CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201803Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Resubmission
Application Number(s)	201-803
Priority or Standard	Standard
Submit Date(s)	December 16, 2011
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Division / Office	DNCE/ODE IV
Reviewer Name(s)	Priscilla Callahan Lyon, M.D.
Review Completion Date	March 14, 2012
Established Name	Sodium Ibuprofen dihydrate
(Proposed) Trade Name	Advil
Therapeutic Class	Analgesic, Antipyretic
Applicant	Pfizer Consumer Healthcare
Formulation(s)	Tablet, Capsule-shaped tablet
Dosing Regimen	One tablet every 4 – 6 hours; if symptoms persist a second tablet may be used; maximum daily dose is 1200 mg
Indication(s)	Temporary relief of minor aches and pains due to: headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pain of arthritis; temporarily relieves fever
Intended Population(s)	Patients age 12 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The proposed drug product, ibuprofen sodium, is acceptable. The drug development program established bioequivalence between ibuprofen sodium and the previously approved ibuprofen product Aleve® Liquigels. The postmarketing data and the clinical trial support the safety of ibuprofen and ibuprofen sodium. The manufacturing deficiencies, which were the cause of the previous FDA Complete Response, have been addressed and the current EES recommendation is 'acceptable.' The recommended regulatory action from a clinical perspective is approval.

1.2 Risk Benefit Assessment

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic activity. It is available in multiple prescription and over-the-counter dosage forms and is approved for use in children as young as six months of age. The subject of this NDA is a new immediate release ibuprofen sodium (IBU Na) tablet containing 256.25 mg of sodium ibuprofen dihydrate. This tablet size provides 200 mg of ibuprofen free acid, the same amount in currently marketed over-the-counter ibuprofen tablets within the United States. The proposed dosing and indications are identical to currently marketed over-the-counter ibuprofen tablets.

Ibuprofen sodium was developed to provide faster absorption of ibuprofen and therefore a potentially faster (per the sponsor) onset of analgesia than standard ibuprofen tablets. The development program consisted of one pivotal pharmacokinetic (PK) and food effects study with the final market formulation demonstrating bioequivalence of ibuprofen Na tablets to Advil Liquigels, an approved and marketed product in the United States. These studies were reviewed as part of the initial NDA submission and found to be acceptable. The sponsor was given a Complete Response, however, after inspection of the San Juan District manufacturing facility revealed several serious deviations from cGMPs.

The sponsor was informed that in addition to responding to the manufacturing site deficiencies, the resubmission of the NDA should include a safety update. There were no additional clinical trials completed in support of the NDA resubmission and review of the safety update is the primary focus of this document.

The safety data submitted were an update to the safety information included in the original NDA submission and included post-marketing data from four databases:

1. Pfizer internal safety database (S^3)
2. World Health Organization (WHO) database
3. FDA Adverse Event Reporting System (AERS)
4. American Association of Poison Control Centers database (AAPCC)

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For each database, Pfizer reviewed the serious case reports as well as topics of special interest including: deaths, drug interactions (particularly warfarin and lithium), drug overdose, drug abuse or misuse, experience during pregnancy or lactation, use in pediatric and geriatric populations, experience in patients with renal insufficiency or cirrhosis, and ,when possible, cases specifically associated with ibuprofen sodium.

The Pfizer Internal Safety Database was searched for any report related to ibuprofen during the time period September 2, 2010 through June 30, 2011 that was classified as serious. The sponsor noted that distinguishing ibuprofen sodium case reports from those related to other ibuprofen formulations is not possible. Pfizer estimates approximately (b) (4) capsules, (b) (4) tablets, (b) (4) gel caps, (b) (4) five ml doses of oral suspension, (b) (4) one ml doses of oral drops, (b) (4) units of oral dose containers, (b) (4) chewable tablets, (b) (4) effervescent tablets, and (b) (4) grams of topical gel were distributed during the reporting period. It is not possible to estimate the number of patients treated with ibuprofen during this period.

During the reporting period, there were 45 cases associated with ibuprofen in which the patient died. Three cases involved clinical studies and 42 were spontaneous reports including 37 from literature. Many of the deaths were due to suicide attempts, drug abuse/misuse, or other medication errors. Review of the case reports with a focus on the topics of special interest as listed above, did not detect any new or unexpected safety findings.

There were 1,819 cases associated with ibuprofen submitted to the WHO database from July 2, 2010 through February 3, 2011; 1,046 cases were determined to be serious. A total of 47 countries submitted at least one case and 24 reported at least one serious adverse event (SAE). The majority of the serious case reports were from the United States (n=526; 50.3%), Germany (n=164; 15.7%), Denmark (n=79; 7.6%), and Canada (n=70; 6.7%). There were 360 serious cases in the WHO data in which the only medication listed was ibuprofen (ibuprofen-only cases). The most frequently reported preferred term (PT) in serious cases was completed suicide (n=106; 10.1%). There were 223 fatalities in the serious cases. Of these 106 were due to suicide; other listed PTs were drug toxicity, poisoning, cardiac arrest, and overdose. There were 11 ibuprofen-only cases with reported death in the WHO database – seven of these cases involved intentional overdose or suicide; the other cases are shown in Table 8.

The WHO data included 58 cases related to sodium ibuprofen; 19 were considered serious, 8 were considered not serious, and 31 had no rating. No deaths were reported. Thirteen cases were ibuprofen-only cases. Most of the serious cases were from the Germany (n=10) and the United Kingdom (n=5). The Preferred Terms for the sodium ibuprofen cases were reviewed and there were no unusual or unexpected findings. Review of the case reports with a focus on the topics of special interest as listed above, did not detect any new or unexpected safety findings. There were 16 pediatric and 16 geriatric cases that were fatal. The details and patient information for these cases were reviewed. It was noted that most of the patients received multiple concomitant medications making it impossible to identify a specific etiologic factor. Additionally, many of the cases had very similar descriptions and duplicate reporting is highly likely. Overall, the

information available for the reporting period supported the known safety profile of ibuprofen and did not identify any differences in the safety profile of the sodium salt.

From January 1, 2010 through September 30, 2010, there were 2,722 cases submitted to the AERS database which included ibuprofen; 2,004 cases were determined to be serious. The majority of the serious cases came from the United States (n=1,362), the United Kingdom (n=136), France (n=127), and Germany (n=90). There were 645 ibuprofen-only serious cases in the AERS data. There were 225 cases with reported death in the AERS data; the most frequently reported PT for cases with reported death was completed suicide (n=71), followed by Drug toxicity (n=43), Death (n=39), Poisoning (n=22), and Overdose (n=20). In 11 fatal cases, ibuprofen was the only reported medication; at least seven of these cases were intentional overdose or suicide.

The AERS data included nine cases related to sodium ibuprofen, all of which were considered serious. The limited information from these cases was reviewed and all but one patient had concomitant medications. No new safety signal or additional information of clinical significance was noted. Review of the case reports with a focus on the topics of special interest as listed above, did not detect any new or unexpected safety findings.

The AAPCC data contained 76,751 cases with ibuprofen exposure during the period from July 1, 2010 through May 31, 2011. Of these cases, 9,369 were determined to be serious and there were 23 deaths (17 of which were Intentional - Suspected suicides). Ibuprofen was ranked as the primary drug exposure that led to the contact with the Poison Control Center (PCC) in 4,579 (48.9%) of the serious cases. During the reporting period, there were 3,012 ibuprofen-only serious cases. The reason for exposure was most often Intentional - Suspected suicide (n=2,626; 87.2%). There was no way to separate sodium ibuprofen from other ibuprofen formulations in this data set. Review of the case reports with a focus on the topics of special interest as listed above, did not detect any new or unexpected safety findings.

Pfizer concludes that review of the updated information from all four databases identified no new finding impacting the safety profile of ibuprofen. The limited information on ibuprofen sodium did not suggest any apparent differences in the safety profile of ibuprofen sodium compared to other ibuprofen formulations.

In summary, Pfizer Consumer Healthcare has provided extensive post-marketing data supporting the safety of ibuprofen. No new safety signals were identified. In addition, though the exposure has been less, there is no evidence of unexpected safety concerns associated with ibuprofen sodium. The available data support a positive risk-benefit analysis for this product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No special post-market risk evaluation and mitigation strategy activities beyond routine pharmacovigilance are recommended.

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1.4 Recommendations for Postmarket Requirements and Commitments

No specific post-market requirements or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Ibuprofen (IBU) is an orally-administered propionic acid derivative, non-steroidal anti-inflammatory drug (NSAID), with analgesic, anti-inflammatory, and antipyretic activity. The subject of this NDA is a new immediate release ibuprofen sodium (IBU Na) tablet containing 256.25 mg of sodium ibuprofen dihydrate. This amount of IBU Na provides 200 mg of ibuprofen free acid, which is the amount in currently marketed over-the-counter ibuprofen tablets in the United States.

The proposed dosing is identical to that of currently marketed OTC ibuprofen 200 mg tablets: one tablet every 4-6 hours while symptoms persist, or if pain or fever does not respond to one tablet, two tablets may be used, with a maximum daily dose of six tablets (1200 mg) in adults and children 12 years of age and over. The proposed indications are also identical to those of currently marketed OTC ibuprofen 200 mg tablets/caplets/liquigels: for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, and the minor pain of arthritis, as well as the temporary reduction of fever.

The intent of this clinical program was to develop an IBU Na tablet; this tablet provides faster absorption of ibuprofen and, potentially, a faster onset of analgesia than standard ibuprofen tablets.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many approved prescription and OTC products for relief of minor pain and temporary reduction of fever. The most commonly used products are aspirin and other salicylate products, acetaminophen, and naproxen. All of these products have the same indications. Naproxen is also a nonsteroidal anti-inflammatory drug with a similar efficacy and safety profile.

2.3 Availability of Proposed Active Ingredient in the United States

Ibuprofen has been available in the United States since 1974 and available over-the-counter since 1984. Over-the-counter ibuprofen is marketed in the United States under the brand names Advil® and Motrin® and is also available as a generic product.

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2.4 Important Safety Issues with Consideration to Related Drugs

Nonsteroidal anti-inflammatory medications are commonly used in the United States. These medications are relatively safe but there are concerns in certain populations. The most common adverse reactions involve the upper gastrointestinal tract. The gastrointestinal effects are usually mild; however, in 5-15% of patients the events are severe enough to require discontinuation of the drug.

Nonsteroidal anti-inflammatory medications are also associated with a relatively high incidence of renal adverse drug reactions. These medications may cause renal impairment, particularly when combined with other nephrotoxic agents such as diuretics or ACE inhibitors. Nonsteroidal anti-inflammatory medications may also increase the risk of cardiovascular events, stroke, and congestive heart failure. Both the cardiac and renal risks are more common in older patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The initial NDA application was submitted July 1, 2010. This application included data demonstrating bioequivalence between sodium ibuprofen dihydrate and Advil Liquigels and a comparison of the pharmacokinetics of ibuprofen sodium and Motrin IB. The postmarketing data and the clinical trial supported the safety of ibuprofen and ibuprofen sodium.

The sponsor was given a Complete Response for this NDA application on April 29, 2011 after inspection of the San Juan District manufacturing facility revealed several serious deviations from cGMPs. Pfizer Consumer Healthcare (PCH) was informed that satisfactory resolution of these deficiencies would be required before the application could be approved. The sponsor was also informed that in addition to responding to these deficiencies, the resubmission of the NDA should include a safety update. This update is the primary content of the current submission and the topic of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was an electronic submission of good quality and integrity. The sponsor responded promptly to our requests for additional information. The clinical data provided was well organized and complete.

The San Juan District facility listed as the manufacturer of the finished drug product was identified as having serious deviations from cGMPs at the time of the original NDA submission. After re-inspection, these issues have been resolved and the manufacturing site status is currently rated as ‘acceptable.’

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3.2 Compliance with Good Clinical Practices

The clinical development plan consisted of one pivotal PK and food effects study. A pilot PK study evaluating prototype ibuprofen Na formulations was also performed. Results of all the clinical studies were included in the previous submission. The studies were conducted in accordance with all applicable international standards and local laws, including ICH GCP guidelines and US Federal Laws pertaining to GCP regulations. No additional clinical studies were conducted for this resubmission.

3.3 Financial Disclosures

Appropriate and adequate financial disclosure documents were submitted and reviewed. The financial arrangements did not raise any questions regarding the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new chemistry, manufacturing, pharmacology, toxicology, pharmacokinetic, stability and controls or pharmacodynamic data were included in this submission. Pfizer Consumer Healthcare confirmed in March 8, 2012 communication that there are no changes to the product formulation from the original NDA was submitted July 1, 2010.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were no additional clinical trials completed in support of this NDA resubmission. One pharmacokinetic study was conducted using the final, to-be-marketed ibuprofen Na formulation. This study (AH-09-08) was reviewed previously. In the original NDA submission, PCH also included data from a pilot study (AH-08-07) comparing three prototype formulations of ibuprofen Na to reference ibuprofen liquigels. The efficacy and safety results of both studies were discussed in the previous clinical review.

5.2 Review Strategy

This review will focus on the safety update included in the NDA resubmission.

6 Review of Efficacy

No additional efficacy data were reviewed. Bioequivalence was demonstrated in the original NDA submission.

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7 Review of Safety

Safety Summary

There were no new clinical studies and no new safety information included in the NDA resubmission. The safety data submitted were an update to the safety information included in the original NDA submission and included post-marketing data from four databases:

5. Pfizer internal safety database (S^3)
6. World Health Organization (WHO) database
7. FDA Adverse Event Reporting System (AERS)
8. American Association of Poison Control Centers database (AAPCC)

These data will be reviewed in detail in section 8.

7.6 Additional Safety Evaluations

7.6.3 Pediatrics and Assessment of Effects on Growth

At the time of the original NDA submission, PCH requested a waiver for pediatric studies for children less than 12 years of age, and stated that the product was appropriately labeled for children 12 years of age and older. The waiver request was based on the sponsor's determination that the drug product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of children from 0 to 11 years of age.

The PeRC did not agree with this rationale – specifically with the reasoning that the product would not be used by a substantial number of children. The final opinion rendered by the PeRC was that, if the company could not prove that fewer than 50,000 children use any ibuprofen product, they "must submit a request for deferral and a pediatric plan to support labeling from ages birth through sixteen years."

On March 3, 2011, the review division conveyed the PeRC recommendations to PCH. It was suggested by FDA that a pharmacokinetic bioequivalence study evaluating an IBU Na pediatric formulation in adult subjects may be adequate to establish the safety and efficacy of IBU Na in the targeted pediatric population. To address this requirement, PCH will develop an oral solution (b) (4). This formulation is intended to provide (b) (4) of the active ingredient, ibuprofen (IBU), in a salt form per (b) (4). The pharmacokinetic profile of this formulation will be assessed in a single-dose, randomized, open-label, in-patient, two-way crossover bioequivalence study in adults.

The proposed timeline is as follows:

- June 2012: Submission of the PK study protocol
- March 2013: Submission of the PK Final Study Report

As ibuprofen has been adequately studied and labeled in children from 6 months to 17 years of age, the proposal of a PK program in adults using bioequivalence to an approved product for

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children is acceptable to the clinical and clinical pharmacology reviewers. This approach was presented to PeRC on April 6, 2011 and found to be acceptable. A waiver for children less than 6 months of age was also acceptable.

8 Postmarket Experience

Pfizer Consumer Healthcare included an update to the safety information submitted with NDA 201-803 to the FDA in October, 2010 with analyses of post-marketing experience with ibuprofen from four databases: 1) the Pfizer internal safety database (S^3); 2) the World Health organization (WHO) database; 3) the US FDA Adverse Event Reporting System (AERS) and: 4) the American Association of Poison Control Centers database (AAPCC). The reporting periods covered for each search are shown in Table 1.

Table 1: Reporting Periods for Databases

Database	Reporting Period
Pfizer S^3	September 2, 2010 to June 30, 2011
WHO	July 2, 2010 to February 3, 2011
FDA AERS	January 1, 2010 to September 30, 2010
AAPCC	July 1, 2010 to May 31, 2011

Table 2 lists the topics of special interest presented for each database in the post-marketing safety update.

Table 2: Reviewed Topics of Special Interest by Database

Topic	Pfizer S^3	WHO	AERS	AAPCC
Deaths	X	X	X	X
Serious Adverse Event		X	X	X
Cases associated with Ibuprofen sodium		X	X	X
Clinical effect (CE) frequency				X
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome	X			
Drug Interactions	X	X[a]	X[a]	X
Renal Insufficiency in Patients with Cirrhosis		X	X	X
Drug Overdose	X	X	X	X
Drug Abuse or Misuse	X	X	X	X
Experience during Pregnancy or Lactation	X	X	X	X
Use in Pediatric Populations	X	X	X	X
Use in Elderly Population	X	X	X	X
Medication Errors	X	X	X	X

a Specifically Lithium and Warfarin

8.1 Pfizer Internal Safety Database (S^3)

This database was searched for any report related to ibuprofen during the time period September 2, 2010 through June 30, 2011 that was classified as serious. PCH notes that it is not possible to

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distinguish ibuprofen sodium from other ibuprofen formulations in the database so all cases in this report are related to a nonspecific ibuprofen formulation.

Pfizer estimates approximately [redacted] capsules, [redacted] tablets, [redacted] gel caps, [redacted] five ml doses of oral suspension, [redacted] one ml doses of oral drops, [redacted] units of oral dose containers, [redacted] chewable tablets, [redacted] effervescent tablets, and [redacted] grams of topical gel were distributed during the reporting period. It is not possible to estimate the number of patients treated with ibuprofen during this period.

Pfizer Consumer Healthcare completed its acquisition of Wyeth on October 16, 2009, and completed the transition to a single database for handling adverse events on November 8, 2010. This report was prepared using safety data extracted from a single safety data warehouse containing both legacy safety databases. There were 644 serious medically confirmed and non-medically confirmed cases that met the identified inclusion criteria. The prior post-marketing safety summary for ibuprofen which covered the period February 2, 2010 to September 1, 2010 included 155 serious spontaneous cases reporting ibuprofen (Advil family trade name or manufacturer unknown). The reason for the increase in the current reporting period may be due to cases reporting ibuprofen as a co-suspect in the combined larger post-integration safety database (Wyeth and Pfizer safety databases). Additionally, following integration of the Pfizer and Wyeth pharmacovigilance systems on November 8, 2010, there was a modification of case processing procedures by Pfizer with the implementation of a list of important medical events considered as 'always serious' for the purpose of expedited reporting. This list is broader than the one used in the prior Post-Marketing Safety Summary by Wyeth for ibuprofen.

Death

During the reporting period, there were 45 cases with a fatal outcome. Three cases involved clinical studies and 42 were spontaneous reports including 37 from literature. The cases are summarized in Table 3.

Table 3: Death Reports Associated with Ibuprofen from Pfizer Database

# of Cases	Details
24	Reported in 2009 Annual Report of AAPCC; described patients who died after ingesting multiple substances in suicide attempt (14), drug abuse/misuse (2), medication error (1), or unknown reasons (7)
3	Overdose of ibuprofen and other substances in suspected suicide
6	Ingestion of ibuprofen and other medications for unspecified reasons
2	Overdose of ibuprofen alone for unspecified reasons
3	Sudden death but all had thromboembolic disorders and other increased risks (increased age, history of diabetes, hypertension, CAD, prolonged ibuprofen use, etc.)
1	Concurrent infection which was likely cause of death
1	Bike accident
5	General health deterioration (multi-organ failure, liver failure, sepsis, DVT, etc.)
45	**No specific safety signal or pattern was noted**

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

During the current reporting period there was one medically confirmed case reporting DRESS Syndrome. This case involved a 46-year-old male patient who received ibuprofen for migraine. The patient's concurrent conditions included high serum ferritin and presumed pharyngitis. A few days after starting ibuprofen, he experienced severe arthralgias, exanthema-like lesions, a few buccal aphthoid lesions (aphthous stomatitis) and chills and was started on cefuroxime. As arthralgias worsened, therapy with ketoprofen and ebastine was introduced. The patient was hospitalized after the arthralgias and cutaneous lesions worsened. On admission, he presented with maculopapular eruption on limbs, arthralgias, and muscle soreness. The patient was diagnosed with crystal arthritis (crystal arthropathy) and therapy with colchicine was introduced. The patient was also diagnosed with DRESS syndrome, which was suggested by skin biopsy. All drugs were withdrawn and corticosteroids were started. At the time of the report he was recovering.

Reviewer Comment: Based upon the temporal relationship, a possible causal relationship between DRESS syndrome and ibuprofen cannot be excluded. Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome are listed as possible adverse events related to ibuprofen. The current labeling advises consumers to stop use and seek medical help for a skin reaction. This case does not identify a new safety signal.

Drug Interactions

During the current reporting period, there were 12 serious cases of drug interaction identified associated with ibuprofen use; three cases had a fatal outcome and are discussed above. The other nine cases are summarized in Table 4.

Table 4: Ibuprofen Serious Cases Reporting Drug Interactions

Category	Co-suspect Interacting Drug(s)	Preferred Term(s) (Comment from Sponsor)
Listed Interactions (3 cases)	1. Apixaban, warfarin 2.Fluinidione 3. Warfarin	1. Subdural hematoma (Apixaban and warfarin have been associated with bleeding events) 2. Subdural hematoma, Increased INR (Fluinidione has been associated with bleeding events; underlying traumatic brain injury may have contributed to he hematoma) 3. Hemorrhage
Event likely associated with patient's medical history (1 case)	Spironolactone, Losartan, Furosemide	Renal failure acute, Hepatic encephalopathy (patient had a history of hepatic cirrhosis; spironolactone has been associated with renal failure; renal failure is listed in the ibuprofen CDS)
Events likely associated with intercurrent disorders (2 cases)	1. Paracetamol, Ginseng, Ginger, Garlic 2. Valproic acid	1. Post procedure hemorrhage (patient experienced poor clot formation same day as tooth extraction; the procedure may have contributed to the event) 2. Ecchymosis, Gingival bleeding, Joint effusion, Anemia, Edema, Petechiae, Platelet disorder, Upper Resp Tract infection (Anemia and thrombocytopenia are listed in the ibuprofen CDS; the URI and Joint disorder are likely associated with intercurrent infection and the patient's underlying pain/swelling in the knee, respectively)
Event listed for ibuprofen (2 cases)	1. Multivitamin 2. HCTZ	1. Anaphylactic reaction (positive rechallenge with ibuprofen; Anaphylactic reaction is listed in the ibuprofen CDS) 2. Renal failure acute (HCTZ is also associated with acute renal failure)
Insufficient information for evaluation (1 case)	Pregabalin	Somnolence (somnolence has been associated with pregabalin)

Source: NDA 201-803 resubmission, Module 5.3.6.9, Table 2, Page 12-13

Reviewer Comment: As noted by the sponsor, the ibuprofen core data sheet (CDS) notes that "If you are taking other NSAIDs, anticoagulants, or any other drugs, consult your physician before using." The Drug Facts labeling advises consumers to ask a doctor or a pharmacist before using ibuprofen if they are taking other medications. The other co-suspect interacting drugs were each reported only once. No pattern of adverse events was identified among the remaining cases.

Drug Overdose

During the current reporting period, 51 serious reports of overdose were identified associated with ibuprofen use; nine of the cases reported a fatal outcome. These cases are discussed above. In 31 of the 51 cases, ibuprofen was the only suspect drug. The Preferred Terms used to report these cases were: Overdose (23), Accidental overdose (4), and Intentional overdose (4). Only two cases had the Preferred Term of "Accidental drug intake by a child."

Reviewer Comment: No new safety signal was identified.

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Drug Abuse, Misuse, and Drug Dependence

During the current reporting period 13 serious reports indicative of drug abuse, misuse and/or drug dependence were identified. After review by the sponsor, two cases involved drugs other than ibuprofen leaving 11 relevant cases. Nine cases were fatal and are included in the Death cases above; in these cases ibuprofen was taken with other co-suspect medications as a suicide attempt. The other two cases were:

1. A 32 year-old female with a history of anxiety, bulimia, chronic lumbago, depression, migraine, and psychotherapy received almotriptan and ibuprofen for approximately 2 years. She experienced headache and "drug abuse" and was hospitalized; according to the case narrative she recovered.
2. A 45 year-old woman with a history of "IV drug use" took 9.6-14.4 grams/day of ibuprofen for several months in the context of dental caries. She experienced Decreased appetite, Gastric ulcer, Lethargy, Microcytic anaemia, Oesophageal stenosis, Toxicity to various agents, and Renal tubular acidosis. The case outcome was unknown at the time of the report.

PCH believes ibuprofen is not generally considered a likely drug of abuse as use of the product has not been associated with psychogenic effects.

Reviewer Comment: The sponsor's conclusion that ibuprofen is not a typical drug of abuse is supported by this data. No additional action is needed at this time.

Experience during Pregnancy and Lactation

The ibuprofen CDS notes "ask your doctor before use if you are pregnant or nursing a baby" and "do not use during the last 3 months of pregnancy." During the reporting period four serious reports of exposure during pregnancy involving three unique pregnancies, were identified. There were no reports of exposure during lactation.

1. A female (age unknown) who ingested an overdose of acetaminophen 12.5 grams and ibuprofen 3.2-12.8 grams while in her third trimester (27 weeks). The baby was born with a soft palate defect. No further information was provided.
2. A 39-year-old female with a history of alcohol use, atypical migraines, and multiple sclerosis who received ibuprofen, interferon beta-1A, and acetaminophen/aspirin/caffeine (doses unknown) and experienced a spontaneous abortion.
3. A mother took ibuprofen (during gestational weeks 16-22), prednisone (throughout pregnancy), and diclofenac (during gestational weeks 0-27). Concomitant medications included adalimumab, paracetamol, and folic acid. During gestational week 27, fetal constriction of the ductus arteriosus was noted, which improved in gestational week 29 and normalized by gestational week 34 after maternal therapy with diclofenac was stopped in gestational week 27. The mother experienced oligohydramnios during gestational week 22 which resolved. The male infant was born at 35+1 weeks; he was "small" for his gestational age, required 24 hours of phototherapy for hyperbilirubinemia, and had undescended testicles.

Reviewer Comment: The labeling for ibuprofen includes warnings for use during pregnancy. These cases raise no new concerns.

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Ibuprofen Use in the Pediatric Population

During the current reporting period there were 138 serious cases involving pediatric patients (age < 17 years); two cases were fatalities and are discussed above. The age breakdown was:

- Neonate 0 to 27 days (n=2)
- Infant, 28 days to 23 months (n=14)
- Child, 2 to 11 years (n=92)
- Adolescent, 12 to 17 years (30)

Serious adverse events occurring three or more times during this reporting period in the pediatric population are shown in Table 5.

