McNeil) on the basis of C_{max} and AUC parameters.

Also, all of three formulations of ibuprofen administrated during the study were well tolerated in subjects.

The Division recommends that the Sponsor should closely follow up severe adverse reaction profiles during postmarketing phase such as abnormal platelet count and aspartate aminotransferase value.

Study No. IUE-P2-134

Based upon data from Study No. IUE-P2-134, Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL (Taro) is bioequivalent to reference formulation, Children's Motrin® oral suspension (McNeil) on the basis of C_{max} and AUC parameters under both fasting and fed conditions.

Also, all of two formulations of ibuprofen administrated during the study were well tolerated in study subjects.

As mentioned before, the Division recommends that the Sponsor should closely follow up severe adverse reaction profiles during postmarketing phase such as increased blood alkaline phosphatase, decreased hemoglobin, increased alanine aminotransferase, and red blood cells in urine were positive.

Although no adverse reactions reported in study No.IUE-P2-134, the Division still recommends that the Sponsor should closely follow up adverse reaction profiles during postmarketing phase.

Study No. 02212

In support of a 505(b) (2) application for Children's Elixsure TM IB (ibuprofen) Oral Suspension (100 mg/5mL), the sponsor has conducted single dose bioequivalence (BE) studies (Study No.IUE-P2-134) in healthy adults. The results demonstrated that Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL is bioequivalent to the reference product (Children's Motrin oral suspension) under both fast and fed conditions. In addition, the sponsor has conducted a bioequivalence study (Study No. 02212) in children (3-12 yr) under fast condition, but their product is not bioequivalent to the reference product in children. In discussion with biopharmcology team regarding this issue, it is felt that adult BE data would take precedence. Because historically, the 90% confidence interval criteria for bioequivalence are derived from adult data, and its utility in pediatric subjects is questionable in regulation sense. Historically for a

similar product, the sponsor would conduct BE studies in adult subjects under fast and fed condition, and just conduct a bioavailability (BA) study for the pediatric patients.

Also, all of two formulations of ibuprofen administrated during the study were well tolerated in children.

In conclusion, the finding in Study No. 02212 of non-bioequivalence in the pediatric subjects for this product is not considered an approvability issue according to Biopharmacology reviewer's comments.

Based upon mentioned above, the bioequivalent study (Study No. 02212) in children (3-12years) conducted by the Sponsor is acceptable for approval at this time.

Study No. IBU-0210

In esophageal transit study (Study No. IBU-0210), all subjects were well tolerated esophageal transit study using videofluoroscopy of 10% barium sulfate in Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL after single 30mL oral doses. The study results demonstrated that normal transit of the 10% Barium Sulfate in Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL through the oropharynx and esophagus occurred without any obstruction and aspiration in all subjects.

Study No. IBU 036

Based upon swallowing study data (protocol No. IBU 036), patients who had more trouble swallowing water than pureed food swallowed Taro's Ibuprofen NonSpil™ Suspension without significant clinical aspiration. The Division reminds the Sponsor that this study is a preliminary safety swallowing study, and that can not conclude any statement regarding above swallowing study results in the labeling. However, clinicians still need to be cautious to use this product in patient with dysphagia.

Study Utilizing Radioactive Labeling of Material

This study will be a phase IV study.

Feeding Tubes Study

As data of feeding tubes study demonstrated, Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL can not be used in patients with 8/12 French NG tubes and 9/18/French J tubes. The Sponsor should reflect above tube study information in the labeling as clinician's reference.

Gastric Tolerability

According to FDA-approved Labeling, serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

As noted above, studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

The Division suggests the sponsor should collect and follow up postmarketing adverse event data on Taro's Children's Elixsure TM IB (ibuprofen) Oral Suspension, 100 mg/5mL closely, especially for gastrointestinal adverse reactions.

Drug Contraindications and Interactions

Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL should not be used in patients with previously demonstrated hypersensitivity to ibuprofen, or in individuals with a history of allergic manifestations to aspirin or other NSAIDs. Severe anaphylactic-like reactions to ibuprofen have been reported in such patients, some with fatal outcome.

Animal studies show that aspirin given with NSAIDs, including ibuprofen yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels.

Labeling Issues

Please see OTC labeling review for details.

Financial Disclosure

In accordance with 21 CFR part 54, a signed form 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) were included with the NDA submission.

Of note, many of the investigators listed participated in the Children's Elixsure TM IB (ibuprofen) Oral suspension, 100 mg/5mL NDA 21-604 under concurrent review. All of clinical investigators were noted to have financial arrangements with the sponsors defined in 21CFR part 54.

Conclusion

Taro Pharmaceuticals U.S.A., Inc. filed NDA21-604 as a 505(b) (2) New Drug Application for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL on December 31, 2002. In this NDA, the Sponsor proposed a liquid delivery system that resists spilling from a spoon that is different from the other approved ibuprofen suspensions currently marketed.

The Sponsor proposes that Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL is indicated as antipyretic and analgesic for children ages 2 to 11 years.

Since the active ingredient in Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL is ibuprofen, its efficacy and safety profiles are well established as mentioned above.

In support of this NDA submission, the Sponsor has submitted clinical safety data summarized from 3 biopharmaceutical studies, 1 fluoroscopic esophageal transit study, 1 open-label swallowing study in patient with dysphagia and feeding tube study with different types of feeding tubes. Also, a study utilizing radioactive labeling of material to evaluate swallow process of Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL will be as a phase IV trial.

In addition, the Sponsor summarized clinical trial efficacy data that was previously reviewed in support of NDA 19-842 for Children's Motrin 100 mg/5mL Oral Suspension sponsored by McNeil Consumer Products Company. In the meantime, the Sponsor also summarized results of an updated worldwide literature review in support of ibuprofen's global efficacy and safety profile in the hope of obtaining OTC marketing approval for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL for the temporary relief of fever and pain.

As mentioned above, the efficacy and safety profiles of ibuprofen are well established. To support the efficacy and safety of Children's Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL in treating fever and sore throat and/or ear pain in children, the Sponsor summarized and submitted clinical efficacy and safety data of oral ibuprofen suspension from different references. Review of these data is acceptable.

No new or unexpected adverse events associated with the use of this proposed formulation of ibuprofen were identified on review of the clinical safety data in this NDA submission. However, since the swallowing study (protocol No. IBU 036) involved only 7 patients, there is not sufficient evidence to rule out the possibility that some patients with dyphagia may have problems with aspiration.

To help complete the swallowing assessment, the Sponsor should submit data of a phase IV study utilizing radioactive labeling of material to evaluate swallow process of Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL to the Division when available. These phase IV study data will not effect approvability for Children's Elixsure ™ IB (ibuprofen) Oral Suspension, 100mg/5mL.

Recommendation for Regulatory Action

Review of the global efficacy and safety data submitted by the sponsor in support of Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL was consistent with what is already known about ibuprofen. Based on the information and data reviewed in this NDA, there are no efficacy or safety issues for this ibuprofen suspension. No significant efficacy or safety deficiencies were found for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL in this NDA submission. Therefore, the proposed indications for Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100mg/5mL are appropriate.

Recommendation

The Sponsor should reflect in the labeling the feeding tube study results, which demonstrate that Taro's Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5mL can not be used in patients with 8/12 French NG feeding tubes and 9/18/French J tubes because they become blocked with this suspension.

Both the Division and the Sponsor agree that the data from the swallowing study in patients with dysphagia (protocol No. IBU 036) is a preliminary safety data, and the Sponsor will not impact the labeling.

Regulatory Action
NDA 21-604 should be approved with language to address the NG and J tubes as noted above.

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Appendix A

Attached AE a report is as follows.

[redacted] Clinical Unit

Form CLP-3018-00(F1)

UNEXPECTED DRUG REACTION REPORT

All pertinent patient information must be collected, including date of occurrence, and if possible the relationship with the tested drug.