Table 5: Ibuprofen – Serious Events in Pediatric Cases

Age Group	Preferred Term	Number of Cases
Infant	Dehydration	3
Child	Urticaria*	13
	Swelling face*	7
	Toxic epidermal necrolysis*	7
	Angioedema*	6
	Renal failure acute*	6
	Stevens-Johnson syndrome*	5
	Condition aggravated	4
	Haematemesis*	4
	Blister	3
	Hypersensitivity*	3
	Hypothermia	3
	Lip swelling	3
	Overdose	3
	Rash*	3

*Adverse event is listed in the April 6, 2011 CDS
Source: NDA 201-803 resubmission, Module 5.3.6.9, Table 5, Page 16-17

There were 13 cases that reported the listed events Toxic epidermal necrolysis and Stevens-Johnson syndrome; 1 case reported both events. Many of the cases originated from France (6). One case reported that Stevens-Johnson syndrome was due to Mycoplasma infection and in another an infectious etiology could not be excluded. Two cases reported that the patients received antibiotics which have been associated with the events (clindamycin and cefaclor). In several of the cases medical history and/or concomitant medications were unknown. PCH review of the events did not identify new safety issues.

During the current reporting period, there were 16 serious cases involving pediatric patients that reported ibuprofen as a suspect medication and events encoding to Preferred Terms in the Acute renal failure SMQ. Nine of these involved children 2 to 11 years of age. There were no fatal cases. The following relevant events were reported: Renal failure acute (8), Renal failure (3), Renal tubular disorder (3), Tubulointerstitial nephritis (2), and Renal impairment (1). The ibuprofen CDS contains a warning/precaution advising patients with kidney disease to consult a

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physician before using the product and to consult a physician before use if your child has not been drinking fluids or lost fluids due to continuous vomiting or diarrhea.

PCH reviewed the cases to identify factors that could contribute to renal impairment. Six cases did not provide information regarding indication; of those cases that did provide indication, most common indications were Pyrexia (4) and Oropharyngeal pain (2). Eight cases reported medications in addition to ibuprofen that could contribute to renal impairment such as amoxicillin (3), "i.v. cephalosporin," ketoprofen, acyclovir, and carbamazepine. One case reported an ibuprofen overdose (4g). Seven cases included medical histories or concurrent events that likely contributed to renal impairment such as *Streptococcus A* erythematous sore throat, chronic nephritis, vomiting, dehydration, Lowe's syndrome, gastroenteritis with diarrhea, and dehydration/chronic autoimmune disease/multi-organ failure. In most cases, the patients had recovered/recovered with sequelae or the outcome was unknown at the time of the report. The sponsor concluded no additional action was needed at this time.

Reviewer Comment: The concern of acute renal failure associated with use of ibuprofen in children was discussed during the original NDA submission (Section 8.1 of the Clinical Review). At that time, it was decided that current labeling provided adequate warnings regarding use of ibuprofen by patients (particularly children) at risk for renal failure or who may be taking other medications. The updated information does not indicate a need to change this decision.

Ibuprofen use in the Elderly

During the current reporting period, there were 80 cases involving elderly patients (age ≥65 years). Eight cases were fatalities and are discussed above. Serious adverse events occurring three or more times during this reporting period in the elderly population are shown in Table 6.

Table 6: Ibuprofen – Serious Events in Elderly Cases

Preferred Term	Number of Cases
Overdose	5
Rash*	5
Blood creatinine increased	4
Blood pressure increased*	4
Duodenal ulcer*	4
Gastrointestinal haemorrhage*	4
Hypotension	4
Renal failure*	4
Renal failure acute*	4
Vomiting*	4
Blood urea increased	3
Drug interaction	3
Gastritis*	3
Melaena*	3
Oedema peripheral*	3

*Adverse event is listed in the April 6, 2011 CDS
Source: NDA 201-803 resubmission, Module 5.3.6.9, Table 7, Page 19

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Reviewer Comment: As noted by the sponsor, most of the adverse events are listed in the ibuprofen CDS. No new safety signal is noted.

Medication Errors
During the reporting period, 21 serious reports containing medication errors were identified. Three cases involved a prescription medication error with another product – these cases are not discussed. The relevant PTs for the other cases included Accidental exposure (5), Accidental drug intake by a child (3), Incorrect dose administered (3), Medication error (3), Drug administration error (2), Wrong technique in drug usage process (2), and Inappropriate schedule of drug administration (1). Four cases had fatal outcomes. Three of these were in the AAPCC Annual Report and limited information was provided. The other fatality resulted after Incorrect dose administration (8 pills a day for several weeks) and is included in the Death cases above.

Of the 14 remaining cases, two involved Overdose and Accidental drug intake by a child. In most of the other 12 cases, there was not adequate information to determine a reason for the error. In the cases where information was available, the errors were attributable to incorrect dose/schedule of administration or the user not following dosing instructions.

Reviewer Comment: No new safety signal was identified.

Sponsor's Conclusion
The information available for the reporting period supports the known safety profile of ibuprofen and supports the overall favorable benefit/risk profile.

Reviewer Conclusion: As noted by the sponsor, the information provided is consistent with previously known risks of ibuprofen and no new safety signal is identified.

8.2 World Health Organization (WHO) Database

The WHO data come from their Programme for International Drug Monitoring. There are currently 104 official member countries that participate in this program including the United States. Each participating country's governing body has designated a National Center for Pharmacovigilance, which is responsible for the collection of individual case reports of adverse events (AEs). Several limitations in the data should be noted:

- It is possible that the same report was entered in more than one database because the FDA is a participant in WHO's Programme for International Drug Monitoring; however, it is not possible to identify the degree of overlap between the two datasets.
- It is possible that an episode can appear in a dataset more than once if reported by different sources and assigned different case numbers. Again, it was not possible to discern the amount of duplicity within a dataset and no attempt was made by PCH to identify duplicate information.
- Appropriate interpretation of AE data depends upon an understanding of the nature and limitation of spontaneous reporting. Generally, there is underreporting of AEs but over-reporting may occur as a result of media attention and litigation.

- Given the limited amount of information available regarding the role of any of the medications identified for a case, establishing a causal relationship to any medication was not always possible.
- Cases specifically involving pregnancy were not identified in the database. While an attempt was made to identify cases that involved pregnant women, it is possible that there are cases of pregnancy that are unaccounted.

During the reporting period, there were 1,819 cases submitted to the WHO database which included ibuprofen. A total of 47 countries submitted at least one case and 24 reported at least one serious adverse event (SAE). 1,046 cases were determined to be serious. The majority of the serious case reports were from the United States (n=526; 50.3%), Germany (n=164; 15.7%), Denmark (n=79; 7.6%), and Canada (n=70; 6.7%). There were 360 serious cases in the WHO data in which the only medication listed was ibuprofen (ibuprofen-only cases). Most serious cases did not include information on age (n=157; 43.6%); 65 patients (18.1%) were <18 years of age, 116 patients (32.2%) were between the ages of 18 and 64 years, and 22 patients (6.1%) were age 65 years or older.

The most frequently reported PT in serious cases was completed suicide (n=106; 10.1%). Adverse events that occurred in ≥3% of the serious cases coded by MedDRA PT are presented in Table 7.

Table 7: WHO Adverse Events by PT in ≥ 3% of Serious Cases

Preferred Term	Number of Cases	% of Reported Adverse Events	% of Cases
Completed Suicide	106	3.3	10.1
Upper GI hemorrhage	77	2.4	7.4
Product quality issue	67	2.1	6.4
Suicide attempt	65	2.0	6.2
Vomiting	63	2.0	6.0
Drug toxicity	62	1.9	5.9
Overdose	57	1.8	5.4
Diarrhea	41	1.3	3.9
Drug abuse	40	1.3	3.8
Renal failure acute	39	1.2	3.7
Intentional overdose	37	1.2	3.5
Poisoning	36	1.1	3.4
Nausea	35	1.1	3.3
Abdominal pain upper	31	1.0	3.0

Source: NDA 201-803 resubmission, Module 5.3.6.10, Table 5, Page 25-26

Death

During the reporting period, there were 223 fatal outcomes in the 1,046 serious cases in the WHO database. Most of these were from the United States (n=187; 83.9%) and Canada (n=12; 5.4%). The most frequently reported PT for cases with reported death was completed suicide

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(n=106) followed by Drug toxicity (n=49), Poisoning (n=35), Death (n= 16), Cardiac arrest (n=14), and Overdose (n=12). There were 11 ibuprofen-only cases with reported death in the WHO database. Details (when available) of these cases are shown in Table 8.

Table 8: WHO Ibuprofen-only Death Cases

Gender	Age (years	Preferred Terms	Ibuprofen Dose
M	52	Erythema, Myocardial infarction, Vomiting	--
M	51	Analgesic drug level therapeutic, Completed suicide	--
U		Haemorrhagic stroke	800 mg
F	56	Completed suicide	--
U	64	Coma, Drug toxicity, Haematemesis. Oliguria, Overdose, Sepsis. Tachycardia	24,000 mg
F	26	Arrhythmia, Cardiac arrest, Drug toxicity, Hemodynamic instability, Hypotension, Intentional overdose, Metabolic acidosis. Loss of consciousness. Myocardial ischemia. Renal impairment	105 gm
M		Hepatic failure, Hepatitis toxic,	--
U	1.33	Apnea, Aspiration, Convulsion, Overdose, Pneumonia aspiration, Sepsis	469 mg/kg
M	26	Drug toxicity, Overdose	--
F		Gastric perforation, Intentional overdose	20,000 mg
F		Death	--

M: male, F: female, U: unknown
Source: NDA 201-803 resubmission, Module 5.3.6.10, Table 9, Page 31

During the reporting period, there were 55 cases in the WHO database that met the definition of serious because there was one or more event that was life threatening. Most of these cases were from the United States (n=28; 50.9%) and Spain (n=7; 12.7%). The most frequently reported PT for life threatening cases was renal failure acute (n=7; 12.7%) followed by Anaphylactic reaction (n=6), Asthenia (n=5), Gastric hemorrhage (n=4), and Stevens-Johnson syndrome (n=4). There were 19 ibuprofen-only cases with life threatening events in the WHO data. The most frequently reported PT in this group was Anaphylactic reaction (n=4; 21.1%) followed by Abdominal pain (n=3).

There were 375 cases in the WHO data that met the definition of serious because of hospitalization; 161 of these were ibuprofen-only cases. The most frequently reported PT in these cases was upper gastrointestinal haemorrhage (n=72 of 375, 68 of 161).

Sodium ibuprofen

Both the WHO and AERS databases were examined for potential differences in the safety profiles of sodium ibuprofen versus all other formulations of ibuprofen. The data sets were searched for product brand names of sodium ibuprofen. The WHO data had 58 cases that included sodium ibuprofen; 19 were considered serious, 8 were considered not serious, and 31 had no rating. No deaths were reported. Thirteen cases were ibuprofen-only cases. Most of the serious cases were from the Germany (n=10; 52.6%) and the United Kingdom (n=5; 26.3%).

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Reviewer Comment: The Preferred Terms for the sodium ibuprofen cases were reviewed and there were no unusual or unexpected findings.

Drug Interactions

The WHO database does not provide sufficient detail to examine drug-drug interactions. Pfizer did review the cases for any reports of interactions of ibuprofen with lithium or warfarin. Lithium was listed as a concomitant medication in three WHO cases; two were serious and are summarized below:

- Case 11234650: A male age 36 reported drug interaction, drug level above therapeutic, polydipsia, polyuria and tremor. Concomitant medications included ibuprofen (dose unknown) and lithium (800 mg). This case did not result in death. This case was from the United Kingdom and the reason the exposure was deemed serious was "other."
- Case 12428961: A female age 79 where the exposure caused or prolonged hospitalization, reported serotonin syndrome and therapeutic agent toxicity. Concomitant medications included furosemide, ibuprofen, levothyroxine, lithium, metoprolol, mirtazapine, valproic acid, and venlafaxine. This case did not result in death. This was a case from Germany.

Warfarin was listed as a concomitant medication in 24 WHO cases, 13 of which were considered serious. The most frequently reported PTs in cases where warfarin was taken along with the use of ibuprofen were drug toxicity, duodenal ulcer, haemoglobin decreased, and renal failure acute (each n=2; 15.4%).

Reviewer Comment: The interaction between ibuprofen and warfarin is well described and labeled. The reports of the thirteen serious cases were reviewed and no new safety signal or unexpected findings were noted.

Renal Insufficiency in Patients with Cirrhosis

There were no cases of renal insufficiency, renal failure, renal failure acute, or renal impairment coincident with a case of cirrhosis in the WHO database.

Drug Overdose

In the WHO data, there were 261 cases with drug overdose events associated with ibuprofen. Of these, 254 were considered serious, four were not serious, and three were not rated. Most of the serious cases were from the United States (n=144; 56.7%) and Germany (n=78; 30.7%). In the overdose events, patients ranged in age from 1.3 years to 86 years; most were between the ages of 18 and 64 years (n=151; 59.4%); 11 (4.3%) cases were age 65 years or older, and 31 (12.2%) cases were less than age 18. Age was missing for 61 (24.0%) cases. The most frequently reported PT in cases with overdose events was Completed suicide (n=106; 41.7%) followed by Suicide attempt (n=65), Overdose (n=57), Intentional overdose (n=37), Multiple drug overdose intentional (n=17), and Accidental overdose (n=15).

There were 35 ibuprofen-only cases with drug overdose events deemed to be serious in the WHO data. The most frequently reported PT was overdose (n=15; 42.9%) followed by Intentional

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overdose (n=9), Accidental overdose (n=5), Accidental drug intake by child (n=4), and Suicide attempt (n=4).

Drug Abuse or Misuse

During the reporting period, there were 55 (3.0%) cases in the WHO data with drug abuse or misuse events (PTs of drug abuse, substance abuse, alcohol abuse, and intentional drug misuse); all were considered serious. The most frequently reported PT in this group was drug abuse (n=40; 72.7%) followed by Suicide attempt (n=28), Overdose (n=24), and Intentional drug misuse (n=13). One case was an ibuprofen-only case.

Experience with Pregnancy or Lactation

During this reporting period, eight cases were received in which a pregnancy was involved. All were considered serious: none were fatal; one case with hospitalization is included above. There were four cases with "other" events and three cases of congenital anomaly/birth defects. Four cases were ibuprofen-only. Table 9 outlines the PTs and other characteristics of the pregnancy cases.

Table 9: WHO Serious Events in Pregnancy Cases

Patient Description (where reported)	Preferred Terms	Concomitant Medications
41yo female	Drug exposure during pregnancy, fetal disorder, heart rate irregular, maternal drugs affecting fetus	Ibuprofen
--	Drug exposure during pregnancy	Cefuroxime, Ephedrine, Ibuprofen (800 mg), Lidocaine, Propofol, Rocuronium, Sevoflurane, Sufentanil, Tramadol
--	Drug exposure during pregnancy	Adapalene and Benzoyl peroxide, Clindamycin, Doxycycline, Ibuprofen,
--	Drug exposure during pregnancy	Amoxicillin and Clavulanic acid, Anesthetics, general, Esomeprozole, Ibuprofen (400 mg), Ketorolac, Metamizole, Morphine, Paracetamol, Prednisone, Pregabalin, Tramadol
--	Drug exposure during pregnancy, Ductus arteriosus stenosis fetal, Overdose	Ibuprofen
--	Drug exposure during pregnancy, Ductus arteriosus premature closure, Overdose	Ibuprofen
0.67 years	Drug exposure during pregnancy, Ductus arteriosus premature closure	Ibuprofen
--	Drug exposure during pregnancy, Intentional overdose	Acetylcysteine, Alverine and Simethicone, Aripiprazole, Clorazepic acid, Codeine, Cyamemazine, Esomeprazole, Fentanyl, Flumazenil, Ibuprofen (6000 mg), Paracetamol, Suxamethonium, Tetrazepam, Venlafaxine

Source: NDA 201-803 resubmission, Module 5.3.6.10, Table 44, Page 77

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Pediatric Cases
During this reporting period, 280 cases were received regarding children less than 18 years of age; 147 were considered serious. Most of the serious WHO pediatric cases were from the United States (n=64; 43.5%) and Canada (n=31; 21.1%). The most frequently reported PT in serious pediatric cases was product quality issue (n=24; 16.3%) followed by Vomiting (n=19), Hypersensitivity (n=16), Diarrhea (n=12), Accidental overdose (n=11), and Renal failure acute (n=10). There were 16 pediatric cases that were fatal.

Elderly Cases
During this reporting period, 190 cases specific to the elderly (age 65 or older) were included in the WHO data; 113 (59.5%) were considered serious. Most of the cases were from the United States (n=42; 37.2%) and Germany (n=21; 18.6%). The most frequently reported PT was Renal failure acute (n=11, 9.7%) followed by Gastrointestinal hemorrhage (n=8), Back pain (n=7), Gastric ulcer (n=6), and Hypotension (n=6). There were 16 elderly cases that were fatalities.

Reviewer Comment: The details and patient characteristics of the fatal pediatric and geriatric cases were reviewed. Most of these patients received multiple concomitant medications. Several of the cases had very similar characteristics and were probably duplicate reports. There was no new safety signal identified.

Medication Errors
Preferred terms related to medication error events were specifically searched and 153 serious cases were found in the WHO data for this reporting period. Most were from the United States (n=60; 39.2%) and Germany (n=58; 37.9%). Most of the cases involved overdose of the medication (accidental or intentional). There were 31 fatalities.

Sponsor's Conclusion
Overall, the information available for the reporting period summarized in this report supports the known safety profile of ibuprofen and does not identify any differences in the safety profile of the sodium salt. The data reviewed in this report are similar to the data from the previous WHO reports, which covered the periods October 1, 2008 through September 30, 2009 and January 1, 2010 through April 23, 2010. In conclusion, no new safety risks were identified in the database.

Reviewer Conclusion: As noted by the sponsor, the information provided is consistent with previously known risks of ibuprofen and there is no new safety signal identified.

8.3 FDA Adverse Event Reporting System (AERS) Database

All of the reports for the AERS database come from the MedWatch System (FDA's Safety Information and Adverse Event Reporting Program). Consumers and healthcare professionals can voluntarily report AEs using the MedWatch System, while manufacturers are required by FDA regulations to report all AEs that are reported to them. The AERS dataset includes limited information on the role of medication, only identifying it as primary suspect, secondary suspect, interacting, or concomitant without assessing causality. In all of the cases reviewed, ibuprofen

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was identified as the primary or secondary suspected medication. Additionally, the trade name was searched to identify sodium ibuprofen products.

During the reporting period, there were 2,722 cases submitted to the AERS database which included ibuprofen. A total of 38 countries submitted at least one case, though 17 cases did not name a country. There were 2,004 cases determined to be serious: 926 cases with hospitalization, 225 cases that resulted in death, 115 cases with life threatening events, 38 cases with disabling events, 13 cases with congenital anomaly, and 997 cases with "other" events, (The total exceeds 2,004 as a case could have had more than one reason why it was considered serious.) The majority of the serious cases came from the United States (n=1,362; 68.0%), the United Kingdom (n=136; 6.8%), France (n=127; 6.3%), and Germany (n=90; 4.5%). There were 645 ibuprofen-only serious cases in the AERS data. All of the ibuprofen-only cases associated with pregnancy were considered serious (n=7) and are included in this report. Table 10 outlines the most commonly reported Preferred Terms for the serious cases.

Table 10: AERS Adverse Events by PT in ≥ 3% of Serious Cases

Preferred Term	Number of Cases	% of Reported Adverse Events	% of Cases
Product quality issue	560	7.7	27.9
Pyrexia	193	2.7	9.6
Vomiting	182	2.5	9.1
Drug Ineffective	138	1.9	6.9
Diarrhea	103	1.4	5.1
Nausea	98	1.4	4.9
Renal failure acute	97	1.3	4.8
Overdose	93	1.3	4.6
Abdominal pain upper	77	1.1	3.8
Completed suicide	72	1.0	3.5
Drug toxicity	70	1.0	3.5
Dyspnea	64	0.9	3.2
Malaise	63	0.9	3.1
Hypersensitivity	63	0.9	3.1

Source: NDA 201-803 resubmission, Module 5.3.6.10, Table 6, Page 27-28

For the 225 cases with reported death in the AERS data, the ages ranged from one month to 87 years; most were between the ages of 18 and 64 years (n=160; 71.1%); 16 (7.1%) cases were less than age 18, and 34 (15.1%) cases were age 65 years or older. Age was missing for 15 (6.7%) cases. The most frequently reported PT for cases with reported death was completed suicide (n=71; 31.6%) followed by Drug toxicity (n=43), Death (n=39), Poisoning (n=22), and Overdose (n=20). There were 11 ibuprofen-only fatalities. A summary of these cases is shown in Table 11.

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Table 11: AERS Ibuprofen-only Death Cases

Gender	Age (years)	Preferred Terms	Ibuprofen Dose
F	56	Completed suicide	--
U	64	Coma, Drug toxicity, Haematemesis, Oliguria, Overdose. Sepsis, Tachycardia	--
U		Hypovolemic shock, Overdose, Self injurious behavior	--
M	1	Product quality issue	1 tsp PO 1-2 doses prior to event
M		Necrotizing colitis, Sepsis neonatal	--
F	26	Drug toxicity, hemodynamic instability, Metabolic acidosis, Overdose	--
M	1.08	Death, Loss of consciousness, Product quality issue	--
F	26	Arrthymia, Cardiac arrest, Drug toxicity, Hemodynamic instability, Hypotension, Intentional overdose, Loss of consciousness, Metabolic acidosis, Myocardial ischemia	105 gm
U		Renal impairment, Death, Product quality issue	--
U	1.33	Apnea, Aspiration, Convulsion, Overdose, Pneumonitis, Sepsis	469 mg/kg
U	1.33	Apnea, Convulsion, Overdose, Pneumonia aspiration, Sepsis	469 mg/kg

M: male, F: female, U: unknown
Source: NDA 201-803 resubmission, Module 5.3.6.10, Table 12, Page 33-34

Reviewer Comment: Most of these cases were related to overdose of medication. Some cases seem similar and may be duplicates. There are also cases which are probably overlapping with WHO case reports.

There were 115 cases in AERS that were considered serious because one or more event was life threatening. The most frequently reported PT for cases with life threatening events was gastrointestinal haemorrhage (n=12; 10.4%) followed by Metabolic acidosis (n=11), Pyrexia (n=11), Hypotension (n=10), Nausea (n=10), Product quality issue (n=10), and Vomiting (n=10). There were 37 ibuprofen-only cases with life threatening events. The most common PT for this group was Product quality issue (n=7).

Sodium Ibuprofen

The AERS data had nine cases that included sodium ibuprofen, all of which were considered serious. Only one of these cases was an ibuprofen-only case and there were no deaths.

Reviewer Comment: The limited information from these cases was reviewed. All but one patient had concomitant medications. No new safety signal or additional information of clinical significance was noted.

Drug Interactions

The AERS database does not provide sufficient detail to examine drug-drug interactions completely. The data is usually incomplete and it is difficult (or impossible) to determine which medications a patient was taking at the time of the adverse event and even more difficult to assess causality. Pfizer conducted specific reviews for reports of interactions between ibuprofen

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and lithium or warfarin. There were two serious cases in AERS where lithium was taken along with ibuprofen:

- In this case from Spain, a female age 44 reported amnesia, anxiety, disorientation, drug abuse, drug dependence, drug toxicity, dysarthria, fall, incorrect dose administration and treatment noncompliance. Concomitant medications included acetaminophen, alprazolam, clomipramine, clonazepam, clorazepate, duloxetine, ibuprofen (up to 600 mg/day), lithium (not recorded), oxaliplatin, paroxetine, pregabalin, and quetiapine. This case did not result in death.
- A male age 56 reported accident, anxiety, depression, dizziness, drug withdrawal syndrome, fall, gastrointestinal haemorrhage, hyperhidrosis, pain, panic attack, rotator cuff syndrome, strabismus, tinnitus, and vision blurred. Concomitant medications included buprenorphine and naloxone, citalopram, dapsone, ibuprofen (dose unknown) and lithium (dose unknown). This case did not result in death and was from the United States.

Warfarin was listed as a concomitant medication in 20 AERS cases, 18 of which were considered serious. The most frequently reported PT in cases where warfarin was taken with ibuprofen was international normalization ratio increased (n=6; 33.3%). Most of these patients (n=11) were age 65 years or older, on multiple medications, and had many other diagnoses.

Reviewer Comment: As noted previously, the interaction between ibuprofen and warfarin is well described and labeled. The reports of these serious cases were reviewed and no new safety signal or unexpected findings were noted.

Renal Insufficiency in Patients with Cirrhosis

There were no cases of renal insufficiency, renal failure, renal failure acute, or renal impairment coincident with a case of cirrhosis in the AERS database.

Drug Overdose Events

In the AERS data, there were 286 cases with drug overdose events that were coincident with use of ibuprofen; 248 were considered serious. Most of the cases were from the United States (n=151; 60.9%), the United Kingdom (n=42; 16.9%) and Germany (n=19; 7.7%). Patients ranged in age from 8 months to 84 years; age was not provided in 40 (16.1%) cases; 145 were between the ages of 18 and 64 years (58.5%); 47 were less than 18 years (19.0%) and 16 (6.5%) were 65 years or older. There were 94 fatalities. The most frequently reported PT in serious cases with overdose events was Completed suicide (n=71; 75.5%) followed by Overdose (n=20), Accidental overdose (n=3), Intentional overdose (n=3), and Multiple drug overdose intentional (n=2).

There were 61 ibuprofen-only drug overdose cases. Patients involved in serious ibuprofen-only drug overdose cases ranged in age from 1 year to 76 years; 17 (27.9%) were less than 18 years of age [16 were less than 10 years of age], 25 (41.0%) were between the ages of 18 and 64 years, and two (3.3%) were age 65 years or older. Age was not recorded for 17 (27.8%) cases.

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Drug Abuse or Misuse

There were 29 cases in the AERS data with drug abuse or misuse events (PTs of drug abuse, substance abuse, alcohol abuse, and intentional drug misuse). All were considered serious; most (n=22, 75.9%) were from the United States. In these 29 cases, the most frequently reported PT was intentional drug misuse (n=15; 51.7%) followed by Drug abuse (n=12) and Substance abuse (n=2). Three of the cases were ibuprofen-only cases.

Experience with Pregnancy or Lactation

During this reporting period, 20 cases reports were received in AERS in which a pregnancy was involved. All were considered serious though none were fatal. One case with hospitalization and nine cases with congenital anomalies/birth defects are included. There were 11 cases with "other" events. Seven cases were ibuprofen-only. Table 12 summarizes the case reports and the PTs.