Project Number: IVE-P1-262 **Drug Tested:** Ibuprofen 200mg

Subject's Initials: [redacted] **Subject's Number:** [redacted]

Treatment Administered: A/B/C: Test-Reference 1 and Reference-2 formulations.

Unexpected Drug Reaction: Thrombocytosis 468 $\times 10^9$/L

Date of Occurrence: [redacted]

Relationship with the test drug:

(Remote or Impossible to judge) [ ]

Possible [✓]

Probable [ ]

Action taken: Yes [✓] No [ ]

Comment and describe all actions taken, pertinent medical history data, pertinent laboratory data, treatment or concomitant drugs prescribed etc.

Baseline at screening: 398 $\times 10^9$/L

The volunteer was called 4 times between the [redacted]

He refused to come for a medical exam and a blood test but he confirmed on [redacted] he was gone on that day at [redacted] hospital for a blood test, we are supposed to receive the ~~results~~ results at the beginning of [redacted]

Clinical Investigator Date (YYYY/MM/DD)

[redacted]

Clinical Director Date (YYYY/MM/DD)

[redacted]

File Name: Z:\Procedures\Templates\CLP-3018-00(F1)cn.doc

[redacted]

He gave his consent on [redacted] and the result came back to [redacted]

Hello ,

I just want to inform you that subject [redacted] experienced a Non Serious Unexpected Drug Reaction at the post-study evaluation. The platelet count reached a clinically significant value of 458 X 10^9/L (normal 125 – 420 X 10^9/L). The baseline at screening was 388 X 10^9/L. A follow-up evaluation was performed about 10 days later and the platelet count had returned to a clinically non-significant value of 435 X 10^9/L.

The Clinical Investigator found no other clinical event to which this thrombocytosis state could be related and found no such adverse event reported in the literature.

As this event occurred at the post study test, the clinical investigator has concluded that the thrombocystosis could have been caused by either the test (ibuprofen 100 mg/5mL oral suspension Lot # (L)S177-52967) or by one of the two references (Motrin 100 mg/5mL oral suspension Lot # DFM014 or Motrin 100 mg chewable tablets Lot # EDM139).

Are you aware of any publications that would report such an event with ibuprofen? If not, this will be described in the clinical report as an unexpected drug reaction.

If you need additional information, do not hesitate to contact me or [redacted]

Best Regards

[redacted]

Michael Yi Yao, M.D.
Medical Officer, DAAODP

James Witter, M.D., Ph.D.
Team Leader, DAAODP

Cc:
IND
HFD-550/Division files
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HFD-550/CSO

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/s/

Michael Yao
10/30/03 04:23:38 PM
MEDICAL OFFICER

James Witter
10/30/03 04:28:53 PM
MEDICAL OFFICER
Concur

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

NDA: 21-604

NAME: Children's ElixSure™ IB (Ibuprofen) Oral Suspension, 100 mg/5 mL

SPONSOR: Taro Pharmaceuticals U.S.A., Inc.

TYPE OF SUBMISSION: Commercial Pharmaceutical

DATE OF SUBMISSION: December 30, 2002

DATE OF REVIEW: August 8, 2003

REVIEWER: Rosemarie Neuner, MD, MPH

Executive Summary

Taro Pharmaceuticals U.S.A., Inc., is the sponsor of this 505(b)(2) new drug application for Children's ElixSure™ IB (Ibuprofen) Oral Suspension, 100 mg/5 mL. Since the proposed product is spill resistant it is different from the other currently approved marketed suspension formulations of ibuprofen. In support of this application the sponsor has submitted a safety database generated from 3 biopharmaceutical studies and 1 fluoroscopic esophageal transit study in the hope of obtaining OTC marketing approval for the above proposed pediatric formulation for the temporary relief of fever and pain. Additionally, the sponsor cited clinical trial safety data that was previously reviewed in support of the innovator's product, and the summarized results of an updated worldwide literature review in support of ibuprofen's global safety profile. No new or unexpected adverse events associated with the use of ibuprofen were identified on review of the safety information generated from the 3 pharmacokinetic studies and the literature contained in this application that were examined by this medical officer.

Final Recommendation:

Review of the global safety database submitted by the sponsor in support of this ibuprofen suspension's safety profile was consistent with what is already known about ibuprofen and did not reveal any new or unexpected adverse events associated with this product. Based on the information reviewed, the current consumer safety warnings for ibuprofen are appropriate and do not need to be updated or changed for this suspension formulation.

I. Introduction and Background

Ibuprofen is a propionic acid derivative that belongs to the nonsteroidal anti-inflammatory class of drugs (NSAIDs). A suspension formulation of ibuprofen (100 mg/5 ml) has been available in the United States as a prescription drug for use in children (age 6 months and older) since 1989. The first pediatric suspension formulation of ibuprofen (50 mg/ 1.25 ml) became available as an over-the-counter (OTC) drug product for the temporary relief of fever and pain in children 2-3 years of age in 1995. Subsequently, the recommended pediatric age range for use of the above suspension formulation of ibuprofen was lowered down to 6 months of age and older following agency review of an extensive pediatric safety database submitted by the innovator, McNeal Consumer Products (NDA 20-603).

The following medical officer's review is a global safety profile of Children's ElixSure™ IB (Ibuprofen) Oral Suspension, 100 mg/5 mL that was done as part of the agency's overall review of Taro Pharmaceuticals U.S.A., Inc.'s, new drug application submission NDA 21-604 in which they are requesting the same pediatric indications as the innovator. Since the proposed product is spill resistant it is different from the other currently approved marketed suspension formulations of ibuprofen.

In support of this application, the sponsor has submitted for Agency review the following safety information:

1. The safety database containing 103 subjects generated from 3 biopharmaceutical studies and 1 fluoroscopic esophageal transit study (Study Numbers: IUE-P1-262, IUE-P2-134, 02212, IBU-0210).
2. Summarized safety data from 11 clinical trials submitted in support of NDA 19-842 by the innovator, McNeal Consumer Products.
3. Summarized safety data from 4 clinical trials submitted in support of the Canadian supplemental new drug submission (SNDS) 9427-MO570-48 for the safety and efficacy of ibuprofen pediatric oral suspension 100 mg/5 mL by McNeal Consumer Products.
4. A summary of pooled adverse events generated from a published meta-analysis of clinical trials found in the worldwide literature up to 1996 that evaluated OTC doses of ibuprofen.

Safety data generated from the clinical studies submitted in support of the innovator's applications to both the U.S. and Canadian regulatory agencies will not be included in this review since it has been reviewed previously by the respective agencies. This global safety review will therefore focus on the clinical data generated by the 3 biopharmaceutical studies listed above and the literature review. An in depth review of the clinical trial safety database generated from the fluoroscopic esophageal transit study can be found in the HFD-550 medical officer's review of this application.

II. Safety database generated from the 3 biopharmaceutical studies (Study Numbers: IUE-P1-262, IUE-P2-134, and 02212).

II.A. Description of Patient Exposure:

The overall safety database submitted in support of this application was generated from the 103 subjects enrolled in clinical studies that were conducted by the sponsor. The following table, Table 1, shows the distribution by drug exposure of these 103 pooled subjects.

Table 1 – Pooled Distribution of Clinical Studies Safety Database Study Population by Drug Exposure

Type of Study	Total Number of Subjects Enrolled in Study	Ibuprofen (Taro) 100mg/5 mL oral suspension	Children's Motrin 100 mg/5 mL oral suspension	Children's Motrin 50 mg chewable tablets
Single-dose	46	26	20	0
Single-dose crossover	57	57	57	27
Total	103	83	77	27