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Table 12: AERS Serious Events in Pregnancy Cases

Patient Description (when reported)	Preferred Terms	Concomitant Medications
--	Drug exposure during pregnancy, Limb hypoplasia congenital	Eletriptan, Ibuprofen
M	Drug exposure during pregnancy, Condition aggravated	Acetaminophen, Ibuprofen
--	Drug exposure during pregnancy; Limb hypoplasia congenital	Eletriptan, Ibuprofen
F 31 years	Drug exposure during pregnancy, Pregnancy	Acetaminophen, Dexamethasone, Tobramycin, Drospirenone, Ethinylestradiol, Fusidic Acid, Hexamide, Ibuprofen (400 mg), Metaclopramide,
F	Drug exposure during pregnancy, Abortion spontaneous	Ibuprofen, Interferon-Beta-1a, Topiramate
F 27 years	Drug exposure during pregnancy, Abortion spontaneous	Ibuprofen, Interferon-Beta-1a, Topiramate
F 27 years	Drug exposure during pregnancy, Antepartum haemorrhage, Abortion spontaneous	Ibuprofen, Interferon-Beta-1a, Topiramate
--	Drug exposure during pregnancy, Ductus arteriosus premature closure	Ibuprofen (7.2 gm)
--	Drug exposure during pregnancy, Ductus arteriosus stenosis fetal	Ibuprofen (6 gm)
F 36 years	Drug exposure during pregnancy, Abortion induced	Amlodipine, Hydrochlorthiazide and Olmesartan, Ibuprofen (1200 mg)
F 36 years	Drug exposure during pregnancy, Abortion induced	Amlodipine, Ibuprofen, Olmesartan
--	Drug exposure during pregnancy	Ibuprofen (7.2 gm)
M	Drug exposure during pregnancy. Convulsion neonatal, Microcephaly, Oxygen saturation decreased, Resp distress	Ibuprofen, Naproxen
F	Drug exposure during pregnancy	Ibuprofen
F	Drug exposure during pregnancy, Premature labor, Overdose, Ductus arteriosus premature closure	Ibuprofen
F	Drug exposure during pregnancy, Abortion spontaneous	Ibuprofen
--	Drug exposure during pregnancy, Ductus arteriosus stenosis fetal	Ibuprofen (6 gm)
F 41 years	Drug exposure during pregnancy	Cefuroxime, Ephedrine, Ibuprofen, Lidocaine, Propofol, Rocuronium, Sevolflurane, Sefentanil, Tramadol
F 27 years	Drug exposure during pregnancy, Antepartum haemorrhage, Urinary tract infection, Uterine hematoma	Ibuprofen (qd & 400 mg TID, sometimes 600 mg all at once), Levothyroxine
M	Drug exposure during pregnancy, Limb asymmetry	Ibuprofen (mother treated with 400 mg TID for pain relief during first trimester0, Levothyroxine, Progesterone

Source: NDA 201-803 resubmission, Module 5.3.6.10, Table 44, Page 79-80

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Reviewer Comment: Several of these cases have similar characteristics and are likely duplicates.

Pediatric Cases
During this reporting period, 727 cases were received in AERS regarding children less than 18 years of age. Of these, 626 were considered serious: 16 fatalities, 41 cases with life threatening events, 291 cases with hospitalization, 12 cases with disabling or incapacitating events, and 367 cases with "other" events. Most of the cases were from the United States (n=503; 80.4%) and France (n=38; 6.1%). The most frequently reported PT was product quality issue (n=343; 54.8%) followed by Pyrexia (n=115), Vomiting (n=100), Drug ineffective (n=80), Diarrhea (n=50), Convulsion (n=43), and Abdominal pain upper (n=40). There were 242 ibuprofen-only serious cases in this group with four reported deaths. These cases are included Table 11.

Elderly Cases
During this reporting period, 389 cases specific to the elderly (age 65 or older) were identified in the AERS data; of these, 251 (64.5%) were considered serious. Most of the serious AERS elderly cases were from the United States (n=132; 52.6%) and the United Kingdom (n=29; 11.6%). The most frequently reported PTs in serious elderly cases were renal failure acute (n=31; 12.4%), Gastrointestinal haemorrhage (n=19), and Hypotension (n=14). There were 62 ibuprofen-only serious elderly cases.

Medication Errors
Preferred terms related to medication error events were specifically searched and 251 serious cases were found in the AERS data for this reporting period. Most were from the United States (n=149; 59.4%) and the United Kingdom (n=42; 16.7%). Most of the cases involved overdose of the medication (accidental or intentional). There were 33 fatalities.

Sponsor's Conclusion
Overall, the information available for the reporting period summarized in this report supports the known safety profile of ibuprofen and does not identify any differences in the safety profile of the sodium salt. The data reviewed in this report are similar to the data from the previous AERS reports, which covered the periods July 1, 2008 through June 30, 2009 and July 1, 2009 through December 31, 2009. In conclusion, no new safety risks were identified in the database.

Reviewer Conclusion: The information provided is consistent with previously known risks of ibuprofen and there is no new safety signal identified.

8.4 American Association of Poison Control Centers (AAPCC) database

Pfizer provided an update from the AAPCC database covering the period from July 1, 2010 through May 31, 2011. The AAPCC data come from the National Poison Data System (NPDS), a comprehensive uniform data set of cases recorded by 57 poison control centers throughout the United States and in Puerto Rico. The dataset consisted of human exposure reports (cases) that included a mention of ibuprofen. Only reports with clinical effects (CEs) that were determined to

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be serious [i.e., death, major effect (a life-threatening event), and/or hospitalizations] or associated with pregnancy were reviewed in detail. The search does have limitations:

- A case may appear more than once if reported by different sources. It was not possible to discern the amount of duplicity and the sponsor made no attempt to identify duplicate cases.
- The AAPCC data do not identify drugs/medications by either their trade name or their full generic name so there was no way to separate sodium ibuprofen from other ibuprofen formulations.

The AAPCC data contained 76,751 cases with ibuprofen exposure during the reporting period. Of these cases, 9,369 were determined to be serious, including 8,926 hospitalizations, 420 major effects and 23 deaths (17 of which were Intentional - Suspected suicides). There were 147 cases associated with pregnancy, 52 of which were considered serious cases because they included hospitalizations. One case associated with pregnancy had major effects but no cases associated with pregnancy included death.

Ibuprofen was ranked as the primary drug exposure that led to the contact with the Poison Control Center (PCC) in 4,579 (48.9%) of the serious cases. Among the serious cases, exposures (to all drugs taken, not specifically or solely ibuprofen unless ibuprofen was the only drug taken) were most often recorded as Intentional - Suspected suicide (n=8,297; 88.6%), and most of the exposures took place in the patient's own residence (n=8,912; 95.1%).

During the reporting period, there were 3,012 ibuprofen-only serious cases. The reason for exposure was most often Intentional - Suspected suicide (n=2,626; 87.2%) and the exposure most often occurred in the patient's own residence (n=2,876; 95.5%). Most patients were between the ages of 18 and 64 years (n=1,838; 61.0%); 1,126 (37.4%) were less than 18 years of age, and 22 (0.7%) cases age 65 years or older. Age was missing for 26 (0.9%) cases. The most common clinical effects in the ibuprofen-only serious cases were Vomiting (n=483; 16.0%), Abdominal pain (n=423), Nausea (n=410), Drowsiness/lethargy (n=371), and Tachycardia (n=358).

Sodium Ibuprofen

There was no way to separate sodium ibuprofen from other ibuprofen formulations in this data set.

Clinical Effect (CE) Frequency

Up to 131 different CEs, which are signs, symptoms, or laboratory abnormalities, can be coded for each AAPCC case. Clinical effects are not recorded using MedDRA terms. During the reporting period, there were a total of 31,596 CEs in the 76,751 cases with ibuprofen exposures, of which 17,100 CEs were associated with the 9,369 serious cases. If a CE was reported as "related" that meant the effect was deemed related to some or all of the drugs taken by the individual. The most commonly reported CEs in the serious cases are shown in Table 13.

Table 13: AAPCC Reported Clinical Effects in >3% of Serious Cases (n=9,369)

Clinical effects	Number of Cases	% of Cases	% 'Not Related'	% 'Related'	% Unknown
Drowsiness/lethargy	2675	28.6	1.0	95.5	3.5
Tachycardia	1968	21.0	4.0	86.7	9.3
Vomiting	1786	19.1	2.2	92.9	4.8
Nausea	1306	13.9	1.1	94.9	3.9
Abdominal Pain	932	9.9	2.6	89.7	7.7
Hypertension	706	7.5	21.2	56.7	22.1
Agitated/irritable	571	6.1	7.2	76.5	16.3
Other	503	5.4	13.1	72.6	14.3
Hypotension	467	5.0	5.8	78.6	15.6
Electrolyte Abnormality	456	4.9	6.8	72.4	20.8
Confusion	421	4.5	3.3	88.6	8.1
Acidosis	337	3.6	3.0	86.4	10.7
Slurred Speech	310	3.3	2.9	93.5	2.6

Related means the CE was felt related to some or all of the drugs taken by the individual
Source: NDA 201-803 resubmission, Module 5.3.6.11, Table 3, Page 15

During the reporting period, ibuprofen was mentioned as the primary (n=1), secondary (n=11), or tertiary (or lower) drug exposure in 23 cases with reported death. The most common reason for exposure was Intentional - Suspected suicide (n=17; 73.9%). The dose of ibuprofen was reported in only five of these cases.

There were 9,337 cases with associated with ibuprofen that resulted in hospitalizations. Of these, 8,926 cases with effects that caused hospitalization did not also include death or a major effect. In this sub-group, ibuprofen was ranked as the primary drug exposure that led to the contact with the PCC in 4,475 (50.1%) of the cases and the secondary drug exposure in 2,395 (26.8%). The most common reason for exposure in the cases with hospitalization was Intentional - Suspected suicide (n=7,936; 88.9%). For the ibuprofen-only hospitalization cases that did not overlap with death or major effect, the majority (n=1,864; 62.8%) were admitted to a psychiatric care facility.

Drug Interactions

The AAPCC data set has insufficient details to examine drug-drug interactions. There were no cases where both lithium and warfarin were listed as medications that were coincident with the use of ibuprofen. There were 18 cases in where warfarin was listed as concomitant medication; 13 of the cases were considered serious and Intentional - Suspected suicide was the reason for exposure in all 13 cases. There was one death:

- A 23 year old male with intentional-suspected suicide the reason for exposure who was admitted to a CCU; medications included warfarin, calcium antagonists, other types of skeletal muscle relaxant, ibuprofen (tertiary - dose unknown), anticholinergic drugs, other types of antidepressant, other antihistamines, beta blockers systemic antibiotics, phenothiazines, and antihyperlipidemics. Clinical events included: asystole, cardiac arrest, fever/hyperthermia, hypotension, respiratory depression, and vomiting.

There were 81 cases where lithium was listed as a concomitant medication; 61 were considered serious. The most common reason for exposure was Intentional - Suspected suicide (n=58;

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95.1%). There were no deaths. The most common clinical effect noted was drowsiness/lethargy (n=31, 50.8%) followed by tachycardia (n=13), confusion, and vomiting (n=7 for each).

Renal Insufficiency in Patients with Cirrhosis
Information on cirrhosis was not provided in the AAPCC database.

Drug Overdose Events
The AAPCC data do not include information specifically pertaining to overdose. Drug abuse and misuse were captured only as the reason for exposure. The information contained in the dataset was related to the entire exposure and can not be attributed to any one drug.

Intentional Drug Misuse
During the reporting period, there were 2,568 cases where the reason for exposure was intentional - misuse. Of these, 202 were serious cases. There were two deaths:

- A 27 year old female who overdosed on multiple medications including acetaminophen, ibuprofen, and ethanol.
- A 73 year old man whose medications included aspirin and ibuprofen. Other clinical effects included acidosis, agitation, cardiac arrest, increased creatinine, fever, tachypnea, and hypotension.

One pregnancy was reported; a 20 year old female whose only medication was ibuprofen. There was no reported medical outcome.

Experience with Pregnancy or Lactation
There were 147 cases with pregnancy, including 88 (59.9%) ibuprofen-only cases. The majority were ages 18-64 (n=111; 75.5%), with 17 (11.6%) being less than 18 years of age. Details on medical outcomes are shown in Table 14. Of the cases with pregnancy, exposure was most often related to Intentional – Suspected suicide (n=84; 57.1%). There were no pregnancy cases with reported death.

Table 14: Medical Outcomes for AAPCC Cases with Pregnancy (n=147)

Medical Outcome	Number of Cases	% of Cases
Major Effect	1	0.7
Minor Effect	35	23.8
Moderate Effect	11	7.5
No Effect	38	25.9
Not followed, judged as nontoxic exposure	9	6.1
Not followed, minimal clinical effects possible	33	22.5
Unable to follow, judged as a potentially toxic exposure	17	11.6
Unrelated effect, the exposure was probably not responsible for the effect(s)	3	2.0

Source: NDA 201-803 resubmission, Module 5.3.6.11, Table 28, Page 39-40

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Pediatric Cases
There were 56,164 (of the 76,751) cases in the AAPCC data of ibuprofen exposures involving children less than 18 years of age; of these 2,779 (4.9%) were serious. The serious pediatric cases constituted 29.7% of all the serious cases and the most common reason for exposure for serious pediatric cases was Intentional - Suspected suicide (n=2,380; 85.6%). The majority were 10-18 years old (n=2,601; 93.6%) and 178 (6.4%) were 0 to 9 years old. There were three deaths; two 17 year-old females and one 16 year-old male, all of whom overdosed on ibuprofen and multiple other medications in suicide attempts.

Of the serious pediatric cases, 1,126 were ibuprofen-only cases. Most (83.7%) were Intentional-Suspected suicide and the majorities (92%) were ages 10 – 18 years. There were no deaths. Two of these cases were 16 year-old females with suicide attempts who were pregnant. The most common clinical effects reported in the serious ibuprofen-only pediatric cases were Abdominal Pain (n=198, 17.6%), Vomiting (n=191), Nausea (n=160), Drowsiness/Lethargy (n=126), and Tachycardia (n=108).

Elderly Cases
There were 636 cases (0.8% of the total) in the AAPCC data of ibuprofen exposure in patients age 65 years and older. Eighty one (12.1%) of these were serious and there were four deaths. The majority of the serious cases (and all four deaths) were Intentional – Suspected suicides (n=56). Of the serious cases, there were 22 ibuprofen-only cases. The most common reason for exposure in this group was Intentional – Suspected suicide (n=13); there were no deaths in this group.

Medication Errors
There were 15,036 cases with medication errors associated with use of ibuprofen identified in the AAPCC data. Of these, 53 were considered serious and there was one death. The most common reason for exposure in the serious cases was unintentional therapeutic error (n=50). The single death occurred in a 45 year-old female who took ibuprofen and acetaminophen. There were 14 ibuprofen-only serious cases; nine of these were in patients < 18 years of age. The most common reason for exposure in these cases was unintentional – therapeutic error (n=13).

Sponsor's Conclusion
In spite of the limitations of the AAPCC database, the data from this reporting period are consistent with the known safety profile of ibuprofen and similar to the data from the previous AAPCC reports of February 1, 2009 – January 31, 2010 and February 2, 2010 – June 30, 2010. No new safety risks were identified.

Reviewer Comment: The information provided is consistent with previously known risks of ibuprofen and there is no new safety signal identified.

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8.5 Conclusion

Sponsor's Overall Conclusion
Review of the updated information from all four databases identified no new finding impacting the safety profile of ibuprofen. The limited information on ibuprofen sodium did not suggest any apparent differences in the safety profile of ibuprofen sodium compared to other ibuprofen formulations. As no new safety risks were identified and the safety profiles for ibuprofen and ibuprofen sodium do not appear different, the current ibuprofen Drug Facts labeling does not require change and is acceptable for use with ibuprofen sodium as proposed.

Reviewer Conclusion: As noted, there was no new safety signal identified in the postmarketing data reviewed. The safety information on ibuprofen sodium is limited, but there is no suggestion of a difference in the safety of this formulation compared to other ibuprofen formulations which have been found to be safe for OTC use.

9 Appendices

9.2 Labeling Recommendations

No new labeling was included in this submission. The proprietary name and the most recent proposed labeling (submitted April 22, 2011) were found to be acceptable prior to the previous Complete Response to the NDA issued by FDA on April 29, 2011. There are no new or additional labeling recommendations at this time. A representative Drug Facts label is shown in Figure 1.

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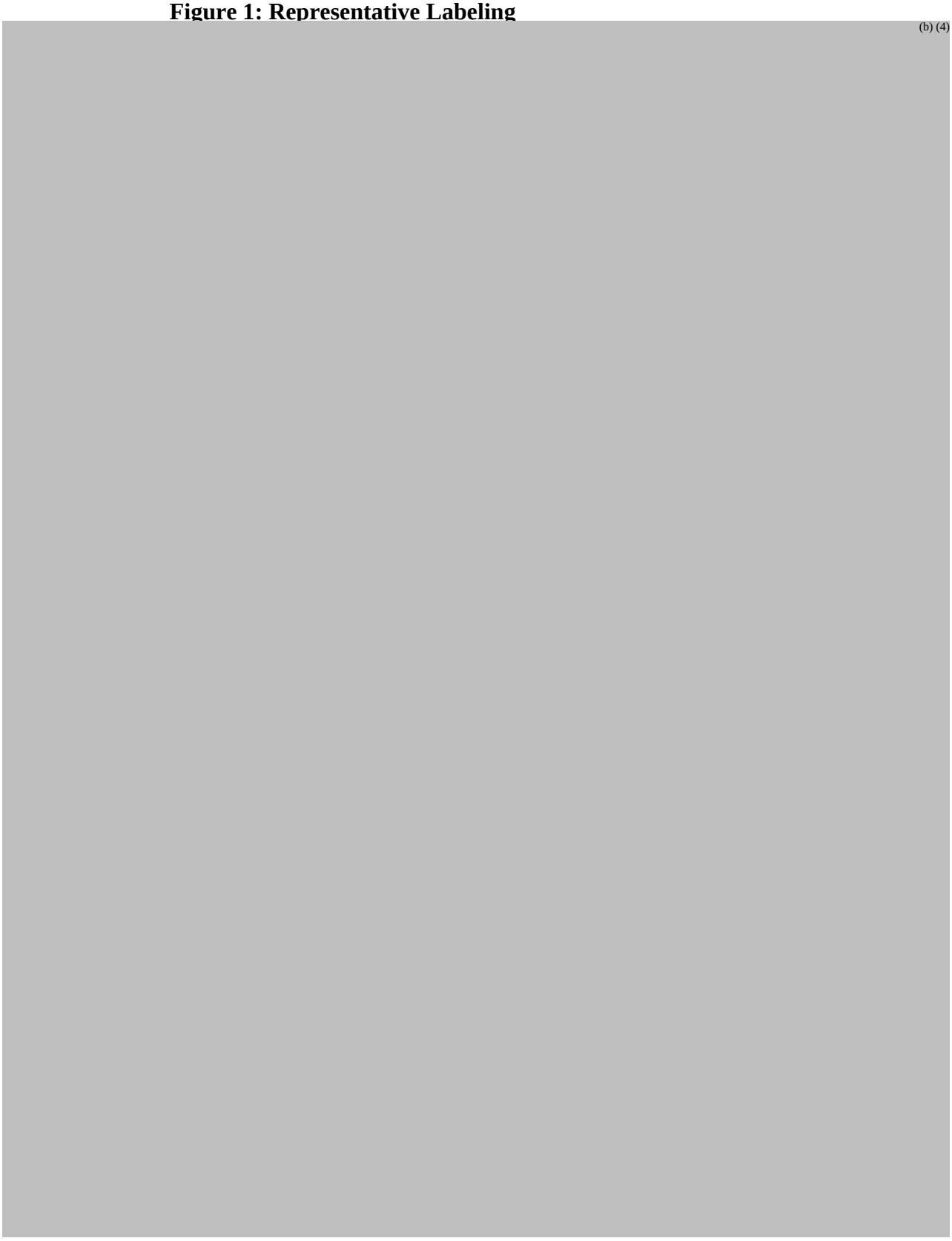
Figure 1: Representative Labeling

(b) (4)



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/s/

PRISCILLA C LYON
03/14/2012

LESLEYANNE FURLONG
03/14/2012
I concur with Dr. Callahan Lyon's recommendation for approval from a clinical perspective. No new safety signals have been identified and labeling is acceptable.

Summary Review for Regulatory Action

Date	April 29, 2011
From	Joel Schiffenbauer
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	201803
Applicant Name	Pfizer Consumer Healthcare
Date of Submission	June 30, 2010
PDUFA Goal Date	May 1, 2011
Proprietary Name / **Established (USAN) Name**	Advil/ sodium ibuprofen dihydrate
Dosage Forms / Strength	Tablet/ ibuprofen 200 mg
Proposed Indication(s)	1. minor aches and pains 2. fever reducer 3.
Action/Recommended Action for NME:	*Complete response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	P. Callahan-Lyons/ L. Furlong
Statistical Review	
Pharmacology Toxicology Review	C. Li/ W. Harrouk/ P. Brown
CMC Review/OBP Review	J. Hill/ T-M Chen
Microbiology Review	J. Cole/ S. Langille
Clinical Pharmacology Review	D. Lee/ S. Doddapaneni
DDMAC	
DSI	
CDTL Review	L. Furlong
OSE/DMEPA	M. Siahpoushan/ Z. Oleszczuk/ K. Taylor/ C. Holquist
OSE/DDRE	
OSE/DRISK	
Other DNRD labeling	K. Phelan/ M. Chang

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

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APPEARS THIS WAY ON ORIGINAL

Signatory Authority Review Template

1. Introduction

The applicant, Pfizer Consumer Healthcare (PCH), has developed a tablet containing ibuprofen as a sodium salt. The tablet contains 200 mg of ibuprofen, provided as 256 mg sodium ibuprofen dihydrate (Na IBU). PCH supported the safety and efficacy of the Na IBU by showing bioequivalence to Advil Liqui-Gels, that is a reference-listed product.

This review will cover the following: 1) the PK data submitted which includes a pivotal PK and food effects study demonstrating bioequivalence to Advil Liqui-Gels (the pivotal PK study also included a Motrin IB arm to provide comparative bioavailability data to the tablet that Advil Liqui-Gels relied upon for its approval); 2) a review of the safety data submitted; 3) a discussion of the pediatric development program and PREA related issues.

2. Background

Ibuprofen has been available in the United States since 1974 and available over-the-counter since 1984. In this application, PCH proposes to market a sodium salt of ibuprofen (Na IBU) in oral tablet formulation for consumers who are 12 years old and older. This new immediate release ibuprofen sodium (IBU Na) tablet containing 256.25 mg of sodium ibuprofen dihydrate. This amount of IBU Na provides 200 mg of ibuprofen free acid, which is the amount in currently marketed over-the-counter ibuprofen tablets within the United States. The proposed dosing is identical to that of currently marketed OTC ibuprofen 200 mg tablets. The proposed indications are also identical to those of currently marketed OTC ibuprofen 200 mg: for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, and the minor pain of arthritis, as well as the temporary reduction of fever.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. The excipients meet quality specifications and are suitable for use in manufacture of the drug product. The microbiology reviewer found the microbial testing and specifications for this non-sterile tablet acceptable and recommended approval. *There are no outstanding issues.*

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4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team found the excipients to be acceptable and there were no impurities or degradants of concern. I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Pivotal PK study AH-09-08 compared the to-be marketed formulation of Na IBU to Advil Liqui-Gels and Motrin IB (all in the fasted state), and compared Na IBU to Advil Liqui-Gels (both in the fed state). The study demonstrated that Na IBU is bioequivalent to Advil Liqui-Gels for the active moiety by Cmax and AUC. The mean Tmax for Na IBU (about 35 minutes) was shorter than the mean Tmax for Advil Liqui-Gels (about 50 minutes). This difference is not anticipated to have an impact on the dosing interval as the PK curves overlap at 6 hours (see Figure 1 and Table 1 in appendix).

In the fed state, Na IBU remains bioequivalent to Advil Liqui-Gels, and both products show a similar food effect. Labeling for Advil Liqui-Gels does not instruct consumers to dose on an empty stomach; in fact, the labeling states, “when using this product, take with food or milk if stomach upset occurs.” (see Table 1 in appendix).

Therefore, I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

No specific efficacy studies were submitted for this application. PCH demonstrated bioequivalence of Na IBU to Advil Liqui-Gels. Advil Liqui-Gels was approved in the United States for OTC use in April 1995 under NDA 20402. Advil Liqui-Gels is listed in the FDA’s Orange Book as a reference listed drug. See section 5 (above), Figure 1 and Table 1 in appendix.

8. Safety

The reader is referred to the MO review by Dr. Priscilla Callahan-Lyon for a detailed analysis of the safety data provided. In general, the primary reviewer concluded that there were no new safety signals noted. I agree.

The applicant provided a summary from four databases for the reporting periods noted in the table below. A four-month safety update submitted during the review cycle provided an additional 4 (WHO) to 7 (Wyeth) months of data for the postmarketing databases.

Postmarketing Databases

Database	Reporting Period
Wyeth S[3]	01 February 2009 to 01 February 2010
WHO	01 October 2008 to 30 September 2009
AERS	01 July 2008 to 30 June 2009
AAPCC	01 February 2009 to 31 January 2010

The WHO and AERs periods represent data available publically at the 1-Feb-2010 cut off date for this report.

There are 2 issue of note discussed by the applicant, and reviewed by the MO, that will be mentioned here.

The applicant's review of the literature and case reports led the applicant to add language about the possibility of increased lithium levels in patients receiving lithium and ibuprofen. Current OTC ibuprofen labeling instructs the consumer to ask a doctor before use if he or she is taking any other medication; lithium labeling informs healthcare providers of the potential interaction. Therefore, the MO recommends that no change in OTC labeling is necessary. I agree.

Regarding acute kidney injury and children, the applicant noted that hypovolemia was a recurring observation in children who had renal impairment associated with NSAID therapy. No change in OTC labeling is planned because OTC labeling for pediatric formulations already contains the advice to ask a doctor if a child has not been drinking fluids, has lost a lot of fluid due to vomiting or diarrhea, or is taking a diuretic. The primary reviewer and the applicant concluded that current ibuprofen labeling is adequate to address the lithium and renal issues, and I agree.

In order to identify any potentially unique adverse events associated with ibuprofen sodium, the applicant examined both the WHO and AERS databases for cases specifically associated with the use of ibuprofen sodium. The WHO data had 49 cases that included ibuprofen sodium. One case included death; in this case, medications included ibuprofen sodium and acetaminophen. Death was due to hepatic failure and attributed to accidental overdose. The AERS database contained 15 cases associated with the use of ibuprofen sodium. Three deaths were reported; all involved other drugs as well. One death was attributed to hepatic failure and accidental overdose, one to large intestinal hemorrhage, and one to toxic shock syndrome.

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According to the primary reviewer, “The WHO and AERS data show a similar pattern. The most common events are those related to medication overdose, frequently associated with a suicide attempt. Cases of renal failure are noted but the frequency is not greater than expected for this drug class.”

I agree that there does not appear to be any new, significant safety signal unique to ibuprofen sodium, that requires additional OTC labeling.

9. Advisory Committee Meeting

No advisory committee meeting was held for this product.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients 0 to < 17 years old unless this requirement is waived, deferred, or inapplicable. After discussions it was determined that a new salt is a new active ingredient and therefore triggers PREA.

The applicant requested a waiver for pediatric studies for children less than 12 years of age, and stated that the product was appropriately labeled for children 12 years of age and older. The waiver request was based on the determination that the drug product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of children from 0 to 11 years of age.

PeRC did not agree with the rationale for children less than 12 years of age based on the lack of data to show that the product would not be used by a substantial number of children (defined by the Agency as 50, 000; see the guidance document *How to Comply with the Pediatric Research Equity Act*).

The final opinion rendered by the PeRC was that, if the company could not prove that fewer than 50,000 children use any ibuprofen product, they “must submit a request for deferral and a pediatric plan to support labeling from ages birth through sixteen years.”

Although there were differences of opinion within the Division (see CDTL review) as to whether a waiver should be granted, it does not appear that, based on the reasons for granting a waiver as enumerated in PREA, there are options other than requesting the data to show that use will be by less than 50, 000 children. PREA does not provide for other options for granting waivers that some of the reviewers considered appropriate in this situation. Therefore I do not agree with the CDTL and agree with PeRC.

On March 3, 2011, the review division conveyed the PeRC recommendations to the applicant

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by teleconference. The Agency suggested that a pharmacokinetic bioequivalence study evaluating an IBU Na pediatric formulation in adult subjects may be adequate to establish the safety and efficacy of IBU Na in the targeted pediatric population. To address this requirement, Pfizer Consumer Healthcare (PCH) will develop an oral solution (b) (4) This formulation is intended to provide (b) (4) of the active ingredient, ibuprofen (IBU), in a salt form per (b) (4). The pharmacokinetic profile of this formulation will be assessed in a single-dose, randomized, open-label, in-patient, two-way crossover bioequivalence study in adults.

The proposed timeline is as follows:

- Submission of the PK study protocol June 2012
- Submission of the PK Final Study Report March 2013

As ibuprofen has been adequately studied and labeled in children from 6 months to 17 years of age, the proposal of a PK program in adults using bioequivalence to an approved product for children is acceptable to the clinical and clinical pharmacology reviewers. This approach was presented to PeRC on April 6, 2011 and also found to be acceptable. A waiver for less than 6 months of age was also acceptable. I agree with this approach.

11. Other Relevant Regulatory Issues

A 483 form was issued to the applicant. Several observations appear to be pertinent to this product (although this product was not named specifically in the 483):

1) Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.
2) The responsibilities and procedures applicable to the quality control unit are not fully followed.
3) Investigations of an unexplained discrepancy did not extend to other batches of the same drug product an other drug products that may have been associated with the specific failure or discrepancy.
4) There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

At the time this review was written, the recommendation from Compliance for the inspection of the manufacturing facility was “withhold.” If this recommendation does not change before the action date, the recommendation from chemistry will be complete response.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of

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Nonprescription Regulation Development (DNRD) provided labeling reviews. In general, the label conformed to the currently approved Advil label.

In compliance with 21 CFR 201.64, the Na IBU label contains a statement in "Other information" that each tablet contains sodium 22 mg. At the maximum of 6 tablets per day a consumer's sodium intake would be 134 mg/day which falls below the amount 140 mg of sodium per day that requires a warning to alert people who must restrict sodium.

DMEPA denied the initial proposed proprietary name, "(b) (4)," because they found it misleading pursuant to 21 CFR 201.10(c)(3) because the word (b) (4) implies superiority over similar products. I agree with this conclusion. Subsequently the applicant submitted the name (b) (4) which DMEPA has also rejected. Subsequently, the applicant submitted 3 additional names as follows: 1) Advil; (b) (4) . DMEPA finds that each of those options would be acceptable, and at the time of writing of this review the applicant has chosen to use the name Advil. I also find this acceptable.

The DNRD labeling review team provided a number of recommendations which I agree with (see review), including the statement of identity (which was extensively discussed with chemistry and agreed on) and the use of the word "tablet" (b) (4) (also discussed with chemistry).

13. Decision/Action/Risk Benefit Assessment

Based on the information presented in this submission, the applicant has provided adequate data to support approval of this product. The PK studies demonstrate equivalence to the reference listed product and the chemistry review did not identify any specific issues. The safety information does not suggest that ibuprofen sodium would have a safety profile that differs from any other approved ibuprofen formulations.

However, it is recommended that this application receive a complete response based on the findings by compliance enumerated in the 483 provided to the applicant. In addition, when approved, the applicant will have a PREA commitment to develop an age appropriate formulation for use in children under 12 years of age.

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Appendix

Figure 1. Mean concentration versus time by treatment arm

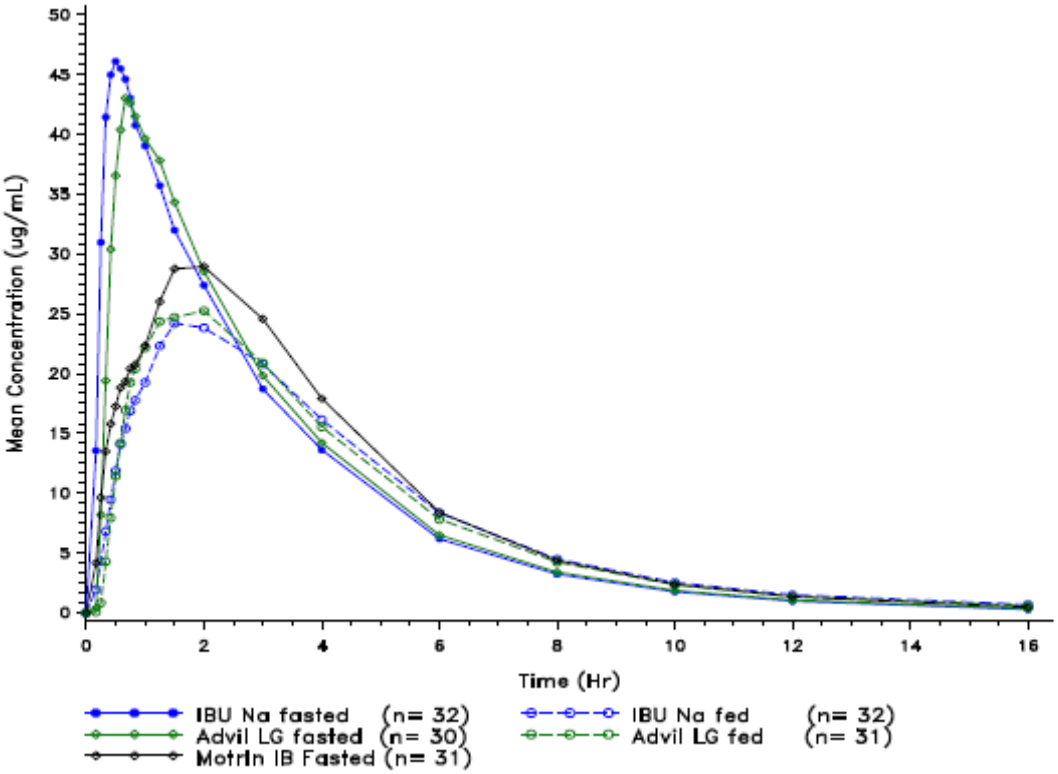

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Table 1. Summary of PK parameters by treatment arm, Study AH-09-08

Treatment/state	AUCI (ug.h/mL) mean(s.d.)	AUCL (ug.h/mL) mean(s.d.)	Cmax (ug/mL) mean(s.d.)	Tmax (min) mean(s.d.)
A: Na IBU fasted (n=32)	147.40 (30.1)	145.89 (29.6)	50.62 (10.3)	34.75 (14.4)
B: Na IBU fed (n=32)	130.71(29.2)	127.28 (28.6)	31.49 (8.8)	114.97 (72.5)
C: Advil liquigel fasted (n=30)	145.67 (33.3)	143.97 (32.6)	48.62 (11.2)	49.87 (29.8)
D: Advil liquigel fed (n=31)	128.96 (30.6)	125.94 (29.7)	34.19 (9.7)	111.00 (67.9)
E: Motrin IB fasted (n=31)	145.66 (32.4)	143.44 (32.2)	37.38 (7.8)	126.45 (66.9)
A/C Ratio^ (90% CI)	102.0 (99.1,105.0)	102.0 (99.1,105.0)	104.2 (96.6,112.4)	--
A/E Ratio^ (90% CI)	101.9 (99.0,104.9)	102.5 (99.6,105.5)	135.0(125.2,145.5)	--
B/D Ratio^ (90% CI)	102.1 (99.2,105.1)	101.7 (98.8,104.7)	91.2 (84.6,98.3)	--

^Based on fitted log-transformed parameters.

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JOEL SCHIFFENBAUER
04/29/2011

Cross-Discipline Team Leader Review

Date	March 14, 2011
From	Lesley-Anne Furlong
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA/BLA # Supplement#	201803
Applicant	Pfizer Consumer Healthcare
Date of Submission	30-Jun-2010
PDUFA Goal Date	1-May-2010
Proprietary Name / Established (USAN) names	To be determined/sodium ibuprofen dihydrate
Dosage forms / Strength	Ibuprofen 200 mg
Proposed Indication(s)	1. temporarily relieves minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, and minor pain of arthritis 2. temporarily reduces fever
Recommended:	*Approval, contingent on satisfactory final labeling and satisfactory results of manufacturing site inspection*

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1. Introduction

The applicant, Pfizer Consumer Healthcare (PCH), has developed a tablet containing ibuprofen as a sodium salt. The tablet contains 200 mg of ibuprofen, provided as 256 mg sodium ibuprofen dihydrate (Na IBU). Proposed labeling includes the indications and general class labeling of approved ibuprofen 200 mg tablets and capsules.

PCH supported the safety and efficacy of the Na IBU by showing bioequivalence to Advil Liqui-Gels, an ibuprofen oral capsule that is a reference-listed product in FDA's Orange Book. PCH also compared the bioavailability of Na IBU to the bioavailability of Motrin IB tablets, the product upon which Advil Liqui-Gels relied for approval.

2. Background

Ibuprofen is a non-selective nonsteroidal anti-inflammatory drug (NSAID) that was approved as a prescription product in the United States in 1974, and approved as an OTC product in 1984. For consumers ages 12 years and older, the OTC dosing instructions for ibuprofen 200 mg tablets are: 1 tablet every 4 to 6 hours; if pain or fever does not respond to 1 tablet, 2 tablets may be used; do not exceed 6 tablets in 24 hours. Age-appropriate ibuprofen formulations are approved for children down to 6 months of age.

In this application, PCH proposes to market a sodium salt of ibuprofen (Na IBU) in oral tablet formulation for consumers who are 12 years old and older. Na IBU has a faster rate of ibuprofen absorption than marketed ibuprofen tablets and the same rate of absorption as Advil Liqui-Gels, a liquid-filled capsule. PCH speculates that the faster absorption will provide a faster onset of analgesia compared with marketed ibuprofen tablets; however, the development program did not test this hypothesis, and PCH has not requested labeling for a faster onset of analgesia. (PCH did not pursue a faster onset of analgesia claim for Advil Liqui-Gels, either.)

At a maximum use of Na IBU of 6 tablets a day, a consumer's sodium intake would be 134 mg/day. This amount falls below the amount 140 mg of sodium per day that requires a warning to alert people who must restrict sodium (21 CFR 201.64).

The new clinical data in the submission includes a pilot PK study of early prototypes and a pivotal PK and food effects study demonstrating bioequivalence to Advil Liqui-Gels. The pivotal PK study also included a Motrin IB arm to provide comparative bioavailability data to the tablet (Motrin IB) that Advil Liqui-Gels relied upon for its approval.

The applicant developed Na IBU under IND 105341. A pre-NDA meeting was held on December 15, 2009 between the IND holder (at that time, Wyeth Consumer Healthcare) and FDA. Agreements reached included

- The NDA should contain a postmarketing safety update covering a 12-month time period with the lockdown date for adverse event data being as close as possible to the NDA.

submission date. To the extent possible, postmarketing data related to ibuprofen sodium that is marketed elsewhere should be analyzed separately.

- Six months accelerated stability data and six months long-term stability data would be acceptable for filing.
- If additional stability data were submitted during the review cycle, FDA could not guarantee review during the review cycle.
- A pediatric plan is required.
- The application will need to cite reliance on Motrin IB, the product that Advil Liqui-Gels relied upon when it was approved by the 505(b)(2) route.
- FDA may approve the NDA using the International Nonproprietary Name as the established name provided that the applicant has started an application for a USAN name.

Na IBU is marketed in Europe but not by the applicant; the applicant presents publicly available literature and postmarketing reports for sodium ibuprofen in the submission.

3. CMC/Device

The drug substance is sodium ibuprofen dihydrate. The drug product is an immediate release tablet submitted in two different presentations: round and "caplet"-shaped. The composition is the same for both presentations. Both presentations contain ibuprofen 200 mg, provided as 256 mg of sodium ibuprofen dihydrate. The applicant has proposed (b) (4) different combinations of bottle types and dosage counts. According to the chemistry review, based on the real-time and supporting stability data provided, an expiry period of 24 months is acceptable when the product is stored in the various proposed container/closure systems. The excipients meet quality specifications and are suitable for use in manufacture of the drug product. The microbiology reviewer found the microbial testing and specifications for this non-sterile tablet acceptable and recommended approval.

Dissolution data were submitted for both tablets. The round tablet was used in the pivotal bioequivalence (BE) study. The CMC biopharmaceutics reviewer found the dissolution methodology acceptable. The round tablets showed comparable mean dissolution profiles to the caplets, which provided a satisfactory link to the BE data. The dissolution specifications were not acceptable on initial review; the applicant was asked to (b) (4) the dissolution specifications from "Q= (b) (4) % at (b) (4) min to Q= (b) (4) % at 15 min." The applicant agreed to implement the requested specifications during a teleconference on 2/25/11, and submitted an amendment to that effect on 3/3/11. There were no outstanding biopharmaceutics issues.

The only outstanding CMC issues at the time this review was finalized were:

- Acceptable cGMP from the Office of Compliance (manufacturing site inspection)
- Final labeling

4. Nonclinical Pharmacology/Toxicology

According to the pharmacology/toxicology review team, "Based on the previous human use experience for ibuprofen, the agency's previous review of the nonclinical information on ibuprofen, as well as the lack of novel significant toxicity findings for Na IBU during the current review, the present NDA can be approved from the nonclinical perspective."

The only new nonclinical pharmacology/toxicology data in the application came from a single oral dose rat toxicology study performed to support an application to a non-U.S. regulatory agency. The study identified a NOAEL of 200 mg/kg, which is approximately 30 times higher than the maximum single human OTC dose (400 mg). Higher dose levels of Na IBU (500 & 600 mg/kg) caused a more pronounced toxicity profile when compared to the currently available ibuprofen. The observed toxicity was primarily in the gastrointestinal tract.

The pharmacology/toxicology review team found the excipients to be acceptable and there were no impurities or degradants of concern.

5. Clinical Pharmacology/Biopharmaceutics

The two clinical studies included in the application were pharmacokinetic (PK) studies, including a pilot study of prototype formulations and a pivotal study of the formulation chosen for marketing. The clinical pharmacology team deemed the application "acceptable," and identified no labeling or approvability issues. According to the clinical pharmacology team leader, the "acceptable" recommendation corresponds to a recommendation for approval. Following inspections of both the clinical and the analytical study sites, FDA's Division of Scientific Investigation recommended that the data from pivotal study be accepted for review.

Table 1 summarizes the main features of the PK studies.

Table 1. Clinical Trials Submitted to Support NDA 201803

Study	Design	Arms	N
AH-08-07	Pilot PK (U.S.) Open-label, 4 way crossover	Four arms prototypes: • Prototype I • Prototype II • Prototype III • Advil Liqui-Gels	17 subjects, male and female, ages 23 to 44 • 16 subjects provided PK data for at least 2 treatment periods • 1 subject discontinued
AH-09-08	Pivotal PK and food effects study (U.S.) Open-label, 5-way crossover	Five arms • Na IBU (fasted) • Advil Liqui-Gels (fasted) • Motrin IB (fasted) • Na IBU (fed) • Advil Liqui-Gels (fed) Dose was 2 tablets or 2 Liqui-Gels (400 mg IBU)	36 subjects enrolled, male and female • 35 subjects dosed • 32 subjects provided PK data • 4 subjects discontinued during or after period I

Source: Created by CDTL from Applicant's Clinical Overview

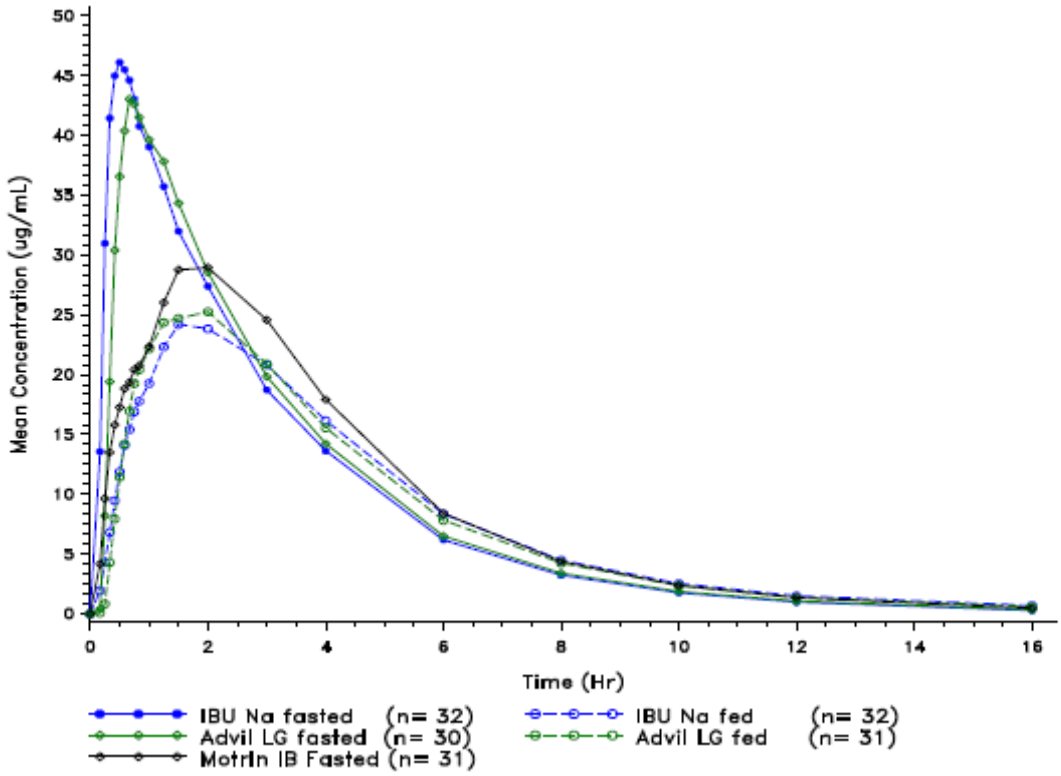
Study AH-08-07 compared three prototypes of Na IBU to Advil Liqui-Gels. All three prototypes were bioequivalent to Advil Liqui-Gels by Cmax and AUC criteria. All three prototypes had a shorter Tmax (means ranging from 33 to 39 minutes) compared with Advil Liqui-Gels (mean Tmax 52 minutes). "Based on the results of the pilot PK study, and considering manufacturing capabilities, a formulation of Na IBU tablets (b) (4) for this application.

Study AH-09-08 compared the to-be marketed formulation of Na IBU to Advil Liqui-Gels and Motrin IB (all in the fasted state), and compared Na IBU to Advil Liqui-Gels (both in the fed state). The study achieved its primary objective by demonstrating that Na IBU is bioequivalent to Advil Liqui-Gels for the active moiety by the standard criteria of Cmax and AUC. As expected from the pilot study, the mean Tmax for Na IBU (about 35 minutes) was shorter than the mean Tmax for Advil Liqui-Gels (about 50 minutes); however, the earlier Tmax should not impact the 6-hour dosing interval as the PK curves essentially coincide at 6 hours (see Figure 1).

In the fed state, Na IBU remains bioequivalent to Advil Liqui-Gels, and both products show a similar food effect. Labeling for Advil Liqui-Gels does not instruct consumers to dose on an empty stomach; in fact, the labeling states, "when using this product, take with food or milk if stomach upset occurs." Table 2 and Figure 1 present the findings in greater detail.

Advil Liqui-Gels, Na IBU, and Motrin IB produced the same systemic exposure, measured by AUC in the fasting state; however, both Advil Liqui-Gels and Na IBU were absorbed faster than Motrin IB, measured by Cmax and Tmax in the fasting state.

Figure 1. Mean concentration versus time by treatment arm



Source: Applicant's Clinical Overview, Section 2.5, page 11

Table 2. Summary of PK parameters by treatment arm, Study AH-09-08

Treatment/state	AUCI (ug.h/mL) mean(s.d.)	AUCL (ug.h/mL) mean(s.d.)	Cmax (ug/mL) mean(s.d.)	Tmax (min) mean(s.d.)
A: Na IBU fasted (n=32)	147.40 (30.1)	145.89 (29.6)	50.62 (10.3)	34.75 (14.4)
B: Na IBU fed (n=32)	130.71(29.2)	127.28 (28.6)	31.49 (8.8)	114.97 (72.5)
C: Advil liquigel fasted (n=30)	145.67 (33.3)	143.97 (32.6)	48.62 (11.2)	49.87 (29.8)
D: Advil liquigel fed (n=31)	128.96 (30.6)	125.94 (29.7)	34.19 (9.7)	111.00 (67.9)
E: Motrin IB fasted (n=31)	145.66 (32.4)	143.44 (32.2)	37.38 (7.8)	126.45 (66.9)
A/C Ratio^ (90% CI)	102.0 (99.1,105.0)	102.0 (99.1,105.0)	104.2 (96.6,112.4)	--
A/E Ratio^ (90% CI)	101.9 (99.0,104.9)	102.5 (99.6,105.5)	135.0(125.2,145.5)	--
B/D Ratio^ (90% CI)	102.1 (99.2,105.1)	101.7 (98.8,104.7)	91.2 (84.6,98.3)	--

^Based on fitted log-transformed parameters.

Source: Applicant's Clinical Overview, Section 2.5, page 10

CDTL comments: Na IBU is bioequivalent to Advil Liqui-Gels; therefore, Na IBU can rely on Advil Liqui-Gels to establish its safety and effectiveness. The shorter time to a higher maximum concentration compared with Motrin IB could potentially provide earlier onset of analgesia; however, the applicant did not choose to explore this possibility in a clinical trial. The earlier Tmax should not impact the 6-hour dosing interval as the PK curves essentially coincide at 6 hours. (see Figure 1)

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

PCH demonstrated efficacy by showing bioequivalence of Na IBU to Advil Liqui-Gels. (see Section 5, above)

Advil Liqui-Gels is a liquid-filled capsule containing ibuprofen 200 mg as a potassium salt and as a free acid. Advil Liqui-Gels was approved in the United States for OTC use in April 1995 under NDA 20402. Advil Liqui-Gels is listed in the FDA's Orange Book as a reference listed drug, which means that applicants seeking approval of a generic drug may rely on a demonstration of bioequivalence to Advil Liqui-Gels to support marketing approval. Advil Liqui-Gels and Na IBU, although different salts and different dosage forms, share the same

active ingredient, and the active ingredient is present in the same molar dose. By showing the same rate and extent of absorption for both products in Study AH-09-08, PCH has satisfactorily demonstrated bioequivalence. (See 21 CFR 320.23)

8. Safety

The main support for safety of Na IBU was the bioequivalence of Na IBU tablets to the approved Advil Liqui-Gels capsules. The applicant also provided a literature summary and a summary of postmarketing spontaneous reports; no new safety issues for ibuprofen or ibuprofen sodium products were identified. Details of the safety findings are provided by Dr. Priscilla Callahan-Lyon in her primary clinical review; a brief summary follows.

8.1 Safety Data from Clinical Trials Submitted in the Application

The clinical data in the submission were provided in studies AH-08-07 and AH-09-08. A total of 52 generally healthy subjects were exposed to at least one dose of a Na IBU formulation.

AH-08-07 was a single dose, crossover PK study of three prototype formulation of Na IBU compared with Advil Liqui-Gels. Seventeen subjects were dosed and 16 subjects completed all four study periods. No deaths, other serious adverse events, or discontinuations due to adverse events were reported. Five subjects reported a total of 14 adverse events, all rated as mild except for one report of nausea and vomiting, rated as moderate. The only adverse event reported more than once was nausea, reported by three subjects.

Study AH-09-08 was a single-dose, five-way crossover, PK study of the Na IBU (fasting and fed) compared with Advil Liqui-Gels (fasting and fed) and Motrin IB (fasting only). Thirty-five subjects received study medication; 32 received all five treatments. No deaths or other serious adverse events were reported. Two subjects discontinued for adverse events after receiving Na IBU in the fed state; one subject discontinued due to nausea and vomiting and another discontinued due to a headache. Fifteen subjects reported a total of 31 adverse events. The adverse events were rated as mild except for one report each of nausea, vomiting, headache, or blurred vision, all rated as moderate. The most commonly reported adverse event was headache (n=6), with 2 reports of headache in the Na IBU fasted arm, and 1 in each of the remaining arms. There were 11 reports of any gastrointestinal AEs, distributed without a clustering of events in any treatment arm.

The primary reviewer evaluated laboratory findings and vital sign data and did not find any clinically significant issues. There were no ECGs performed in either study.

Comment: The primary reviewer concluded that there were no new safety signals noted in the PK studies. I concur.

8.2 Postmarketing Summary

The applicant provided a summary from four databases for the reporting periods noted in Table 3, as requested by FDA at the preNDA meeting. A four-month safety update submitted during the review cycle provided an additional 4 (WHO) to 7 (Wyeth) months of data for the postmarketing databases.

Table 3. Postmarketing Databases

Database	Reporting Period
Wyeth S[3]	01 February 2009 to 01 February 2010
WHO	01 October 2008 to 30 September 2009
AERS	01 July 2008 to 30 June 2009
AAPCC	01 February 2009 to 31 January 2010

The WHO and AERs periods represent data available publically at the 1-Feb-2010 cut off date for this report.

Source: The Applicant's submission, Section 5.3.6 post-marketing-experience.pdf, page 5

Comment: Postmarketing data have substantial limitations, including, but not limited to, overlap among cases in the databases, duplication of reports within databases, incomplete reports, unknown extent of underreporting, unknown number of people exposed, lack of control group to provide baseline rate of occurrence of event, stimulated reporting from lawsuits or media reports, etc.

Wyeth Database

The Wyeth database contains spontaneous reports (foreign and domestic), literature reports, and reports from investigational studies. Over the year and 7 months reported, Wyeth distributed approximately (b) (4) adult tablets or capsules, (b) (4) children's chewable tablets, (b) (4) mL of liquid/suspension/drops, (b) (4) grams of gel, and 940 mL of spray. It was not possible to distinguish ibuprofen sodium from ibuprofen in the Wyeth database.