Out of the total of 103 study subjects who participated in the 4 clinical studies included in support of this submission, 83 patients received single doses of the sponsor's proposed formulation. (See the preceding table, Table 1.) The safety data generated from the 6 patients who were enrolled in the single-dose, fluoroscopic esophageal transit study is discussed and commented on by the medical officer who reviewed these studies, and thus will not be repeated here. (Refer to the HFD-550 medical officer's review of this application.) The remaining 97 subjects were enrolled in the 3 biopharmaceutical studies. Two of these 3 studies were single-dose, crossover comparative bioavailability studies in which 57 subjects received 200 mg of the sponsor's proposed 100 mg/5 mL ibuprofen suspension, 57 received 200 mg of the approved innovator's Children's Motrin 100 mg/5 mL suspension, and 27 received 200 mg of Children's Motrin 50mg (4x50mg tablets) Chewable Tablets. The following table, Table 2, lists the disposition of these 97 pooled study subjects. (Note: A further description and the agency's analysis of the data generated from these pharmacokinetic studies can be found in the review by the Division of Biopharmaceutics [HFD-780] of this application.)

Table 2- Disposition of Pooled Subjects Enrolled in the 3 Pharmacokinetic Studies (Studies IUE-P1-262, IUE-P2-134, and 02212).

	All Subjects	
	Number	Per Cent
All Subjects Randomized:	97	100%
Subjects Lacking Complete Study Data:	4	4.1%
Subjects Included for Safety	97	100%
Subjects Who Completed All Phases of the Studies:	93	96%
Subjects Who Dropped Out:	2	2.1%
Reason for Study Discontinuation/Drop Out:		
Adverse Event	1	1.0%
Voluntary Withdrawal	2	1.9%
Lab Error	1	1.0%
Protocol Violations	2	1.9%

Of the 4 subjects who failed to complete all phases of the studies, 1 study subject failed to finish all of the dosing phases of the cross-over study he was enrolled in due to an adverse event (i.e., diarrhea) that was deemed mild in nature (Study Number IUE-P2-134). Due to problems with the lab analysis that occurred with blood specimens collected from another participant in this study, that participant's blood samples had to be discarded from 2 out of the 4 phases of the crossover study. Data generated from this subject is included in the safety database. Two (2) subjects withdrew voluntary consent and failed to complete the second and third dosing phases of the study (Study Number IUE-P1-262). Another 2 subjects that were

enrolled in the pediatric pharmacokinetic study (Study 02212) were subsequently found not to meet study entry criteria for age-adjusted physical growth percentiles for height and weight after having completed the study. They were subsequently classified as protocol violations. Data generated from these 2 pediatric subjects and the 1 subject whose blood samples were discarded are included in the safety analysis of the final reports for these studies.

II.B. Pooled Demographic Profile

The following table, Table 3, lists the demographic characteristics of the 97 subjects enrolled in the 3 pharmacokinetic studies.

Table 3 – Demographic Summary of the Subjects Enrolled in the 3 Pharmacokinetic Studies (Studies IUE-P1-262, IUE-P2-134, and 02212)

Demographic Characteristics	All Subjects (N=97)		
	Study IUE-P1-262	Study IUE-P2-134	Study No. 02212
Gender: Male	27	30	14
Female	0	0	26
Race: Caucasian	27	25	0
Black	0	4	6
Asian	0	1	0
Hispanic	0	0	34
Age (yrs.): Mean	38	37	9
Standard Deviation	8	9	-
Range	23-49	20-50	3-12

Medical Reviewer's Comments: *Review of the demographic parameters for the population from the pooled pharmacokinetic studies reveals a skewed population of healthy, Caucasian adult males which is not representative of the target population for this proposed product. The target population for this product is the pediatric age group. Although the population studied in support of this application is not entirely representative of the proposed target population for this product, it is acceptable given the current design of pharmacokinetic bridging studies required by the regulations governing 505(b)(2) applications.*

II.C. Safety Findings

II.C. 1. Deaths and Serious Adverse Events

Although there were no deaths or hospitalizations that were reported to have occurred during any of the 3 pharmacokinetic studies, there was 1 serious adverse event reported that occurred in a subject enrolled in Study IUE-P1-262. The individual (Subject Number 02) was a 46 year old Caucasian male who developed an elevated platelet count (thrombocytosis) (platelet count = 468 $x10^9$/L) which was noted on completion of the study and that remained elevated on follow-up testing (Platelet count = 435 $x10^9$/L). Although the subject's private physician deemed the thrombocytosis as being clinically insignificant, the study investigator reported it as a serious adverse event. (Refer to Table 4 below.)