No unexpected signals were identified. Details of the analysis of the Wyeth database can be found in the primary clinical review. Overall, there were 30 reports of death, and the most frequently reported cause of death (n=16) was suicide. Most of the remaining deaths were confounded by coexisting conditions, such as pneumonia or lung cancer, or the use of other drugs. In some cases, reports of death included adverse events that are known risks of NSAID use, such as hemorrhagic gastrointestinal events and renal failure.

As part of the safety update, the applicant performed focused reviews of two issues:
1) drug interaction between ibuprofen and lithium
2) children and acute kidney injury

Details of the focused reviews can be found in the primary clinical review. Summaries follow.

Regarding lithium, the applicant's review of the literature and case reports led the applicant to add language about the possibility of increased lithium levels in patients receiving lithium and ibuprofen. Current OTC ibuprofen labeling tells the consumer to ask a doctor before use if he

or she is taking any other medication; lithium labeling informs healthcare providers of the potential interaction. As lithium is a chronic medication with a narrow therapeutic window, consumers using lithium will be under a physician's care. No change in OTC labeling is necessary.

Regarding acute kidney injury and children, the applicant's review included a search of multiple literature databases as well as their internal postmarketing database. The review noted that hypovolemia was a recurring observation in children who had renal impairment associated with NSAID therapy. As a result of the review, the applicant stated that their reference safety information is being updated to advise consultation with a physician before ibuprofen use if the child may be in a hypovolemic state. No change in OTC labeling is planned because OTC labeling for pediatric formulations already contains the advice to ask a doctor if a child has not been drinking fluids, has lost a lot of fluid due to vomiting or diarrhea, or is taking a diuretic.

Comment: The primary reviewer and the applicant concluded that current ibuprofen labeling is adequate to address the lithium and renal issues. I concur.

WHO and AERS Databases

The reader is referred to the primary clinical review for a detailed review of the summary data from the WHO Database and the AERS Database. Only highlights of the review will be mentioned here. These databases contain primarily spontaneous reports related to any marketed brand of ibuprofen (not only the applicant's products) and there is considerable overlap between the two databases. Table 4 shows the number of cases and serious cases in the initial submission and the safety update for both databases.

Table 4. Summary of Case Reports to WHO and AERS Database

	WHO 10/1/08 – 9/30/09	WHO 1/1/10 – 4/23/10	AERS 7/1/08 – 6/30/09	AERS 7/1/09 – 12/31/09
# Cases mentioning ibuprofen	1351	294	1397	648
# Serious cases	919	233	1344	633
# Countries reporting	40	18	40	31
#(%) Serious cases				
from United States	492 (53.5)	77 (33.1)	704 (52.4)	234 (37)

Source: Page 47 of primary clinical review

Regarding reports in which ibuprofen was the only drug listed, the WHO database contained 28 reports of death and the AERS database contained 22 reports of death. The most frequent preferred term for other adverse events in these reports was overdose.

The primary clinical review compared the pattern of adverse events between databases and evaluated adverse events by age. No unexpected findings were noted except for a cluster (n=14) of reports of osteonecrosis in the AERS summary. The primary reviewer did a search of AERS and determined that all reports of osteonecrosis were the same 42-year-old female patient from the United Kingdom who was taking sertraline and ibuprofen. The ibuprofen was started for knee pain and it is not clear, therefore, whether the osteonecrosis antedated ibuprofen use.

The applicant examined both databases for cases associated with the use of ibuprofen sodium. Both WHO and AERS databases contained reports for ibuprofen sodium under 17 different brand names. The WHO data had 49 cases that included ibuprofen sodium. One case included death; in this case, medications included ibuprofen sodium and acetaminophen. Death was due to hepatic failure and attributed to accidental overdose. The AERS database contained 15 cases associated with the use of ibuprofen sodium. Three deaths were reported; all involved other drugs as well. One death was attributed to hepatic failure and accidental overdose, one to large intestinal hemorrhage, and one to toxic shock syndrome.

Comment: According to the primary reviewer, "The WHO and AERS data show a similar pattern. The most common events are those related to medication overdose, frequently associated with a suicide attempt. Cases of renal failure are noted but the frequency is not greater than expected for this drug class. There does not appear to be a new, significant safety signal that requires additional OTC labeling." I concur.

American Association of Poison Control Centers (AAPCC) Database

The AAPCC Database contains reports from 60 poison control centers throughout the United States and Puerto Rico. This database did not allow differentiation between ibuprofen and ibuprofen sodium products. The reader is referred to the primary clinical review for a detailed review of these data.

The submission summarized 122,779 cases reporting use of ibuprofen; 39 were reports of death, and one death included ibuprofen as the only medication listed. Among patients with SAEs, exposures to all drugs taken were most often recorded as Intentional – suspected suicide.

There were no cases of death in children. Approximately 30% of all serious cases involved children. Among the ibuprofen-only cases, most (83%) were Intentional–suspected suicide.

There were 22,591 reports of medication error in the AAPCC Database over the entire reporting periods.

Comment: According to the primary reviewer, "The AAPCC data follows a pattern similar to the WHO and AERS data. Intentional overdose/suicide attempt cases are the most common reason for clinical events. There is no significant safety signal identified that would require a change in OTC labeling." I concur.

Additional Safety Information

To support the gastrointestinal safety of Na IBU, PCH provided summaries of two postmarketing studies they conducted to assess the safety implications the higher Cmax of Advil Liqui-Gels compared to standard ibuprofen products. Because Na IBU is bioequivalent to Advil Liqui-Gels, PCH reasoned that these two studies provide support for the safety of the Na IBU.

The first study compared ibuprofen tablets, liquigels, and placebo. There were approximately 400 subjects in each arm; subjects received 400 mg ibuprofen or placebo three times daily for 10 consecutive days. Gastrointestinal AEs were reported in 16% of the placebo subjects, 20% of the liquigel subjects, and 18% of the tablet subjects.

The second study of similar design compared ibuprofen liquigels, celecoxib, and placebo. The incidence of GI adverse events was 21.9% in the liquigel group, 21.3% in the placebo group, and 18.5% in the celecoxib group.

Additionally, PCH provided a review of published endoscopy studies involving various ibuprofen products, the details of which can be found in the primary clinical review. The relevance of endoscopy studies to gastrointestinal adverse events can be debated, and cross-study comparisons have limitations. Nonetheless, PCH concluded that the studies were reassuring as ibuprofen sodium did not appear to produce more endoscopic lesions than other ibuprofen products.

Comment: The postmarketing studies and the literature revealed no unexpected gastrointestinal safety findings.

Overall, the safety data did not reveal any new safety signal, and current ibuprofen safety labeling is acceptable.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients 0 to < 17 years old unless this requirement is waived, deferred, or inapplicable.

A question about whether the application triggered PREA came up during an internal discussion among members of the review division. The question hinged on whether or not Na IBU contains the same active ingredient as marketed ibuprofen products. From a scientific standpoint, Na IBU has the same active ingredient. The review team agreed that the active ingredient is ibuprofen; there is no reason to believe that sodium treats fever or pain. This agreement about the active ingredient is, in fact, the underpinning of the applicant's proposal to gain marketing approval for Na IBU based on bioequivalence studies. The team sought an FDA legal opinion on the point from the lawyers who advise the PeRC.

The legal opinion was as follows: "We have always said that a new salt is a new active ingredient and this longstanding policy has applied not only in the PREA context but also in

the generic approval context (where ANDAs are required to have the same active ingredient as their reference listed drug)." … "Thus, consistent with longstanding policy, the sodium salt of ibuprofen is a new active ingredient, and PREA is triggered by this application."

The applicant requested a waiver for pediatric studies for children less than 12 years of age, and asserted that the product was appropriately labeled for children 12 years of age and older. The clinical review team agreed with the applicant, and put forward the following PREA rationale to FDA's Pediatric Review Committee (PeRC):

> The drug product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of children from 0 to 11 years of age.

The review team anticipated that the PeRC would agree. (b) (4)

Nonetheless, the PeRC did not agree with the rationale for children less than 12 years of age. In the following few paragraphs, I summarize events related to the pediatric review to date.

While the PeRC agreed that the drug product does not represent a meaningful therapeutic benefit over existing therapies, Dr. Robert Nelson from the PeRC asserted that "not likely to be used in a substantial number of children" contingency had not been adequately addressed. In guidance, FDA has interpreted "substantial" to mean more than 50,000. Dr. Nelson interpreted "the drug product" to mean any ibuprofen product, and noted that the applicant had not proven that ibuprofen would not be used in more than 50,000 children.

While there was some discussion among PeRC members about Dr. Nelson's interpretations, the final opinion rendered by the PeRC was that, if the company could not prove that fewer than 50,000 children use any ibuprofen product, they "must submit a request for deferral and a pediatric plan to support labeling from ages birth through sixteen years. If a deferral request and plan is submitted, the Sponsor must also submit evidence that planned or ongoing studies are proceeding, projected date for the submission of the pediatric assessment (deferral date), and applicant certification that this is true. " Although the opinion was not put to a formal vote by the PeRC, no one on the PeRC raised objections to this summary opinion. The PeRC sent a summary e-mail containing the advice above to the review division.

Comment: Given the applicant's data on distribution of their own ibuprofen formulations, the applicant will be unable to prove that fewer than 50,000 children use any ibuprofen product or might use this particular product. Certainly more than 50,000 children use any OTC painkillers/fever reducers. Potential usage of this particular product would depend on marketing decisions. (As noted above, the PeRC took a different stance and accepted the argument for a waiver for cetirizine orally disintegrating tablets, approved in 2010.)

(b) (4)

On March 3, 2011, the review division conveyed the PeRC recommendations to the applicant by teleconference. At the time this review was finalized, the applicant's response is pending.

Comments: Developing and studying a pediatric formulation of Na IBU is unnecessary because of the plethora of appropriately labeled, single-ingredient ibuprofen products that are available for children. Ibuprofen products for children are supported by adequate safety and efficacy data, and available products are labeled down to six months of age. FDA's Orange Book lists more than twenty single-ingredient ibuprofen products, produced by numerous companies, for children. There is no known benefit to Na IBU over existing ibuprofen products.

Adding one more ibuprofen product to the OTC market will add, albeit incrementally, to consumer confusion, and provides no clear benefit to the health of children. Inadvertent overdose of ibuprofen in children has been reported postmarketing, and, at times, parents have used different ibuprofen products concurrently. Requiring the development of a pediatric label for Na IBU puts the FDA in the difficult position of requiring unnecessary studies for an unnecessary product. I have shared this opinion with members of FDA's Pediatric Review Committee (PeRC).

The legal opinion that Na IBU triggers PREA because it contains a new active ingredient because it is a new salt is at odds with the science. There is no reason to think that sodium, a necessary and ubiquitous cation in human tissues, treats fever or pain. Scientifically, the active ingredient in Na IBU is ibuprofen.

The PeRC has interpreted PREA more conservatively for this product than for a previous NDA for which I was the CDTL.[1] It is unclear to me why this product should be treated differently.

For the reasons above, I do not believe that the approvability of this application should be contingent on the submission of a pediatric plan that satisfies FDA's PeRC. In response to the strict interpretation of PREA recommended by the PeRC, the Division has requested that the applicant submit a pediatric plan; that submission is currently pending.

11. Other Relevant Regulatory Issues

Both the clinical and the analytical site have been inspected by FDA's Division of Scientific Investigations (DSI), and DSI recommended that the data from study AH-09-08 be accepted for review.

PCH certified that it did not use the services of any person debarred from performing studies in connection with the application, and that there were no financial arrangements with the investigator that could affect the outcome of the study. PCH also certified that there are no outstanding patents that claim the drug or a use of the drug.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Nonprescription Regulation Development (DNRD) provided labeling reviews.

In general, the label conformed to the currently approved Advil label. In compliance with 21 CFR 201.64, the Na IBU label contains a statement in "Other information" that each tablet contains sodium 22 mg. At a maximum use of 6 tablets today, a consumer's sodium intake would be 134 mg/day. This amount falls below the amount 140 mg of sodium per day that requires a warning to alert people who must restrict sodium (21 CFR 201.64).

DMEPA denied the initial proposed proprietary name, "(b) (4)," because they found it misleading pursuant to 21 CFR 201.10(c)(3). In particular, DMEPA stated that the word (b) (4) implies superiority over similar products. (b) (4) is currently under consideration by DMEPA.

The DNRD labeling review team sent the following labeling requests to the applicant during the review cycle:

- Change the listing of the established name under the statement of identity from (b) (4) to "Ibuprofen Tablets 200 mg (provided as ibuprofen sodium 256 mg)" followed by the pharmacological categories on the outer carton principle display panels (PDPs) of all SKUs, on the side panel that can serve as an alternate PDP of the (b) (4)-count tablet SKU, and on the immediate containers of all SKUs per USP33-NF28 S2 Reissue Chapter 1121.

- "Caplet" is not a USP officially recognized dosage form. Define the term "Caplets"by placing an asterisk immediately following the word "Caplets" and define the asterisk as "*capsule shaped tablet" in the declaration of net quantity of contents statement for all SKUs.

- Wherever Active ingredient is listed, either in Drug Facts or other labeling of all SKUs, change the listing of the active ingredient from "(b) (4) to "Ibuprofen 200 mg (provided as ibuprofen sodium 256 mg)" per USP33-NF28 S2 Reissue Chapter 1121.

- Remove "(b) (4) from the PDPs of all SKUs that bear this statement. The term (b) (4) cannot be quantified. A different statement with a measurable time and supporting data may be proposed to describe the absorption action.

- Change the statement on the 8-count tablets immediate container (vial) from (b) (4) to "Open here to view more product information" or another statement that does not imply the label contains complete Drug Facts.

- Change the color scheme of the 40-count capsule-shaped tablets outer container to make the statement of identity "prominent and conspicuous" as required in 21 CFR 201.61.

- Provision for the lot/control number (21 CFR 201.17) and expiration date (21 CFR 201.18) on the 2-count pouch must be provided.

DMEPA provided three additional recommendations regarding the presentation of the proprietary name, adding "per tablet" to the presentation of quantity on the 2-count pouch, and increasing the prominence of the "Lift Here" labels on the 8-count vial.

A final label has not yet been negotiated.

Comment: The team's labeling recommendations are acceptable to me. I have no clinical objection to the name, (b) (4) *however, DMEPA's review of the name has not been finalized and DMEPA will make the final determination on the name.*

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action:
I recommend approval of NDA 201803 pending

- final agreement on labeling
- satisfactory inspection of the manufacturing site

Risk Benefit Assessment:
Na IBU should provide the same safety and efficacy profile as the approved product, Advil Liqui-Gels, and therefore the risk/benefit assessment is acceptable.

Recommendation for Postmarketing Risk Evaluation and Management Strategies:
Not applicable

Recommendation for other Postmarketing Requirements and Commitments:
Not applicable

Recommended Comments to Applicant:
None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LESLEYANNE A FURLONG
03/14/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201-803 **Applicant: Pfizer Consumer Healthcare** **Stamp Date: June 30, 2010**

Drug Name: Sodium Ibuprofen dihydrate **NDA/BLA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Efficacy based on bioequivalence study
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	Efficacy based on bioequivalence study
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b) (2)			Motrin IB (NDA 19-012)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: AH-09-08 Indication: Demonstrate bioequivalence of sodium ibuprofen to RLD	X			Only one study as efficacy based on bioequivalence

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201803	ORIG-1	PFIZER CONSUMER HEALTHCARE	Sodium Ibuprofen, 256 mg (ibuprofen 200 mg)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRISCILLA R CALLAHAN-LYON
08/05/2010

LESLEYANNE A FURLONG
08/05/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201-803
Priority or Standard	Standard
Submit Date(s)	June 30, 2010
Received Date(s)	June 30, 2010
PDUFA Goal Date	May 1, 2011
Division / Office	DNCE/ODE IV
Reviewer Name(s)	Priscilla Callahan-Lyon, M.D.
Review Completion Date	February 25, 2010
Established Name	Sodium Ibuprofen dihydrate
(Proposed) Trade Name	Advil (b) (4)
Therapeutic Class	Analgesic, Antipyretic
Applicant	Pfizer Consumer Healthcare
Formulation(s)	Tablet
Dosing Regimen	One tablet every 4 – 6 hours; if symptoms persist a second tablet may be used; maximum daily dose is 1200 mg
Indication(s)	Temporary relief of minor aches and pains due to: headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pain of arthritis; temporarily relieves fever
Intended Population(s)	Patients age 12 and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The proposed drug product, ibuprofen sodium, is acceptable. The drug development program established bioequivalence between ibuprofen sodium and the previously approved ibuprofen product Aleve® Liquigels. The postmarketing data and the clinical trial support the safety of ibuprofen and ibuprofen sodium. The recommended regulatory action from a clinical perspective is approval pending satisfactory completion of site inspections, approval of brand name, resolution of the possible need for a pediatric plan, and negotiation of labeling.

1.2 Risk Benefit Assessment

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic activity. It is available in multiple prescription and over-the-counter dosage forms and is approved for use in children as young as six months of age. The subject of this NDA is a new immediate release ibuprofen sodium (IBU Na) tablet containing 256.25 mg of sodium ibuprofen dihydrate. This tablet size provides 200 mg of ibuprofen free acid, the same amount in currently marketed over-the-counter ibuprofen tablets within the United States. The proposed dosing and indications are identical to currently marketed over-the-counter ibuprofen tablets.

Ibuprofen sodium was developed to provide faster absorption of ibuprofen and therefore a potentially faster (per the sponsor) onset of analgesia than standard ibuprofen tablets. The development program consisted of one pivotal pharmacokinetic (PK) and food effects study with the final market formulation demonstrating bioequivalence of ibuprofen Na tablets to Advil Liquigels, an approved and marketed product in the United States. To document safety of this product, Pfizer evaluated adverse events during the clinical trials and submitted a post-marketing analysis of ibuprofen over the last 12 months along with a four-month update from all the examined databases. When available, data for ibuprofen sodium was separated from data for all ibuprofen products.

Two studies are included in this application: a pilot PK study (AH-08-07) performed on prototype ibuprofen Na tablets and a pivotal PK and food effects trial (AH-09-08) conducted on the final ibuprofen Na tablet formulation.

Study AH-08-07 was a phase 1 study comparing the rate and extent of ibuprofen absorption from ibuprofen sodium prototype tablets to that of ibuprofen liquigels. A total of 17 healthy, non-smoking, male and female subjects were enrolled and 16 subjects completed the study. All treatments provided 400 mg ibuprofen administered under fasting conditions. This was a single-dose, randomized, open-label, in-patient, four-way crossover study. Each of the three prototypes was bioequivalent to Advil Liquigels with respect to both extent (AUCL) up to 6 hours, and rate

(C_{max}) of ibuprofen absorption, with the confidence limits for each ratio of the test vs. reference formulation contained well within the conventional range (80-125%) for bioequivalence. All three formulations were rapidly absorbed and reached their respective peak concentrations (T_{max}) within 40 minutes on average, somewhat faster relative to Advil Liquigels, which showed a mean T_{max} of ~52 minutes. Overall, prototype II formulation exhibited the fastest PK profile with shortest times to relevant plasma concentration thresholds and the highest C_{max}.

Study AH-09-08 was a Phase 3, single-dose, randomized, open-label, five-way crossover, bioequivalence, and food effects study. A total of 36 healthy subjects, male and female, were enrolled and 32 completed the study. This study compared the rate and extent of ibuprofen absorption from IBU Na 256 mg tablets to Advil (ibuprofen) 200 mg Liquigels in the fasted state, the rate and extent of ibuprofen absorption from IBU Na 256 mg tablets to standard Motrin IB (ibuprofen) 200 mg tablets in the fasted state, and the rate and extent of ibuprofen absorption from IBU Na 256 mg tablets to Advil (ibuprofen) 200 mg Liquigels in the fed state.

The 90% confidence intervals for AUCL and C_{max} for the comparison of IBU Na tablets relative to Advil Liquigels in the fasted state were within the pre-specified limits (80-125%), demonstrating an equivalent rate and extent of ibuprofen absorption in the fasted state. IBU Na had an earlier median (30.4 versus 40.5 min) and mean T_{max} than Advil Liquigels. The 90% confidence intervals for C_{max} for the comparison of the IBU Na tablets relative to Motrin IB tablets in the fasted state was above the pre-specified limit (80-125%) for bioequivalence, but that for AUCL was within these pre-specified limits. Compared to Motrin, IBU Na had an equivalent extent of absorption but a faster rate of ibuprofen absorption in the fasted state. The median and mean T_{max} for IBU Na were significantly earlier than that of Motrin IB (median 30.4 versus 120.0 minutes). In the fed state, the 90% confidence intervals for AUCL and C_{max} for the comparison of IBU Na tablets relative to Advil Liquigels were within the pre- specified limits (80-125%) indicating equivalent rate and extent of ibuprofen absorption. The median T_{max} for IBU Na and Advil Liquigels in the fed state was the same (90.0 minutes).

The sponsor concludes that in the fasted state, IBU Na tablets were bioequivalent to Advil Liquigels both in terms of the rate and the extent of ibuprofen absorption. IBU Na tablets, however, reached peak plasma concentration about 10 minutes earlier than Advil Liquigels and about 90 minutes sooner than Motrin IB in the fasted state. IBU Na and Advil are bioequivalent in the fed state, in this case with similar T_{max} values. The sponsor believes the faster absorption of ibuprofen could indicate an earlier onset of clinical activity – particularly analgesia. This has not been demonstrated in a clinical trial, however, and the significance, if any, of the earlier T_{max} is unknown.

Data concerning drug safety was obtained during the pharmacokinetic studies through collection of adverse events. The PK studies also included laboratory testing. All subjects underwent a pre-study laboratory evaluation, including a complete blood count, complete urinalysis, and serum chemistry profile as well as tests for hepatitis B, hepatitis C, and human immunodeficiency virus. A post-study laboratory evaluation was completed as part of study AH-08-07 and consisted of hematology and chemistry analyses of blood samples and a urine pregnancy test for female

subjects. These tests were also performed if a subject was prematurely discontinued from the study. There was no post-study laboratory evaluation in study AH-09-08. In study AH-08-07, fourteen of the seventeen subjects (82.4%) had at least one abnormal lab finding in the pre-study analysis and eleven of seventeen (64.7%) had at least one abnormality in the post-study testing. In study AH-09-08, twenty-three of the thirty-six subjects (63.9%) had at least one abnormal lab finding in the pre-study analysis. None of the abnormalities were of clinical significance.

In both studies, all subjects had a pre-study medical history and physical examination including heart rate, blood pressure, weight, height, and BMI determination. A post-study physical examination, including vital signs but excluding height and BMI, was repeated for all subjects after the completion of the final study period and prior to study discharge. This examination was also performed if a subject prematurely discontinued from the study. There were no clinically significant changes in the vital signs or physical examinations from the baseline to end of study measurements. No ECGs were completed on the subjects in these pharmacokinetic studies.

A total of 52 normal, healthy subjects were exposed to at least one dose of an IBU Na formulation. Though the exposure to this drug product was limited, it is adequate for this application as the active drug product has been used extensively for many years. The sponsor has also referred to the established safety records of NDAs 19-012, 20-402, and 18-989 (all ibuprofen products) and submitted extensive postmarketing data.

In study AH-08-07, five subjects reported a total of 14 adverse events. The investigator believed most of the adverse events were unrelated to the study treatment. There were no serious adverse events. Many of the adverse events were experienced by two subjects (#20003 and 20008). In study AH-09-08, 15 subjects reported a total of 31 adverse events. All adverse events were rated as mild except one report each of nausea, vomiting, headache, and blurred vision; these were of moderate severity. Fourteen of the 31 AEs were considered by the investigator to be related to the study medications. There were no unexpected or serious adverse events.

As part of the NDA application, PCH evaluated the quantity of sodium a patient using ibuprofen sodium would be consuming and the implications for populations potentially at risk. The proposed formulation contains (b) (4) mg of sodium in each tablet meaning up to 134 mg/day of additional sodium would be ingested by a consumer taking the maximum daily dose. This quantity should produce a minimal effect on blood pressure and falls below the limit of 140 mg of sodium/day requiring a warning to alert patients on restricted diets to consult their doctors before using the product.

During the December 15, 2009 pre-NDA meeting, FDA agreed the sponsor would provide post-marketing safety information covering a 12-month period from several safety databases as well as safety data of ibuprofen sodium marketed in other countries. An additional safety study on the ibuprofen Na formulation was not needed. PCH included post-marketing data from four sources: Wyeth safety database (this product was developed by Wyeth but the company was sold to Pfizer and they are the application sponsor), World Health Organization (WHO) database, FDA AERS database, and the American Association of Poison Control Centers (AAPCC) database. The

exact reporting periods varied but for each database, a one year period was searched and additional data was included with the four-month safety update. For each database, the sponsor reviewed cases of ibuprofen use associated with patient death, drug interactions, drug overdose, drug abuse or misuse, experience during pregnancy and lactation, and use by special populations (pediatric, elderly, and patients with renal insufficiency and cirrhosis).

The databases are not exclusive; many reports are likely in more than one database. Also, there is probably significant 'under-reporting' of serious adverse events and there is no way to know how many consumers have taken the products (i.e., the denominator); this makes interpretation of the data challenging. PCH estimates approximately (b) (4) caplets, (b) (4) fast gel caps, (b) (4) liquid gel capsules, (b) (4) grams of gel, (b) (4) gel caplets, (b) (4) hard caps, (b) (4) milliliters of spray liquid, and (b) (4) tablets of adult strength ibuprofen were distributed from February 1, 2009 to January 31, 2010. In addition, approximately (b) (4) milliliters of liquid/suspension/drops, and (b) (4) chewable tablets of children's strength ibuprofen were distributed during this period. During the Feb 2, 2010 to Sept 1, 2010 time period, PCH estimates approximately (b) (4) caplets, (b) (4) fast gel caps, (b) (4) liquid gel capsules, (b) (4) grams of gel, (b) (4) gel caplets, (b) (4) hard caps, (b) (4) milliliters of spray liquid, and (b) (4) tablets of adult strength ibuprofen were distributed. In addition, approximately (b) (4) milliliters of liquid/suspension/drops, and (b) (4) chewable tablets of children's strength ibuprofen were distributed during this period.

The Wyeth safety database was searched for serious case reports identifying ibuprofen as the suspect drug for the February 2009 – February 2010 and February 2010 - September 2010 time periods. There were 30 deaths reported during this period; the most frequently reported cause of death was completed suicide (16 cases). Of the eight serious reports of drug interactions, seven were interactions with drugs that have warnings about use with NSAIDs. The other report described a lack of effect for treatment of pyrexia. There were 68 reports of overdose coincident to ibuprofen use. Many of these were fatal (18) and most involved overdose of multiple drugs. The sponsor does not believe ibuprofen is a likely drug of abuse.

The Wyeth data included three serious reports of exposure during pregnancy and one case where the infant was exposed in utero as well as during breastfeeding. In two cases, the exposure occurred during late pregnancy and the infant had premature closure of the ductus arteriosus. The ibuprofen core data sheet states use of ibuprofen during the third trimester of pregnancy is contraindicated.

In the initial reporting period, 10 reports described acute renal failure occurring in adolescents and coincident to ibuprofen use. All of the reports were medically confirmed; eight of the cases were from France. Several of the patients had complex co-morbid conditions and medical histories including sepsis, pneumonia, multidrug overdose, kidney stones, Fanconi's syndrome, polyuria, and solitary kidney. The update added five serious reports describing renal events in pediatric patients. The patients in the renal event cases were experiencing significant co-morbid

conditions including dehydration (n=3), sickle cell anemia (n=1) and hospitalization for vomiting (n=1).

As part of the safety update, PCH conducted a review of ibuprofen case report data from internal and external sources covering a one year time period identifying reports of acute kidney injury in pediatric patients. A search of Medline, Embase, BIOSIS, CAB abstracts, Current Content and Derwent, going back to January 2000, was conducted to identify articles pertaining to ibuprofen and renal failure in a pediatric population. A recurring observation from the case series and case reports was underlying hypovolemia in children who had renal impairment associated with NSAID therapy. The proposed product is not indicated for children under 12 years of age and current labeling of ibuprofen products warns patients to ask a doctor before using ibuprofen if they are taking a diuretic or have kidney disease. Additionally, PCH reports labeling of ibuprofen products intended for use in children under 12 years of age already includes additional warnings regarding use of ibuprofen if the child has not been drinking fluids, has been vomiting or having diarrhea, is taking a diuretic, or has kidney disease.

The initial reporting period covered for the WHO data was October 1, 2008 through September 30, 2009 and the update covered January 1, 2010 through April 23, 2010. In all cases ibuprofen was identified as the suspected or interacting medication. The most common adverse events in the WHO database were: suicide attempt (78 cases), overdose (73 cases), completed suicide (70 cases), drug toxicity (56 cases), and renal failure acute (49 cases). These are listed by preferred term (PT) and some cases may have more than one AE coded. There were 202 fatalities among the serious cases; the most common PT was completed suicide (n=70).

There were 494 serious cases in the WHO database in which ibuprofen was the only listed medication. Twenty-eight deaths were reported and the most frequently reported preferred term for these cases was overdose (n=6). The WHO data included 49 cases (25 considered serious) related to ibuprofen sodium. The one death in this group was due to hepatic failure and attributed to accidental overdose.

There were 360 cases in the WHO data that met the definition of serious because the event caused or prolonged hospitalization. The most frequently reported PTs associated with prolonged hospitalization were renal failure acute (n=31), intentional overdose (n=26), and suicide attempt (n=24). The WHO data have insufficient details to thoroughly examine drug-drug interactions. There were nine cases involving ibuprofen exposure during pregnancy. In most cases, the relationship of ibuprofen to the outcome is not clear though one case of premature closure of the ductus arteriosus was noted.

There were 161 serious AE cases in the WHO data of ibuprofen administration in children less than 18 years of age. The most common AEs coded by MedDRA PT for serious cases in pediatrics included: renal failure acute (19), vomiting (13), accidental overdose (13), accidental drug intake by child (13, overdose (12), hypersensitivity (8), and hypothermia (8). There were 152 serious cases in the WHO data of ibuprofen administration in the elderly (age 65 or older). The most common AEs coded by MedDRA PT included: anaemia (12), gastric haemorrhage

(10), condition aggravated (8), completed suicide (7), gastrointestinal haemorrhage (7), renal failure acute (7), and dizziness (6). PCH believes the information available from the WHO database supports the known safety profile of ibuprofen.

The AERS database was searched for cases where ibuprofen was identified as the primary or secondary suspect medication. Data was collected from July 1, 2008 through June 30, 2009 and July 1, 2009 through December 31, 2009. The most common adverse events in the AERS database were: renal failure acute (117 cases), overdose (86 cases), condition aggravated (84 cases), vomiting (82 cases), and completed suicide (72 cases). There were 263 fatalities among the serious cases; 72 were completed suicides (the most common PT).

There were 530 cases in the AERS database which only listed ibuprofen. This included 22 deaths. Fifteen cases included ibuprofen sodium. There were three deaths in this group; one due to hepatic failure and overdose, one due to large intestinal hemorrhage, and one due to toxic shock syndrome.

A total of 998 cases in the AERS database were serious because the event caused or prolonged hospitalization. The most frequent PTs in this group was renal failure acute (91 cases). In the initial AERS data, there were 183 cases of drug overdose that were coincident with the use of ibuprofen. Of these, 181 were considered serious. The majority of the cases (100 of 181) were from the United States. There were 14 cases of ibuprofen exposure during pregnancy described in the AERS database. The relationship of ibuprofen to the effects noted is not clear though ductus arteriosus complications were noted in one case.

There were 387 serious AE reports in the AERS database of ibuprofen administration in children less than 18 years of age. The most common AEs were: condition aggravated (46), renal failure acute (43), accidental overdose (29), vomiting (25), and accidental drug intake by a child (15). There were 337 serious cases in the AERS data of ibuprofen administration in the elderly (age 65 or older). The most common AEs coded by MedDRA PT included: anaemia (18), drug interaction (18), gastrointestinal hemorrhage (14), and gastric ulcer (9). PCH believes the information available from the AERS database for the reporting periods support the known safety profile of ibuprofen.

An analysis of the American Association of Poison Control Centers (AAPCC) data was performed covering February 1, 2008, through January 31, 2009 with an update covering February 2, 2010 through June 30, 2010. The AAPCC data contained 88,315 cases of ibuprofen exposure in children and adults during the initial reporting period; 9,272 were determined to be serious adverse events. There was one death where the only medication listed was ibuprofen. The AAPCC update contained 34,464 cases of ibuprofen exposure in children and adults; 4,039 were determined to be serious and 12 deaths (nine of which were Intentional - Suspected suicides).

Each AAPCC case is coded for Clinical Effect (CE) frequency. The most common CEs listed in the serious AE reports were: drowsiness/lethargy, tachycardia, vomiting, nausea, and abdominal pain. In both the initial and the update reports, the most common reason for exposure was

Intentional-Suspected suicide. The 39 ibuprofen-only hospitalizations of pregnant women ranged in age from 17 years to 40 years and all but one were Intentional-Suspected suicides. For the 1,623 ibuprofen-only SAE cases in children, 1,352 were Intentional-Suspected suicide. There were 35 ibuprofen-only serious cases in the elderly (age 65 or older) and 23 were Intentional-Suspected suicide.

PCH concluded that limitations of the AAPCC data make interpretation of causality difficult and it is not possible to distinguish ibuprofen sodium from other ibuprofen formulations. In spite of these limitations, however, PCH believes the information available for the reporting periods is consistent with the known safety profile of ibuprofen.

In summary, Pfizer Consumer Healthcare has provided extensive post-marketing data supporting the safety of ibuprofen. No new safety signals were identified. The data for ibuprofen sodium is also supportive. The pharmacokinetic study demonstrating bioequivalence of ibuprofen sodium to a currently marketed ibuprofen product supports the efficacy of the proposed product. Additionally, the adverse event data collected during the PK studies support safety of ibuprofen sodium. Taken as a whole, the data show a positive risk-benefit analysis for this drug product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No special post-market risk evaluation and mitigation strategy activities beyond routine pharmacovigilance are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No specific post-market requirements or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Ibuprofen (IBU) is an orally-administered propionic acid derivative, non-steroidal anti-inflammatory drug (NSAID), with analgesic, anti-inflammatory, and antipyretic activity. As with other nonselective NSAIDs, the exact mechanism of action is not known. The primary mechanism of drug activity is thought to be reduction of prostaglandin biosynthesis by non-selective inhibition of cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2). Many types of pain result from inflammation and tissue injury. In response to injury, the body releases arachidonic acid from cell membranes which is converted to prostaglandins via cyclooxygenase enzymes. Increased prostaglandin levels have been implicated in the production of both pain and fever. Traditional (i.e., non-selective) NSAIDs, such as ibuprofen, inhibit the cyclooxygenase enzymes COX-1 and COX-2, thereby decreasing prostaglandin biosynthesis.

The subject of this NDA is a new immediate release ibuprofen sodium (IBU Na) tablet

containing 256.25 mg of sodium ibuprofen dihydrate. This amount of IBU Na provides 200 mg of ibuprofen free acid, which is the amount in currently marketed over-the-counter ibuprofen tablets within the United States. The proposed dosing is identical to that of currently marketed OTC ibuprofen 200 mg tablets: one tablet every 4-6 hours while symptoms persist, or if pain or fever does not respond to one tablet, two tablets may be used, with a maximum daily dose of six tablets (1200 mg) in adults and children 12 years of age and over. The proposed indications are also identical to those of currently marketed OTC ibuprofen 200 mg tablets/caplets/liquigels: for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, and the minor pain of arthritis, as well as the temporary reduction of fever.

The intent of this clinical program was to develop an IBU Na tablet, which would provide faster absorption of ibuprofen, and potentially a faster onset of analgesia, than standard ibuprofen tablets. The results of the pivotal PK study, AH-09-08, indicate that IBU Na is absorbed faster than standard ibuprofen tablets, and as fast as IBU liquigels. The sponsor expects, therefore, that IBU Na tablets will provide comparable overall efficacy and safety to IBU tablets and liquigels, but with an onset of analgesia faster than IBU tablets and comparable to that of IBU liquigels.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many approved prescription and OTC products for relief of minor pain and temporary reduction of fever. The most commonly used products are aspirin and other salicylate products, acetaminophen, and naproxen. All of these products have the same indications. Naproxen is also a nonsteroidal anti-inflammatory drug with a similar efficacy and safety profile.

2.3 Availability of Proposed Active Ingredient in the United States

Ibuprofen has been available in the United States since 1974 and available over-the-counter since 1984. Over-the-counter ibuprofen is marketed in the United States under the brand names Advil® and Motrin® and is also available as a generic product.

2.4 Important Safety Issues with Consideration to Related Drugs

Nonsteroidal anti-inflammatory medications are commonly used in the United States. These medications are relatively safe but there are concerns in certain populations. The most common adverse reactions involve the upper gastrointestinal tract. The gastrointestinal effects are usually mild; however, in 5-15% of patients the events are severe enough to require discontinuation of the drug. Risk of more serious gastrointestinal events, such as ulceration or perforation, increases with increased duration of therapy and higher doses.

Nonsteroidal anti-inflammatory medications are also associated with a relatively high incidence of renal adverse drug reactions. These medications may cause renal impairment, particularly when combined with other nephrotoxic agents such as diuretics or ACE inhibitors. Nonsteroidal

anti-inflammatory medications may also increase the risk of cardiovascular events, stroke, and congestive heart failure. Both the cardiac and renal risks are more common in older patients.

Photosensitivity is an additional concern with NSAIDs. This is more likely with the 2-arylpropionic acids but must be considered with any drugs in the NSAID class.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An IND submission for ibuprofen sodium was received June 22, 2009. The stated intent of the clinical development program was development of an ibuprofen sodium tablet which delivers 200 mg of ibuprofen free acid per tablet. The sponsor (Wyeth Consumer Healthcare) had developed an immediate release tablet containing 256.25 mg of ibuprofen sodium dihydrate that was expected to provide faster dissolution and absorption of ibuprofen, and therefore a potentially faster onset of analgesia than standard ibuprofen tablets. At the time of IND submission, the sponsor had completed a pilot study comparing three prototype formulations to ibuprofen liquigel capsules. A Phase II pharmacokinetic study was proposed to further characterize the profile of a new, immediate-release ibuprofen sodium tablet.

A pre-NDA meeting was held December 15, 2009. The data included with the pre-NDA submission demonstrated the bioequivalence of ibuprofen Na to Advil Liquigels. The following points and action items were discussed during the meeting:

- The sponsor will provide safety data from the suggested safety databases as well as safety data of ibuprofen sodium marketed in other countries. An additional safety study on the ibuprofen Na formulation is not needed.
- FDA agreed that a 12-month time period of post-marketing safety information is acceptable for the NDA submission.
- FDA recommended that the sponsor submit all of the stability data to support the proposed NDA at the time of submission.
- FDA will provide further clarification on the approvability of an NDA without a USAN name in the meeting minutes as a post meeting addendum.
- The sponsor will provide a pediatric plan, including justifications for any waiver proposals, in the NDA submission.
- The sponsor was notified of the clinical pharmacology concern that the proposed product is a racemic mixture. The sponsor will clarify if there are any differences in the pharmacokinetics of the individual enantiomers.

A post-meeting addendum added the following two points:

- Advil Liquigels was approved as 505(b)(2). The sponsor will need to cite reliance on the same product(s) (Motrin IB) relied upon to support the approval of Advil Liquigel application, to support the safety and efficacy of this proposed ibuprofen sodium product.
- If an INN (International Nonproprietary Name) is available for the proposed drug substance, FDA may approve the NDA using the INN as the established name provided that your application for a USAN name has started.

It is also noted that following the acquisition of Wyeth by Pfizer, Inc. in 2009, Wyeth Consumer Healthcare is now a wholly-owned subsidiary of Pfizer, Inc. doing business as Pfizer Consumer Healthcare. Some of the documents in the NDA still refer to the Wyeth name.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was an electronic submission of good quality and integrity. The sponsor responded promptly to our requests for additional information. The clinical data provided was well organized and complete. The clinical site inspection has been completed and the final report is pending. The analytical site inspection is also complete and no issues that would delay drug approval were identified.

3.2 Compliance with Good Clinical Practices

The clinical development plan consisted of one pivotal PK and food effects study. A pilot PK study evaluating prototype ibuprofen Na formulations was also performed and the results are included in this application. Both studies were conducted in accordance with all applicable international standards and local laws, including ICH GCP guidelines and US Federal Laws pertaining to GCP regulations.

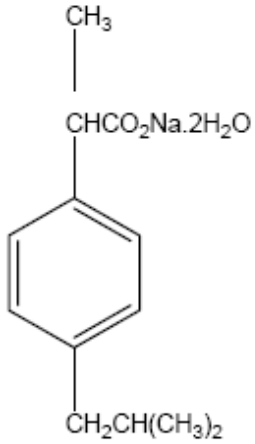
3.3 Financial Disclosures

Appropriate and adequate financial disclosure documents were submitted and reviewed. The financial arrangements did not raise any questions regarding the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemical structure of sodium ibuprofen dihydrate is:



Sodium ibuprofen dihydrate is a white, crystalline powder which is freely soluble in water. The pH of a 1% solution of sodium ibuprofen dihydrate in water is 7.32. Sodium ibuprofen dihydrate does not exhibit polymorphism.

The immediate release tablet developed by PCH contains 256.25 mg of sodium ibuprofen dihydrate. The tablet dosage form is referred to in terms of the ibuprofen free acid content. Sodium ibuprofen tablets, 200 mg refers to dosages containing 256.25 mg of sodium ibuprofen dihydrate, equivalent to 200 mg of ibuprofen free acid (the amount in currently marketed ibuprofen tablets within the United States).

Sodium ibuprofen dihydrate is manufactured by [redacted] (b) (4). Commercial production of the sodium ibuprofen dihydrate drug substance will be performed in [redacted] (b) (4) has fully validated their manufacturing process for the production of the sodium ibuprofen dihydrate drug substance. Further review of the manufacturing process is in the CMC review.

Table 1 summarizes the composition of sodium ibuprofen tablets and the function of the excipients in the formulation. There are no novel excipients and no excipients of human or animal origin. PCH included six months accelerated stability data for ibuprofen Na 200 mg in the original NDA submission. In addition, PCH proposes to provide a stability data amendment during the initial FDA review cycle. The stability data amendment will include twelve months long-term stability data (25°C/60%RH), twelve months intermediate stability data (30°C/65%RH) and six months accelerated stability data (40°C/75%RH). An amendment, filed Sept 30, 2010, included twelve months of stability data. Based on the satisfactory stability data

provided in the amendment, PCH is proposing an expiration dating period of (b) (4) months for sodium ibuprofen tablets, 200 mg when stored at room temperature (20°C to 25°C). This data will be reviewed in detail by the FDA chemists.

Table 1: Composition of Sodium Ibuprofen Tablets, 200 mg

Ingredient	Grade/Quality Standard	Unit Dose (mg/du)	Function
Sodium Ibuprofen Dihydrate	DMF	256.25	Active Ingredient
Colloidal Silicon Dioxide	NF, Ph. Eur.	(b) (4)	
Mannitol	USP, Ph. Eur.		
Microcrystalline Cellulose	NF, Ph. Eur.		
Sodium Lauryl Sulfate	NF, Ph. Eur.		
(b) (4)	DMF		
Acesulfame Potassium	NF, Ph. Eur.		
Sucralose	NF		
(b) (4)	DMF		
Carnauba Wax	NF, Ph. Eur.		
(b) (4)	DMF		
	USP, Ph. Eur.		
	USP, Ph. Eur.		
Total:		446.2	

a. Essentially removed during processing.
Source: NDA 201-803, Module 2.3.P.1, Page 1, Table 1-1

4.2 Clinical Microbiology

This does not apply.

4.3 Preclinical Pharmacology/Toxicology

While there is no preclinical information on ibuprofen sodium, there is substantial information on ibuprofen. Ibuprofen was developed in 1960 by Laboratoires Boots, and had primary pharmacodynamic properties generally consistent with other non-steroidal anti-inflammatory drugs: analgesic, antipyretic, and anti-inflammatory effects. It was initially marketed as a prescription medication for its anti-rheumatic activity. Ibuprofen was introduced in the United Kingdom in 1966 and in the United States in 1974, and was the first non-steroidal anti-inflammatory drug approved for over-the-counter use in the United States in 1984.

NDA 18-989 (Advil® sponsored by Wyeth Consumer Healthcare) provides extensive nonclinical data supporting the safe use of ibuprofen at OTC doses of up to 400 mg every 4 – 6 hours with a maximum daily dose of 1200 mg. In addition, PCH conducted an online search for

ibuprofen in the published literature (Medline/PubMed, Ovid, Embase, and Toxnet/Toxline) from 1966 through January 2006. The search did not produce any nonclinical citations of significant relevance to suggest modification of previous regulatory findings on the safety of ibuprofen for its use in adults or children. Based on this, no preclinical studies were performed in support of this application.

A 14-day single dose rat toxicology study was recently conducted on ibuprofen Na in support of an application to a non-US regulatory agency. The purpose of this study was to compare the acute oral toxic potential of a reference ibuprofen and ibuprofen Na, and evaluate the difference in toxicity and mortality between the two compounds. No toxicokinetics, clinical chemistry, or histopathology was performed. The study was performed in accordance with Good Laboratory Practice Regulations.

Groups of 5 male and 5 female rats were administered a single oral dose of the reference ibuprofen or ibuprofen Na and observed over 14 days. The doses used were 200, 500, and 650 mg/kg. All 200 mg/kg dosed rats survived to Day 14 with tarry feces observed on Day 1. Tarry feces increased in frequency with increasing dose. For rats dosed with 500 mg/kg, three rats dosed with the reference ibuprofen and two with ibuprofen Na were found dead or moribund and were sacrificed on Days 2 - 7. Rats dosed at 500 mg/kg exhibited reduced body weight gain, piloerection, passivity, rough pelage, hunched back, pot-bellied appearance, and tarry feces, lasting from 7 – 10 days after dosing. At 650 mg/kg, 3 rats dosed with reference ibuprofen and 7 with ibuprofen Na were found dead or moribund and were sacrificed on Days 2 - 5 and Days 1 – 6 respectively. Clinical observations found at 500 mg/kg were also present at 650 mg/kg and were more pronounced with ibuprofen Na.

There were no significant gross necropsy findings at the 200 mg/kg dose. Based on a) onset, incidence, severity and duration of clinical observations, b) mortalities and c) necropsy findings, there was no significant difference in toxicity and necropsy findings between ibuprofen Na and reference ibuprofen at the 200 and 500 mg/kg doses. These findings confirm a previous study determining the No Observed Adverse Effect Level (NOAEL) was 200 mg/kg. The maximum OTC single human dose of ibuprofen is 400 mg. The NOAEL is therefore approximately 30 times higher than the maximum single human dose - based on a 60 kg human. In conclusion, the current study at high doses further illustrates the known gastrointestinal side-effects of ibuprofen in humans. Further discussion of this study is in the Pharmacology-Toxicology review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ibuprofen is a propionic acid derivative non-steroidal anti-inflammatory drug with analgesic, anti-inflammatory, and antipyretic activity. The mechanism of action is attributed to reduction of prostaglandin biosynthesis by non-selective inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Many types of pain result from inflammation and tissue injury. In

response to the injury, the body sets into motion a variety of mechanisms, including the liberation of arachidonic acid from cell membranes. The arachidonic acid is subsequently converted to prostaglandins via cyclooxygenase enzymes. Increased prostaglandin levels have been implicated in the production of both pain and fever. Non-selective NSAIDs, such as ibuprofen, inhibit the cyclooxygenase enzymes COX-1 and COX-2, thereby decreasing prostaglandin biosynthesis.

4.4.2 Pharmacodynamics

There were no additional pharmacodynamic studies submitted to this NDA.

4.4.3 Pharmacokinetics

Pfizer Consumer Healthcare has developed an ibuprofen Na product which delivers 200 mg of ibuprofen free acid per tablet intended for over-the-counter (OTC) use. The ibuprofen Na tablet was developed to provide faster absorption of ibuprofen, and therefore a potentially faster onset of analgesia than standard ibuprofen tablets. The proposed dosing regimen and indications are identical to those of currently marketed OTC ibuprofen 200 mg products. The development program consisted of one pivotal pharmacokinetic (PK) and food effects study on the final market formulation demonstrating bioequivalence of ibuprofen Na tablets to Advil Liquigels, an approved and marketed product in the United States.

The design of the clinical program was discussed with FDA at a pre-NDA Type B meeting on December 15, 2009. At that meeting, FDA confirmed that a safety study would not be required. The final FDA minutes of that meeting also indicated that it would be acceptable to submit this application under 505(b)(2) with cross-reference to Advil Liquigels (NDA 20-402) and Motrin IB (NDA 19-012).

Two studies are included in this application: A pilot PK study (AH-08-07) performed on prototype ibuprofen Na tablets and a pivotal PK and food effects trial (AH-09-08) conducted on the final ibuprofen Na tablet formulation that is the subject of this application. The studies are reviewed in detail in Section 5.3.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Only one clinical trial (pharmacokinetic) study was conducted using the final, to-be-marketed ibuprofen Na formulation. This study (AH-09-08) is reviewed in Section 5.3. PCH also submitted the results of a pilot study (AH-08-07) conducted comparing three prototype formulations of ibuprofen Na to reference ibuprofen liquigels. For completeness, this study is also reviewed in Section 5.3. The safety results from both studies are reviewed in Section 7.

5.2 Review Strategy

The clinical development program included the demonstration of bioequivalence between sodium ibuprofen dihydrate and Advil Liquigels and a comparison of the pharmacokinetics of ibuprofen sodium and Motrin IB. A summary of the pharmacokinetic study results, as presented by the sponsor, is included in this section of the review. A more detailed discussion of the clinical data is in the efficacy and safety sections of the review.

5.3 Discussion of Individual Studies/Clinical Trials

Study AH-08-07 was conducted by Wyeth Consumer Healthcare from September 15, 2008 – October 2, 2008. The objective of this phase 1 study was to compare the rate and extent of ibuprofen absorption from ibuprofen sodium prototype tablets to that of ibuprofen liquigels. A total of 17 healthy, non-smoking male and female subjects were enrolled and 16 subjects completed the study. All treatments were equivalent to 400 mg ibuprofen and all were administered under fasting conditions. There were four treatments:

- Treatment A: Two ibuprofen sodium 256 mg prototype tablets formulation I
- Treatment B: Two ibuprofen sodium 256 mg prototype tablets formulation II
- Treatment C: Two ibuprofen sodium 256 mg prototype tablets formulation III
- Treatment D: Two Advil ® Liquigels 200 mg (reference therapy)

This was a single-dose, randomized, open-label, in-patient, four-way crossover study. The subjects were randomly assigned to one of four dosing sequences and received a dose of each ibuprofen formulation following an overnight fast in each of the study periods. Dosing for each study period was separated by at least 48 hours. Eighteen blood samples (3 mL each) were collected from each subject for the analysis of racemic ibuprofen over 6 hours during each of the four study periods. Subjects were housed on-site for the duration of the study.

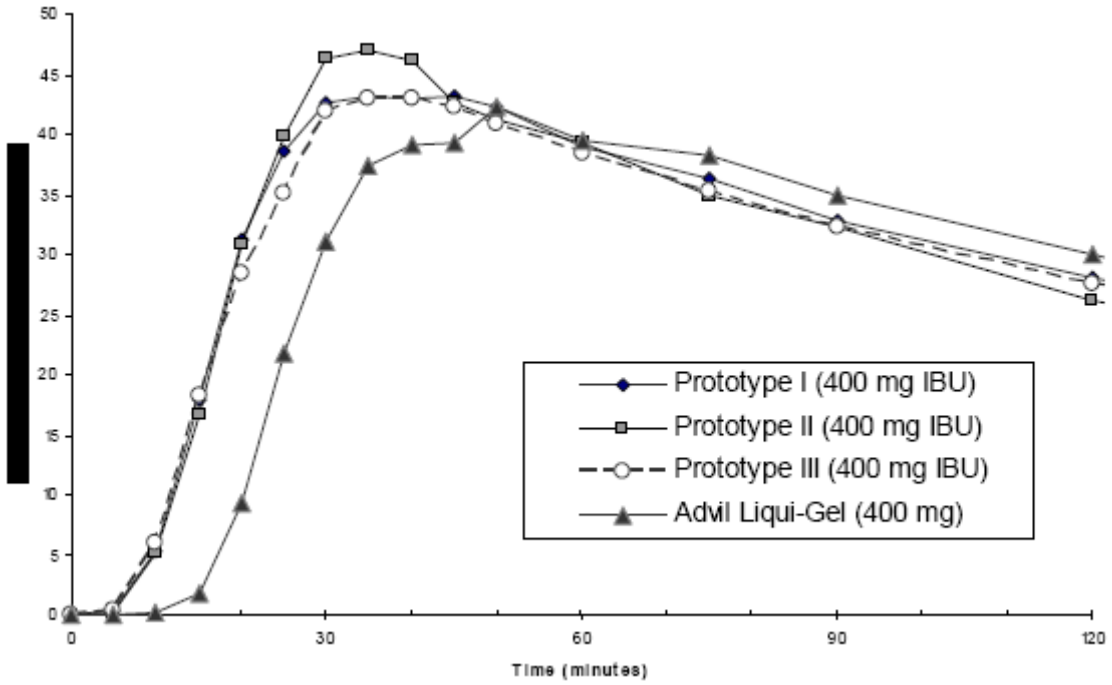
The key results are summarized in Table 2. Each of the three prototypes was bioequivalent to Advil Liquigels with respect to both extent (AUCL) up to 6 hours, and rate (C_{max}) of ibuprofen absorption, with the confidence limits for each ratio of the test vs. reference formulation contained well within the conventional range (80-125%) for bioequivalence. All three formulations were rapidly absorbed (as seen in Figure 1), and reached their respective peak concentrations (T_{max}) within 40 minutes on average, somewhat faster relative to Advil Liquigels, which showed a mean T_{max} of ~52 minutes. Overall, prototype II formulation exhibited the fastest PK profile with shortest times to relevant plasma concentration thresholds and the highest C_{max}.