II.C. 2. Dropouts Due to Adverse Events

None of the subjects enrolled in the 3 pharmacokinetic studies dropped out due to an adverse event while participating in the study. One subject (Subject Number 02) was unable to complete all 4 phases (i.e., completed 2 out of the 4 phases) of the crossover study due to diarrhea that was felt by the study investigator to be unrelated to the study medication. (See

Tables 2 and 4.) Although this individual is considered a partial discontinuation of the crossover pharmacokinetics portion of the study, he is included in the trial's safety report.

II.C. 3. Other Significant Adverse Events

A total of 24 out of the 97 subjects (24.7%) enrolled in the 3 biopharmaceutical studies reported having an adverse event that was graded to be mild to severe in intensity. Table 4 shown below is a tabular listing of the 24 reported adverse events that occurred in the various treatment groups during the 3 pooled pharmacokinetic studies.

Table 4 - Tabular Listing of the Pooled Adverse Events Reported During the 3 Pharmacokinetic Studies (Studies IUE-P1-262, IUE-P2-134, and 02212)

Adverse Event	Possibly Related to Study Medications	Unrelated to Study Medications
Abnormal Labs:		
Elevated Platelet Count*	**1**	**0**
Increased Alkaline Phosphatase	**0**	**1**
Increased Alanine Aminotransterase	**0**	**1**
Increased Aspartate Aminotransterase	**1**	**0**
Decreased Hemoglobulin	**0**	**1**
Hematuria	**0**	**1**
Diarrhea	**0**	**1**
Eye Injury	**0**	**2**
Flatulence	**1**	**0**
Headache	**6**	**1**
Heart Rate:		
Decreased	**0**	**1**
Increased	**0**	**1**
Nasal Pharyngitis	**0**	**2**
Rhinorrhea	**1**	**0**
Skin Lesion	**0**	**1**
Sore Throat	**0**	**1**
Total Adverse Events Reported:	**10**	**14**

*Reported by the study investigator to be serious in nature.

As demonstrated in Table 4, the most frequently reported adverse event possibly related to the study medications (i.e., ibuprofen) was headache (6 reports), followed by elevated platelet count (1 report), increased aspartate aminotransferase (1 report), flatulence (1 report), and rhinorrhea (1 report).

Medical Reviewer's Comments: *Examination of the above summarized data does not reveal any potential signal or new information regarding the safety profile of ibuprofen. All of the adverse events listed in preceding table, Table 4, have been reported to occur with the use of ibuprofen. Further review of the case report form of the study subject who developed a serious adverse event (i.e., thrombocytosis) reveals that he smoked 10 packs per day of cigarettes which could account for his thrombocytosis. Thus, this adverse event was probably not study related.*

III. Literature Review

Reference:

1. Rainsford KD, Roberts SC, Brown S. Ibuprofen and paracetamol: relative safety in non-prescription dosages. J Pharm Pharmacol 1997;49:345-376.

In support of the overall safety of their proposed ibuprofen suspension, the sponsor submitted the above referenced article by Rainsford et al[1] which is a meta-analysis of pooled trials published in the world literature through 1996 which studied OTC doses of ibuprofen. Review of this meta-analysis failed to identify any new pediatric safety issues associated with the use of ibuprofen in the proposed product's target population.

Medical Officer's Comments: *No comments.*

VI. Medical Reviewer's Conclusions:

Review of the safety database generated from the 3 biopharmaceutical studies and the global safety database submitted by the sponsor in support of this product's safety profile did not reveal any new or unexpected adverse events associated with ibuprofen suspension.

VII. Medical Reviewer's Final Recommendations:

Based on the information reviewed, the current consumer safety warnings for ibuprofen are appropriate and do not need to be changed or updated for this pediatric formulation of ibuprofen suspension.

Rosemarie Neuner, MD, MPH
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CC: NDA 21-604 and 21-604 Files
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