Table 2: AH-08-07 Summary of Ibuprofen Pharmacokinetic Parameters (mean and standard deviation)

Treatment	AUC (mcg•h/mL)	C_{max} (mcg/mL)	T_{max} (min)
A: Ibuprofen prototype I	125.80 (21.5)	47.41 (8.6)	38.75 (10.8)
B: Ibuprofen prototype II	123.98 (20.0)	49.58 (7.8)	32.76 (6.1)
C: Ibuprofen prototype III	123.44 (16.5)	47.06 (9.0)	36.70 (12.3)
D: Advil Liquigels (reference product)	121.52 (18.8)	47.61 (8.9)	52.36 (16.7)

Source: NDA 201-803, Module 5.3.3.1.3, Page R-36, Table 9-1

Figure 1: AH-08-07 Mean Ibuprofen Plasma Concentration over the First Two Hours



Source: NDA 201-803, Module 5.3.3.1.3, Page R-34, Figure 9-3

The sponsor concluded ibuprofen sodium was bioequivalent to Advil Liquigels for AUC, but was absorbed faster with a slightly higher C_{max} and faster T_{max}.. The sponsor also concluded these data suggest the ibuprofen sodium tablets tested may provide an onset of analgesia faster than standard ibuprofen tablets and at least as fast as ibuprofen liquigels.

Reviewer Comment: While the data supports the bioequivalence conclusion, the sponsor's assumption that faster absorption leads to more rapid onset of analgesia has not been demonstrated.

Study AH-09-08 was conducted by Pfizer Consumer Healthcare from July 29, 2009 - August 7, 2009. This was a Phase 3, single-dose, randomized, open-label, five-way crossover,

bioequivalence, and food effects study. The primary objective of this study was to compare the rate and extent of ibuprofen absorption from IBU Na 256 mg (equivalent to 200 mg ibuprofen) tablets to Advil (ibuprofen) 200 mg Liquigels in the *fasted* state. Secondary objectives were to compare the rate and extent of ibuprofen absorption from IBU Na 256 mg tablets to standard ibuprofen 200 mg tablets in the *fasted* state, and to compare the rate and extent of ibuprofen absorption from IBU Na 256 mg tablets to Advil (ibuprofen) 200 mg Liquigels in the *fed* state.

The study used five treatments:

1. **Treatment A:** 2 × 256 mg IBU Na tablets (total dose = 400 mg ibuprofen) in the *fasted* state
2. **Treatment B:** 2 × 256 mg IBU Na tablets (total dose = 400 mg ibuprofen) in the *fed* state
3. **Treatment C (Reference for Treatment A):** 2 × 200 mg Advil (ibuprofen) Liquigels (total dose = 400 mg ibuprofen) in the *fasted* state
4. **Treatment D (Reference for Treatment B):** 2 × 200 mg Advil (ibuprofen) Liquigels (total dose = 400 mg ibuprofen) in the *fed* state
5. **Treatment E (Reference for Treatment A):** 2 × 200 mg Motrin IB (ibuprofen) tablets (total dose = 400 mg ibuprofen) in the *fasted* state

A total of 36 healthy subjects, male and female, were enrolled and 32 completed the study. Each treatment period was separated by a washout period of at least 48 hours. Blood samples (3 mL each) were drawn at the following intervals: pre-dose (0 hour), and 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90 minutes and 2, 3, 4, 6, 8, 10, 12, and 16 hours post dose. A total of approximately 315 mL of blood was drawn from each subject during the study (plus approximately 30 mL of blood required for safety evaluations.)

For each comparison, bioequivalence was declared if the 90% two-sided confidence interval for the ratio was between 80% and 125% for log transformed parameters. AUCL and C_{max} were considered the primary parameters. Other pharmacokinetic parameters, T_{max}, $t_{1/2}$, Kel (elimination rate), Vd (volume of distribution), and Cl (clearance) were also calculated. The results are summarized in Table 3 and Figure 2.

Of the five treatments tested, IBU Na tablets in the fasted state had the shortest T_{max} (median = 30.4 min), followed by Advil Liquigels in the fasted state (median = 40.5 min). The two formulations under the fed state had relatively similar T_{max} values (median = 90.0 min each). Motrin IB in the fasted state had the longest median T_{max} of 120.0 minutes. The mean half-life, elimination rate, clearance, and volume of distribution were the same across the five treatments (about 2.5 hr, 0.30 hr-1, 3 L/hr, and 10 L, respectively).

The 90% confidence intervals for AUCL and C_{max} for the comparison of IBU Na tablets relative to Advil Liquigels in the fasted state were within the pre-specified limits (80-125%). Therefore, compared to standard Advil Liquigels, IBU Na tablets had an equivalent rate [A/C ratio for C_{max} = 104.2%, 90% CI = (96.6, 112.4%)] and extent [A/C ratio for AUCL = 102.0%, 90% CI = (99.1, 105.0%)] of ibuprofen absorption in the fasted state. In terms of T_{max}, IBU Na tablet had

an earlier median than Advil Liquigels (30.4 versus 40.5 min). Similar differences were seen in the mean T_{max} values.

The 90% confidence intervals for C_{max} for the comparison of the IBU Na tablets relative to Motrin IB tablets in the fasted state was above the pre-specified limit (80-125%) for bioequivalence, but that for AUCL was within these pre-specified limits. Therefore, compared to Motrin IB tablets, IBU Na tablets had an equivalent extent [A/E ratio for AUCL = 102.4%, 90% CI = (99.5, 105.4%)] but a significantly faster rate [A/E ratio for C_{max} = 135.0%, 90% CI = (125.2, 145.5%)] of ibuprofen absorption in the fasted state. In terms of T_{max}, the IBU Na tablet had an earlier median than Motrin IB tablets (30.4 versus 120.0 min). Similar differences were seen in the mean T_{max} values.

The 90% confidence intervals for AUCL and C_{max} for the comparison of IBU Na tablets relative to Advil Liquigels in the fed state were within the pre-specified limits (80-125%). Therefore, compared to standard Advil Liquigels, IBU Na tablets had an equivalent rate [B/D ratio for C_{max} = 91.2%, 90% CI = (84.6, 98.3%)] and extent [B/D ratio for AUCL = 101.7%, 90% CI = (98.8, 104.7%)] of ibuprofen absorption in the fed state. In terms of T_{max}, IBU Na tablets and the Advil Liquigels had the same median (90.0 min). Similar results were seen in the mean T_{max} values.

The sponsor concludes that in the fasted state, IBU Na tablets were bioequivalent to Advil Liquigels both in terms of the rate (C_{max}) and the extent (AUCL) of ibuprofen absorption. However, IBU Na tablets reached peak plasma concentration (T_{max}) about 10 minutes earlier relative to Advil Liquigels in the fasted state. These two formulations were also bioequivalent to each other when taken in the fed state, in this case with similar T_{max} values. The rate of ibuprofen absorption as measured by C_{max} was higher for IBU Na tablets and reached peak plasma concentration about 90 minutes sooner compared to Motrin IB tablets when both products were administered in the fasting state.

Please refer to the clinical pharmacology review for additional FDA analysis of the pharmacokinetic parameters.

Reviewer Comment: Similar to the pilot study, the data support the bioequivalence of ibuprofen sodium and Motrin IB for extent of exposure. The ibuprofen sodium is absorbed considerably faster than Motrin IB but the clinical significance of this has not been demonstrated.

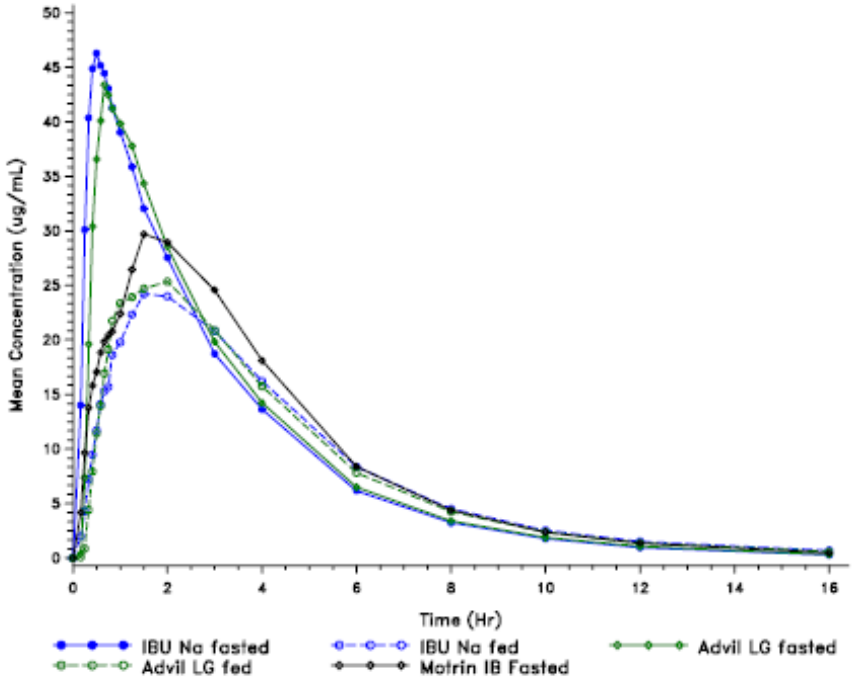
Table 3: AH-09-08 Summary of Pharmacokinetic Results

(Mean, Standard, Deviation, Median, and 90% Confidence Interval)

Treatment	AUCL (mcg•h/mL) Mean (SD)	AUCI (mcg•h/mL) Mean (SD)	C_{max} (mcg/mL)	T_{max} (min) Mean (SD) [median]
A: IBU Na Tablet Fasted	145.7 (29.6)	147.2 (30.1)	50.6 (10.3)	35.1 (14.3) [30.4]
B: IBU Na Tablet Fed	127.2 (28.6)	130.6 (29.2)	31.5 (8.8)	115.1 (72.5) [90.0]
C: Advil Liquigel Fasted	143.8 (32.6)	145.5 (33.2)	48.6 (11.2)	50.1 (29.7) [40.5]
D: Advil Liquigel Fed	125.9 (29.7)	128.9 (30.6)	34.2 (9.7)	111.0 (67.9) [90.0]
E: Motrin IB Tablet Fasted	143.4 (32.2)	145.6 (32.4)	37.4 (7.8)	126.5 (66.9) [120.0]
Ratio (90% Confidence Interval)				
A/C Ratio 90% CI	102.0 (99.1 – 105.0)	102.0 (99.1 – 105.0)	104.2 (96.6 – 112.5)	--
A/E Ratio 90% CI	102.4 (99.5 – 105.4)	101.8 (98.9 – 104.8)	135.0 (125.2 – 145.5)	--
B/D Ratio 90% CI	101.7 (98.8 – 104.7)	102.1 (99.2 – 105.1)	91.2 (84.6 – 98.3)	--

AUCL – Area under plasma concentration versus time curve to last measurable concentration
AUCI - Area under plasma concentration versus time curve to infinity
Source: NDA 201-803, Module 5.3.3.1.2, Page R-12, Table S.1

Figure 2: AH-09-08 Mean Plasma Concentration over Time (All Subjects)



Source: NDA 201-803, Module 5.3.3.1.2, Page R-13, Figure S.1

6 Review of Efficacy

Efficacy Summary

No efficacy studies were performed as part of this NDA. The sponsor relied on the demonstration of bioequivalence (study AH-09-08) between ibuprofen sodium and Advil Liquigel and the comparative bioavailability between ibuprofen sodium and Motrin IB to support the safety and efficacy of this product. While both Advil Liquigel and Motrin IB are approved drugs, Advil Liquigel was approved as a 505(b)(2) application with Motrin IB as the reference listed drug product. The sponsor was informed after the pre-NDA meeting that the application will need to cite reliance on Motrin IB, the product that Advil Liquigels relied upon when approved by the 505(b)(2) route.

6.1 Indication

Ibuprofen was the first non-steroidal anti-inflammatory drug approved for over-the-counter use in the United States. NDAs 18-989 (Advil®) and 19-012 (Motrin) were approved May 18, 1984. Ibuprofen is indicated for the temporary relief of headache, backache, muscular aches, toothache, minor pain of arthritis, menstrual cramps, minor aches and pain associated with the common cold, sore throat, and reduction of fever. NDA 18-989 (sponsored by Wyeth Consumer

Healthcare) provides extensive nonclinical data supporting the safe use of ibuprofen at OTC doses of up to 400 mg every 4 – 6 hours with a maximum daily dose of 1200 mg.

6.1.1 Methods

PCH established efficacy for the proposed formulation by showing bioequivalence to an approved formulation. PCH believes that bioequivalence has been established between the study drug, sodium ibuprofen dihydrate, and the reference drug, Advil Liquigels, and concludes that sodium ibuprofen dihydrate has similar therapeutic properties as the reference drug. The pharmacokinetic bioequivalence approach is based on the rationale that once absorbed, sodium ibuprofen dihydrate is expected to deliver an equivalent level of ibuprofen which will be metabolized and eliminated in the same manner as in the Advil Liquigel product. Successful demonstration of bioequivalence between the sodium ibuprofen dihydrate and Advil Liquigels allows use of the same efficacy claims as the reference drug.

6.1.2 Demographics

The demographic characteristics for the 17 subjects enrolled in the pilot PK study are summarized in Table 4.

Table 4: Demographic Data Study AH-08-07

	Gender n (%)	**Race n (%)**	**Age (years)**	**Weight (kg)**	**Height (cm)**
Male	8 (47%)	--	--	--	--
Female	9 (53%)	--	--	--	--
White	--	11 (64.7%)	--	--	--
Black	--	3 (17.6%)	--	--	--
Asian	--	2 (11.8%)	--	--	--
Other		1 (5.9%)			
Hispanic (yes/no)	--	Yes: 8 (47%) No: 9 (53%)	--	--	--
Mean			30.59	68.01	167.24
Minimum			23	50.0	154
Maximum			44	87.9	183

Source: Source: NDA 201-803, Appendix 16.2.4

The demographic characteristics for the 36 subjects enrolled in the bioequivalence study are summarized in Table 5.

Table 5: Demographic Data Study AH-09-08

	Gender n (%)	Race n (%)	Age (years)	Weight (kg)	Height (cm)
Male	18 (50%)	--	--	--	--
Female	18 (50%)	--	--	--	--
White	--	31 (86.1%)	--	--	--
Black	--	4 (11.1%)	--	--	--
Asian	--	1 (2.8%)	--	--	--
Hispanic (yes/no)	--	Yes: 17 (47.2%) No: 19 (52.8%)	--	--	--
Mean			27.36	68.42	169.14
Minimum			18	50.8	155
Maximum			45	94.3	190

Source: NDA 201-803, Module 5.3.3.1.3, Page R-52, Table A.1

6.1.3 Subject Disposition

One subject withdrew voluntarily from study AH-08-07. She received one dose of IBU Na, Prototype III. No reason for her voluntary withdrawal was recorded.

Four subjects discontinued study AH-09-08 during or after completing the first treatment period. Two subjects (Subject 10021 and 10022) withdrew voluntarily from the study; both withdrew two days after dosing, due to painful blood collections. One subject (Subject 10004) discontinued from the study within one hour of dosing due to emesis and one subject (Subject 10020) discontinued from the study two days after dosing due to headache. Details of the discontinued subjects are summarized in Table 6.

None of the discontinued subjects provided data for at least two treatment periods and thus, per the study protocol, were excluded from the pharmacokinetic analysis. All subjects were exposed to at least one 400 mg dose of ibuprofen and were included in the safety population.

Table 6: Discontinued Subjects Study AH-09-08

Subject ID No.	Age (yrs)	Weight (kg)	Gender	Race	Reason for Discontinuation	Time from Last Dose (days)	Treatment Received	Investigator Comment
10004	21	75.1	Male	Black	Adverse Event	0	IBU Na (fed)	Subject withdrew due to emesis; no treatment period completed
10020	39	81.7	Male	Black	Adverse Event	2	IBU Na (fed)	Subject withdrew due to headache
10021	19	50.8	Female	White	Voluntary	2	IBU Na (fasted)	Subjects withdrew due to painful blood collections
10022	19	75.4	Male	White	Voluntary	2	IBU Na (fed)	

Source: NDA 201-803, Module 5.3.3.1.6, Page R-2173, Appendix 16.2.1 and R-354, Appendix 16.1.7

6.1.4 Analysis of Primary Endpoint(s)

The results of study AH-09-08 are reviewed in Section 5.3. Further analysis of the endpoints is in the Clinical Pharmacology Review.

7 Review of Safety

Safety Summary

PCH has provided safety information from the pharmacokinetic trials conducted for the NDA. In addition, the sponsor refers to the established safety records of NDAs 19-012, 20-402, and 18-989 (all ibuprofen products). PCH submitted postmarketing data from the Wyeth, FDA AERS, WHO, and AAPCC databases. The postmarketing data are reviewed in detail in section 8 of this document. An analysis of the sodium content of ibuprofen sodium and the results of several endoscopy studies were also included. Details of the studies are presented below. After review of the information submitted, no unexpected findings or concerns were noted with ibuprofen sodium. The safety profile is comparable to that of the other approved over-the-counter ibuprofen products. The risk-benefit assessment is favorable.

7.1 Methods

This application refers to the following NDAs for general safety and efficacy of ibuprofen:

- Motrin IB (NDA 19-012)
- Advil Liquigels (NDA 20-402)
- Advil Tablets, Caplets and Gel-Caplets (NDA 18-989)

In addition to the established safety record for the previously approved NDA products, the sponsor submitted safety results of their two clinical trials, AH-08-07 and AH-09-08, and a published endoscopy study evaluating IBU Na and IBU arginate. To put the endoscopy study results into perspective, results from another endoscopy trial of IBU arginate and prescription

doses of ibuprofen are summarized. The sponsor also included an analysis of the sodium content in IBU Na (discussed in section 7.3.5).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Ibuprofen sodium tablets are bioequivalent to Motrin IB tablets in terms of AUC, but the Cmax observed with IBU Na is higher than that observed with Motrin IB. Ibuprofen sodium tablets are bioequivalent to IBU liquigels for both AUC and Cmax. Pfizer Consumer Healthcare conducted two maximum use safety and tolerance (MUST) studies to assess the safety implications of the higher Cmax of liquigels compared to standard IBU tablets in patients. Even though these studies were performed with IBU liquigels, the PK profile is nearly identical that of IBU Na tablets and the sponsor believes the results of these studies are relevant to the current application. Three prospective, randomized, double-blind, clinical trials were conducted to evaluate the overall and gastrointestinal safety of ibuprofen under maximum non-prescription use conditions (1200 mg/day for up to 10 days).

- Study PV-96-04[i] was conducted to fulfill a post-approval commitment for NDA 20-402 (Advil Liquigels). This trial compared ibuprofen tablets and liquigels with placebo. Approximately 400 subjects participated in each arm of the study; each received 400 mg IBU three times daily for 10 consecutive days. Gastrointestinal AEs were the primary endpoint and were reported in 16% of the placebo subjects, 20% in the IBU liquigel group, and 18% in the IBU tablet group. The sponsor concluded that these results indicate the overall and gastrointestinal safety profile of the ibuprofen tablet, ibuprofen liquigels, and placebo are comparable and the safety profile of ibuprofen sodium would be expected to be equally favorable.
- A second trial[ii] was similar in design and compared ibuprofen liquigels, celecoxib, and placebo. In this study, the incidence of GI adverse events was also low and no significant differences were observed between treatment groups (21.9% with IBU, 21.3% with placebo, and 18.5% with celecoxib).
- A large prospective clinical trial[iii] examined almost 9000 patients who required short term (1-7 days) analgesic treatment. Subjects were treated with ibuprofen (up to 1200 mg/day), aspirin (up to 3 grams/day), and acetaminophen (up to 3 grams/day). No serious gastrointestinal events occurred

The sponsor believes that taken together, these studies show the gastrointestinal tolerability of short-term ibuprofen use is favorable. In addition, these studies demonstrate that the higher Cmax seen with the liquigels does not alter the favorable safety profile. Since the ibuprofen sodium has a similar Cmax, PCH concludes these studies support a favorable safety profile for this formulation.

Although the clinical relevance of the surrogate endpoints used in GI endoscopy trials has been debated, PCH included the results of two published endoscopy studies which examined the effects of standard formulations of ibuprofen. In the first study[iv], subjects received 1200 mg/day of ibuprofen for seven days. Endoscopic examinations showed no gastric ulcerations and minimal mucosal damage. The second study[v] compared the effect of aspirin 1.5 g/day, IBU 600

mg/day, indomethacin 75 mg/day, and phenylbutazone 600 mg/day given in three divided daily doses to five subjects for seven days. Ibuprofen provided less acute gastric mucosal damage than aspirin but no statistical analysis was conducted.

An additional endoscopy study compared the gastrointestinal effects of ibuprofen sodium and ibuprofen arginate.[vi] This was a double-blind, single-center crossover trial of 15 subjects who received IBU Na and IBU arginate in doses providing 400 mg of ibuprofen three times daily for 10 doses. After treatment, all subjects with IBU Na had endoscopy scores of 2-4 and after treatment with IBU arginate, most subjects (93.3%) had scores of 2-4.

> Scores were defined as: 0 = no visible lesion; 1 = one hemorrhage or erosion; 2 = 2-10 hemorrhages or erosions; 3 = 11-25 hemorrhages or lesions; and 4 = more than 25 hemorrhages or erosions or an invasive ulcer.

A total of 87 post-dose AEs were reported in 14 subjects: 41 events in 12 subjects after IBU Na and 46 in 12 subjects after IBU arginate. One moderate AE was reported in one subject after receiving IBU Na, and one event of invasive ulcer was observed after receiving IBU arginate. No significant changes in vital signs, ECG, clinical laboratory variables, or physical findings were reported.

The sponsor notes that the study results for IBU Na and IBU arginate are worse than the endoscopy results reported by Lanza and Puscas which administered ibuprofen doses of 600 – 1200 mg/day. The results also differ from results of another endoscopy study evaluating prescription doses of IBU arginate. This study[vii] was a prospective, parallel, randomized, multiple-dose, open-label trial comparing effervescent ibuprofen and IBU arginate at dose of 600 mg four times daily for three days. The endoscopists were blinded to subject treatment. The mean endoscopic Lanza score was lower in the IBU arginate group (1.5 ± 1.1) than in the effervescent IBU group (1.75 ± 1.1, NS).

> Gastric endoscopic lesions were classified using a Lanza score, as 0 = no visible lesion; 1 = mucosal hemorrhages only; 2 = 1-2 erosions; 3 = 3-10 erosions; and 4 > 10 erosions or an ulcer

In total, 16 AEs were reported in 8/12 (67%) of subjects receiving IBU and 7 AEs were reported in 6/12 (50%) of subjects receiving IBU arginate (p=0.016).

PCH noted that the studies used different scoring systems; the scoring system used by Sörgel classified erosions and hemorrhages together while the one used by Gisbert classified these separately. The sponsor believes the scoring system used by Sörgel and the inclusion of subjects with GI lesions at baseline could easily explain the higher scores observed with IBU Na and IBU arginate in that study. The dose of IBU arginate used in the Gisbert study is higher yet fewer lesions were observed, further supporting this reasoning.

PCH concludes that given the more favorable safety profile for IBU arginate relative to ibuprofen in the Gisbert study and the similar results for IBU arginate and IBU Na in the Sörgel study, IBU Na would not be expected to have any increased risk of GI lesions relative to ibuprofen. Further, the bioequivalence of IBU Na to IBU liquigels, which have an excellent safety profile as demonstrated in the two MUST studies (Doyle et al, 1999; Ashraf et al, 2002) and in over 10 years of marketing experience in the US, also indicate that IBU Na would have a favorable safety profile.

There were two pharmacokinetic studies conducted as part of the development program. Adverse event and safety monitoring data from these studies are included in this safety evaluation. Details of the adverse events reported in the two pharmacokinetic studies are discussed in section 7.4.1.

Study AH-08-07: This study evaluated three prototype formulations of ibuprofen sodium. Seventeen subjects were dosed in this study and 16 completed all four study periods. These 16 subjects were exposed to a single 400 mg dose of each of the three prototype treatments and IBU liquigels. Throughout the study, five subjects reported a total of 14 adverse events. There were no serious adverse events, deaths, or subject discontinuations due to an adverse event.

Study AH-09-08: In this study, a total of 32 subjects were each exposed to a single dose of 400 mg ibuprofen in five different treatment periods. Throughout the study, 15 subjects reported a total of 31 adverse events. There were no serious adverse events, deaths, or subject discontinuations due to an adverse event.

7.1.2 Categorization of Adverse Events

Adverse events for the PK studies were coded using the MedDRA dictionary. The verbatim terms used by the patients and the investigators were reviewed and the preferred terms used for the coding were felt to be appropriate and adequate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

A pooled analysis of both studies was not performed since the pilot PK study evaluated multiple prototype formulations of IBU Na while the pivotal PK study tested the final market formulation.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 52 normal, healthy subjects were exposed to at least one dose of an IBU Na formulation. In study AH-08-07, (a four-way crossover design) 17 subjects were administered study medication; 16 were exposed to a single 400 mg dose of all four treatments (IBU Na prototypes I, II, III, and IBU liquigels), and one subject completed only one treatment period (prototype III). In study AH-09-08 (a five-way crossover design), 35 subjects were dosed with study medication. Thirty-two received a single 400 mg dose of all five treatments (IBU Na in the fasted and fed state, IBU liquigel in the fasted and fed state, and IBU tablet in the fasted state). Four subjects received only one treatment (3 dosed with IBU Na in the fed state, and 1 dosed with IBU Na in the fasted state).

The demographic data for subjects in the pharmacokinetic studies is reviewed in section 6.1.2. The extent and quantity of exposure to IBU Na is minimal as these were bioequivalence pharmacokinetic studies. The exposure is adequate for this application, however, as the active drug product has been used extensively for many years.

7.2.4 Routine Clinical Testing

The monitoring methods used during the pharmacokinetic studies were adequate for assessing the safety information. In addition to physical examination, subjects had clinical laboratory testing and vital signs measurements. The monitoring for adverse events was appropriate. Results of the testing are discussed in section 7.3.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse event evaluations performed by the sponsor were appropriate for the study designs. Over-the-counter ibuprofen is intended for short-term use and most of the common problems associated with NSAIDs are more likely to occur when the drugs are used in higher doses and for longer durations. The evaluation was appropriate for an OTC indication particularly since the focus was bioequivalence, not efficacy.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths.

7.3.2 Nonfatal Serious Adverse Events

There were no serious, potentially serious, or significant adverse events.

7.3.3 Dropouts and/or Discontinuations

In study AH-08-07, no subjects discontinued due to an adverse event. In study AH-09-08, two subjects discontinued due to an adverse event, both after administration of IBU Na in the fed state. One subject discontinued due to nausea and vomiting and another discontinued due to a headache. Subject disposition for study AH-09-08 is reviewed in detail in section 6.1.3.

7.3.4 Significant Adverse Events

There were no significant adverse events.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All adverse events that occurred in the PK studies were summarized by MedDRA (version 9.0) System Organ Class and Preferred Term, according to severity and relationship to study medication.

In study AH-08-07, five subjects reported a total of 14 adverse events. These are summarized in Table 7.

Table 7: AH-08-07 Summary of Adverse Events

Adverse Events (by MedDRA version 9.0 SOC and PT)	**Prototype I (N=16)**		**Prototype II (N=16)**		**Prototype III (N=17)**		**Advil Liquigels (N=16)**	
	n	**Related**	**n**	**Related**	**n**	**Related**	**n**	**Related**
Any SOC	**3**	--	**5**	--	**5**	--	**1**	--
Eye Disorders	**0**	--	**1**	--	**0**	--	**0**	--
Eye irritation	0		1	no	0		0	
Gastrointestinal Disorders	**0**	--	**1**	--	**3**	--	**0**	--
Nausea	0		1	no	2	1 yes 1 no	0	
Vomiting	0		0		1	yes	0	
General Disorders & Admin Site Conditions	**0**	--	**0**	--	**1**	--	**0**	--
Catheter site reaction	0		0		1	no	0	
Metabolism and Nutrition Disorders	**1**	--	**0**	--	**0**	--	**0**	--
Dehydration	1	no	0		0		0	
Musculoskeletal & Connective Tissue Disorders	**0**		**1**	--	**0**	--	**0**	--
Pain in extremity	0		1	no	0		0	
Nervous System Disorders	**1**	--	**0**	--	**0**	--	**1**	--
Headache	1	no	0		0		0	
Somnolence	0		0		0		1	no
Renal & Urinary Disorders	**1**	--	**0**	--	**0**	--	**0**	--
Pollakiuria	1	yes	0		0		0	
Respiratory, Thoracic, & Mediastinal Disorders	**0**	--	**2**	--	**0**	--	**0**	--
Cough	0		1	no	0		0	
Throat irritation	0		1	yes	0		0	
Skin & Subcutaneous Tissue Disorders	**0**	--	**0**	--	**1**	--	**0**	--
Blister	0		0		1	no	0	

Related = Treatment medication and adverse event related per sponsor (yes or no)
n = Number of subjects experiencing AEs
Source: NDA 201803, Module 5.3.3.1.3 Appendix, Table C.1 and C.2, Pages R-62 – R-65

Many of the adverse events were experienced by two subjects (#20003 and 20008). The adverse events by subject number are as listed in Table 8. Most of the adverse events were believed by the sponsor to be to unrelated to the treatment medication and none were serious.

Table 8: AH-08-07 Adverse Events by Subject Number and Severity

Subject Number	Adverse Event Preferred Terms	Severity	Correlation to Treatment	
			Related	Unrelated
20003	Dehydration, Headache, Eye Irritation, Nausea, Pain in Extremity, Cough	Mild		X
	Throat Irritation	Mild	X	
20007	Pollakiuria	Mild	X	
10002	Nausea	Mild		X
20008	Nausea, Vomiting	Moderate	X	
	Catheter Site reaction, Blister	Mild		X
20006	Somnolence	Mild		X

Source: NDA 201803, Module 5.3.3.1.3 Appendix, Table C.3, Page R-66-69

Reviewer Comment: No new safety signals were noted in Study AH-08-07.

In study AH-09-08, 15 subjects reported a total of 31 adverse events. All adverse events were rated as mild except one report each of nausea, vomiting, headache, and blurred vision; these were of moderate severity. Fourteen of the 31 AEs were considered by the sponsor to be related to the study medications. The adverse event information for this study is summarized in Table 9.

The two most common organ systems for adverse events were gastrointestinal and nervous system (each with 11 adverse events reported). The most common adverse event among all treatments was headache (six reports across all treatments). There was no significant difference in the type or frequency of adverse events reported between the treatment groups.

Table 9: AH-09-08 Summary of Adverse Events by SOC, Preferred Term, and Relationship

Adverse Event (SOC and PT)	IBU Na Fasted		IBU Na Fed		Advil Liquigel Fasted		Advil Liquigel Fed		Motrin IB Fasted	
	n	Rel	n	Rel	n	Rel	n	Rel	n	Rel
Any SOC	**6**	--	**10**	--	**3**	--	**6**	--	**6**	--
No. of Subjects	5		7		2		4		4	
Eye Disorders	**0**	--	**1**	--	**0**	--	**0**	--	**0**	--
Vision Blurred	0		1	no	0		0		0	
Gastrointestinal Disorders	**3**	--	**2**	--	**1**	--	**2**	--	**3**	--
Constipation	1	no	0		1	no	0		1	yes
Nausea	0		1	no			0		1	yes
Abdominal distention	0		0		0		0		1	yes
Abdominal pain	1	yes	0		0		0		0	
Diarrhea	0		0		0		1	yes	0	
Dyspepsia	0		0		0		1	yes	0	
Flatulence	1	no	0		0		0		0	
Vomiting	0		1	no	0		0		0	
General Disorders	**0**	--	**1**	--	**0**	--	**0**	--	**0**	--
Fatigue	0		1	yes	0		0		0	
Infections/Infestations	**0**	--	**0**	--	**0**	--	**1**	--	**0**	--
Herpes simplex	0		0		0		1	no	0	
Musculoskeletal Disorders	**0**	--	**1**	--	**0**	--	**0**	--	**1**	--
Back pain	0		0		0		0		1	no
Pain in extremity	0		1	no	0		0		0	
Nervous System Disorders	**3**	--	**2**	--	**2**	--	**2**	--	**2**	--
Headache	2	1 yes 1 no	1	no	1	yes	1	yes	1	yes
Dizziness	1	no	0		1	no	0		1	no
Paraesthesia	0		0		0		1	no	0	
Somnolence	0		1	yes	0		0		0	
Respiratory/Thoracic/Mediastinal Disorders	**0**	--	**1**	--	**0**	--	**0**	--	**0**	--
Nasal congestion	0		1	no	0		0		0	
Pharyngolarygeal pain	0		1	no	0		0		0	
Skin/Subcutaneous Disorders	**0**	--	**0**	--	**0**	--	**1**	--	**0**	--
Alopecia	0		0		0		1	no	0	
Dry skin	0		1	no	0		0		0	

Rel = Treatment medication and adverse event related per sponsor (yes or no)
Source: NDA 201803, Module 5.3.3.1.3 Appendix, Table C.2, Pages R-104 – R-108

Reviewer Comment: There were no serious or unexpected adverse events. No new safety signals were identified during Study AH-09-08.

7.4.2 Laboratory Findings

Study AH-08-07 and AH-09-08:
All subjects underwent a pre-study laboratory evaluation, including a complete blood count (CBC), complete urinalysis, and serum chemistry profile as well as tests for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). The serum chemistry profile consisted of albumin, alkaline phosphatase, bilirubin (total), blood urea nitrogen (BUN), calcium, serum bicarbonate test (CO2/HCO3), chloride, cholesterol (total), creatinine, gamma-glutamyl transpeptidase (gamma GT), globulin, glucose, lactate dehydrogenase (LDH), phosphorous, potassium, protein (total), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), sodium, triglycerides, and uric acid. Serum pregnancy testing was also conducted for all females. At check-in prior to Period I, all subjects had a urine drug screen, and female subjects had a urine pregnancy test.

A post-study laboratory evaluation was completed as part of study AH-08-07 and consisted of hematology and chemistry analyses of blood samples and a urine pregnancy test for female subjects. These tests were also performed if a subject was prematurely discontinued from the study. There was no post-study laboratory evaluation in study AH-09-08.

In study AH-08-07, fourteen of the seventeen subjects (82.4%) had at least one abnormal lab finding in the pre-study analysis and eleven of seventeen (64.7%) had at least one abnormality in the post-study testing. These were reviewed and found to be of no clinical significance.

In study AH-09-08, twenty-three of the thirty-six subjects (63.9%) had at least one abnormal lab finding in the pre-study analysis; none were clinically significant.

7.4.3 Vital Signs

Study AH-08-07 and AH-09-08:
At the pre-study evaluation, all subjects provided a medical history and received a physical examination, including heart rate, blood pressure, weight, height, and BMI determination. Completion of the pre-study physical examination was required within 21 days prior to the start of Period I dosing.

A post-study physical examination, including vital signs but excluding height and BMI, was repeated for all subjects after the completion of the final study period, and prior to study discharge. This examination was also performed if a subject prematurely discontinued from the study.

There were no clinically significant changes in the vital signs or physical examinations from the baseline to end of study measurements.

7.4.4 Electrocardiograms (ECGs)

No ECGs were completed on the subjects in these pharmacokinetic studies.

7.4.5 Special Safety Studies/Clinical Trials

As part of the NDA application, PCH evaluated the quantity of sodium a patient using ibuprofen sodium would be consuming and the implications for populations potentially at risk. The formulation of IBU Na proposed contains (b) (4) of sodium in each tablet. The maximum OTC recommended dose is six units per day; therefore, up to 134 mg/day of additional sodium would be ingested by a consumer taking the maximum recommended daily dose. This quantity should produce a minimal effect on blood pressure. Additionally, this amount falls below the amount of 140 mg of sodium/day which requires a warning to alert patients who are on sodium-restricted diets to consult their doctors before using the product.

The current Drug Facts for ibuprofen includes warnings to alert consumers and healthcare professionals to consult a physician before using the product in patients with asthma, heart disease, hypertension, or kidney disease. This labeling should help to decrease the risk for individuals with severe hypertension or renal disease. Over-the-counter use of ibuprofen is limited to 10 days, which should also reduce the risk of chronic intake of increased sodium or chronic ibuprofen.

7.5 Other Safety Explorations

The pharmacokinetic studies performed for this NDA did not evaluate adverse events with regards to dose dependency, time dependency, demographics, or diseases. The subjects were healthy and received single doses of the study medications. NSAIDs are known to have increased risk of gastrointestinal events when used for longer duration or in higher doses. NSAIDs may also cause renal impairment and are associated with an increased risk of congestive heart failure. Both the cardiac and renal risks are increased in older patients.

7.5.5 Drug-Drug Interactions

There was no drug interaction study performed for ibuprofen sodium. Prescription strength ibuprofen (dosed up to 3200 mg daily) includes the following drug interaction warnings:

- ACE-Inhibitors: There are reports that NSAIDs may decrease the antihypertensive effect of ACE-Inhibitors. This should be considered in patients taking both types of medications.
- Aspirin: When ibuprofen tablets are administered with aspirin, the protein binding is reduced, although the clearance of free ibuprofen is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of ibuprofen and aspirin is not generally recommended because of the potential for increased adverse effects.
- Diuretics: Clinical studies, as well as post marketing observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response

has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure.

- Lithium: Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.
- Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate NSAIDs could enhance the toxicity of methotrexate; caution should be used when these are administered concomitantly.
- Warfarin-type anticoagulants: Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin times or other clotting factors when administered to individuals on warfarin - type anticoagulants. However, because bleeding has been reported when ibuprofen and other NSAIDs have been administered to patients on warfarin, the physician should be cautious when administering ibuprofen to patients on anticoagulants. The effects of warfarin and NSAIDs on GI bleeding are synergistic. OTC labeling includes a warning about “stomach bleeding” in people who “take a blood thinning (anticoagulant) or steroid drug.”

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no carcinogenicity studies performed as part of this NDA application. Previously conducted preclinical studies (for prescription strength ibuprofen) have not indicated carcinogenic potential.

7.6.2 Human Reproduction and Pregnancy Data

Due to the relatively small number of subjects in both PK studies, and the fact that both studies enrolled young, healthy subjects, no analyses in special groups were performed. The active moiety in IBU Na is ibuprofen, so the same drug interactions and precautions for use during pregnancy and lactation are appropriate as for standard ibuprofen. These precautions (from prescription labeling) include:

- Teratogenic effects - Pregnancy Category C: Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Ibuprofen should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Nonteratogenic effects: Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.

- Labor and Delivery: In rat studies with NSAIDs an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of ibuprofen on labor and delivery in pregnant women are unknown.
- Nursing Mothers: It is not known whether this drug is excreted in human milk. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer Comment: The OTC labeling warns against use of ibuprofen by pregnant or breast-feeding women. The labeling specifically warns against use of ibuprofen during the last three months of pregnancy due to potential problems for the unborn child or complications during delivery. The labeling is worded is consumer-friendly language and is appropriate.

7.6.3 Pediatrics and Assessment of Effects on Growth

This application refers to the following NDAs for safety and efficacy of ibuprofen in the pediatric population to support a partial waiver of pediatric studies in children under the age of 12 and the proposed pediatric plan for adolescents age 12-17:

- Children's Advil Suspension (NDA 20-589 and NDA 19-833)
- Infant's Advil Drops (NDA 20-812)

Ibuprofen Na tablet will have the same labeled indications and is intended for the same consumer population as currently-marketed ibuprofen. The proposed product is not intended for use by children under 12 years of age. PCH does not believe ibuprofen Na tablets represent a meaningful therapeutic benefit over existing therapies. PCH also believes ibuprofen Na is unlikely to be used in a substantial number of children ages 2 month to 11 years of age.

PCH is requesting a partial waiver for pediatric studies for children less than 12 years of age based on the following:

- There are existing clinical data on ibuprofen, the active ingredient in ibuprofen Na tablets, in children under age 12 demonstrating safety and efficacy for the labeled indication when used according to the age- and weight-based dosing on the labeling.
- The pharmacokinetic study included in the NDA submission (AH-09-08) demonstrated bioequivalence of ibuprofen Na tablets to ibuprofen liquigels for both the rate and extent of ibuprofen absorption. Previous clinical studies have demonstrated bioequivalence of the ibuprofen liquigels to currently-marketed children's ibuprofen. Therefore an ibuprofen Na product would not represent a meaningful therapeutic benefit over existing children's ibuprofen products.
- Multiple ibuprofen products of different strengths and dosage forms specifically designed for infants (6 -23 months) and children (2-11 years) are currently available OTC. Any potential use of an ibuprofen Na pediatric product would be limited as there is no meaningful therapeutic benefit over the currently available pediatric ibuprofen products. Furthermore, there are a large number of pediatric acetaminophen-containing pain reliever/fever reducer options available OTC.

The proposed product is indicated for use by patients age 12 years and older. PCH does not believe further studies in the 12 to 17 year old age group are necessary as ibuprofen, the active ingredient in ibuprofen Na, is currently approved and marketed for use by this age group. The Pediatric Plan proposed consists of cross-references to existing adolescent clinical studies in NDAs 19-833 and 20-402, as well as published literature. PCH concludes that existing data on ibuprofen in adolescents ages 12 – 17 years demonstrates:

- Ibuprofen is safe and effective as a pain reliever/fever reducer in the adolescent population
- The appropriate dose of ibuprofen for this population is 200 mg and the directions for use are the same for adolescents and adults.
- Based on the pharmacokinetic/bioequivalence study (AH-09-08), ibuprofen Na tablets are expected to have the same efficacy and safety profile as standard ibuprofen tablets and liquigels.

The sponsor's proposed pediatric plan and the request for a waiver for children under 12 years of age was presented to the Pediatric Review Committee (PeRC) on February 16, 2011. After considerable discussion, the PeRC agreed that while this product would not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, there is no evidence that the product will not be used in a substantial number of patients less than 12 years of age. The committee believes that if the sponsor is to be granted a waiver using this criterion, they will need to provide data to support that the product will not be used in > 50,000 patients less than 12 years of age. If the data is not available, PeRC believes the sponsor should submit a request for a deferral and a pediatric plan to support labeling for patients from ages birth through 16 years. The recommendation from the Pediatric Review Committee is being discussed within the Division of Nonprescription Clinical Evaluation and a final decision on how to proceed and what type of additional information will be requested from the sponsor is pending.

Reviewer Comment: This product offers no clinical advantage over the many (more than 20) other currently available ibuprofen products for children less than 12 years of age. There are millions of units of ibuprofen in pediatric dosage forms sold each year in the United States; the active drug product is commonly used. It is impossible to predict exactly how many consumers would use this particular formulation instead of the many others currently marketed; use would depend on many factors including, for example, pricing and advertising. If anything, having another ibuprofen product for children increases the likelihood of consumer confusion and accidental overdose. With no clear clinical advantage and the extensive availability of very similar products, I see no reason this company should be required to develop a pediatric plan for this drug to be used in children less than 12 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No analyses in special groups were performed as part of this NDA application. PCH believes there are no concerns for drug abuse, withdrawal and rebound, or precautions related to driving or operating machinery and mental ability associated with use of this product.

Reviewer Comment: I agree with the sponsor's conclusions regarding potential for abuse of this product.

7.7 Additional Submissions / Safety Issues

There are no additional submissions or safety issues identified which are not integrated into the review.

8 Postmarket Experience

The sponsor including post-marketing data from four sources:

- Wyeth safety database – initial reporting period February 1, 2009 to February 1, 2010 and update February 2, 2010 to September 1, 2010
- World Health Organization (WHO) database – initial reporting period October 1, 2008 to September 30, 2009 and update January 1, 2010 through April 23, 2010
- FDA AERS database – initial reporting period July 1, 2008 to June 30, 2009 and update July 1, 2009 through December 31, 2009
- American Association of Poison Control Centers (AAPCC) database – reporting period February 1, 2009 to January 21, 2010 and update February 2, 2010 to June 30, 2010.

For each database, the sponsor reviewed cases of ibuprofen use associated with patient death, drug interactions, drug overdose, drug abuse or misuse, experience during pregnancy and lactation, and use by special populations (pediatric, elderly, and patients with renal insufficiency and cirrhosis).

8.1 Wyeth Safety Database

The initial report covered the Feb 2009 to Feb 2010 time period and was limited to information from case reports classified as serious. A four-month safety update with the same search criteria covered the 2 Feb 2010 to 1 Sept 2010 time period. The database was searched to identify serious reports containing ibuprofen as a suspect drug. It is not possible to distinguish ibuprofen sodium formulation from other ibuprofen formulations in the safety database.

PCH estimates approximately (b) (4) caplets, (b) (4) fast-gel caps, (b) (4) liquid-gel capsules, (b) (4) grams of gel, (b) (4) gel-caplets, (b) (4) hard-caps, (b) (4) milliliters of spray liquid, and (b) (4) tablets of adult strength ibuprofen were distributed from February 1, 2009 to January 31, 2010. In addition, approximately (b) (4) milliliters of liquid/suspension/drops, and (b) (4) chewable tablets of children's strength ibuprofen were distributed during this period.

During the Feb 2, 2010 to Sept 1, 2010 time period, it is estimated that approximately (b) (4) caplets, (b) (4) fast-gel caps, (b) (4) liquid-gel capsules, (b) (4) grams of gel, (b) (4) gel-caplets, (b) (4) hard-caps, (b) (4) milliliters of spray liquid, and (b) (4) tablets of adult strength ibuprofen were distributed. In addition,

approximately (b) (4) milliliters of liquid/suspension/drops, and (b) (4) chewable tablets of children's strength ibuprofen were distributed during this period. Due to different indications, presentations, and various dosage regimens, it is not possible to estimate the number of patients treated with ibuprofen during the period of this review.

The Wyeth database contains marketed adverse experience (AE) reports, both foreign and domestic, from consumers, health care professionals, registries, licensing partners, and literature reports of serious AE's for Wyeth products. Additionally, the database contains serious AE reports from investigational studies conducted by Wyeth Clinical Research and Development (CR&D) and from non-CR&D post-marketing studies, regardless of causality.

During the initial reporting period, five reports described events with fatal outcomes; three of these reports were medically confirmed. In two reports, the use of ibuprofen and the patient's death were linked temporally. In the remaining three reports the causes of death - perforated ulcer, acute renal failure, and hemorrhagic gastritis - are adverse events listed in the Undesirable Events section of the Reference Safety Information (RSI) for ibuprofen. The patient with the perforated ulcer was receiving celecoxib as well as ibuprofen. The patient suffering acute renal failure as a cause of death was elderly and received ibuprofen for approximately 5 ½ years. The report for the patient with hemorrhagic gastritis and pneumonia lists the start of ibuprofen therapy as five days prior to onset of abdominal pain and seven days before the patient's death. The role of ibuprofen in this patient's death, if any, is not clear.

There were 25 reports of deaths during the Feb 2010 to Sept 2010 reporting period. Twenty-one of these were reported in the 2008 Annual Report of the American Association of Poison Control Centers. The four remaining reports were from healthcare professionals, and one was from a study. Patients ranged in age from 13 to 87 years, with average age of 41 years. The majority of patients were male (n=15). The most frequently reported cause of death was completed suicide (16 cases). In 23 of the 25 cases, one or more other medications with potential for toxicity in addition to ibuprofen were involved. In the remaining two cases, patients were elderly and were receiving ibuprofen for therapeutic reasons. An 87-year-old male who died of Stevens-Johnson syndrome had evidence of Mycoplasma infection and was receiving many medications, including allopurinol and ibuprofen, both of which have been associated with Stevens-Johnson syndrome. In the last case, a 67-year-old male developed renal failure. However the reported cause of death was pleural effusion and lung cancer progression and it is unlikely ibuprofen played a significant role.

Of the six serious reports of drug interaction identified in the initial reporting period coincident to ibuprofen use, four were medically confirmed. One case reported a negative de-challenge. Four cases report an interaction with drugs that have warnings about the use with concomitant NSAIDs. The sixth report described a lack of effect for the treatment of pyrexia.

The safety update included two serious reports of drug interactions; both were medically confirmed. Both reports described bleeding tendencies. The first described gastrointestinal bleeding is a patient also receiving aspirin therapy. The second described bruising, eye

hemorrhage, and post-procedure hematoma associated with use of venlafaxine and ibuprofen. Both of these interactions are described and recognized complications. No further action is thought to be needed at this time.

During the update reporting period, a focused review was conducted regarding a drug interaction between ibuprofen and lithium. Lithium usage is usually chronic as opposed to episodic or acute and the therapeutic range of lithium is relatively narrow. Based on this review of the literature and case reports received by the marketing authorization holder (MAH), there is reasonable suspicion that a drug interaction may occur in patients receiving lithium salts and ibuprofen resulting in an increased blood lithium level. Based on this review, the sponsor states a drug-drug interaction between ibuprofen and lithium salts will be added to the ibuprofen core data sheet (CDS).

In the initial reporting period, of the thirty-two serious reports of overdose identified coincident to ibuprofen use, twenty-two reports were medically confirmed. One overdose case was fatal and involved ingestion of multiple drugs. Seventeen reports were for single drug overdose where ibuprofen was the only suspect drug. The remaining 15 reports are confounded due to the multiple drug ingestions. During this reporting period, there were four serious reports of abuse or misuse received for ibuprofen with no fatal outcomes.

During the safety update period, 36 serious reports of overdose were identified coincident to ibuprofen use. Seventeen cases reported fatal outcomes and all of these cases involved ingestion of multiple drugs. During this period there were three serious reports of drug abuse or intentional misuse; two were fatal and included in the death totals above.

Ibuprofen is generally not considered a product of abuse as neither therapeutic doses nor overdose have been associated with psychogenic effects. However, misuse of ibuprofen may occur if a consumer does not follow recommended dosing frequency and duration. Based on this review, no action is warranted at this time.

During the initial reporting period, one report of exposure during pregnancy and one report of exposure during pregnancy and during breastfeeding were received for ibuprofen. The first case, which is a medically confirmed case from the United Kingdom, describes a 29 year-old female who received ibuprofen during the sixth week of pregnancy for an unknown duration of use and reportedly delivered a normal male infant at 38 weeks gestation via cesarean section. The second case, a non-medically confirmed case from the United States, describes a male infant who received ibuprofen tablet therapy transplacentally in the third trimester and was born with a hole in his heart. The baby's mother had also been taking 8 tablets per day while breast feeding for the past few months and the baby experienced arrhythmias. Maternal and neonatal medical histories were not provided. Concomitant medications were not reported. An outcome to the baby’s adverse events was not provided.

During the safety update period, two serious reports of exposure during pregnancy were identified. The first case was an infant exposed to a 6 gm overdose of ibuprofen at 30 weeks

and was delivered prematurely at 34 weeks with constriction of the ductus arteriosus. Maternal medical history, pregnancy history, concomitant medications, and neonatal outcome were not provided. The second was an infant delivered at 37 weeks gestation by emergency cesarean section 36 hours after maternal ingestion of 7.2 gm of ibuprofen in one dose. The infant was diagnosed with suspected premature closure of the ductus arteriosus at birth. Similarly, maternal medical history, pregnancy history, concomitant medications, and neonatal outcome were not provided. The ibuprofen core data sheet states use of ibuprofen during the third trimester of pregnancy is contraindicated. OTC labeling addresses the pregnancy risks and advises consumers to discuss use of ibuprofen with a healthcare profession if pregnant or breast-feeding. The labeling also warns against use of ibuprofen during the last three months of pregnancy due to potential for problems in the unborn child or complications during delivery. Based on review of the additional the current labeling, no additional action is warranted at this time.

During the initial reporting period, 137 serious reports were received pertaining to ibuprofen use in pediatric (n=104) and elderly (n=33) populations. There were 10 reports identified describing acute renal failure occurring in adolescents and coincident to ibuprofen use. All of the reports were medically confirmed; eight of the cases were from France. Several of the patients had complex co-morbid conditions and medical histories including sepsis, pneumonia, multidrug overdose, kidney stones, Fanconi's syndrome, polyuria, and solitary kidney. Five of the reports contain information on the use of concomitant medication which confounds the role of ibuprofen use. Additionally, some of the concomitant medications are reported to be associated with acute renal failure.

Of the 33 cases reported in the elderly, 24 reports were medically confirmed with one fatal outcome identified. Three reports described renal impairment or acute pre-renal failure coincident with ibuprofen use. These cases were reviewed and found to be confounded by co-morbid conditions of rhabdomyolysis, digestive disorders, and acute blood loss that resulted in renal effects.

In the safety update, 68 serious reports were noted pertaining to ibuprofen use in pediatric (n=42) and elderly (n=26) populations. There were five serious reports describing renal events in pediatric patients. The patients in the renal event cases were experiencing significant co-morbid conditions dehydration (n=3), sickle cell anemia (n=1) and hospitalization for vomiting (n=1). The cases involving the elderly population noted no unexpected adverse events.
During the initial reporting period no reports were identified that contained medical history preferred terms within the MedDRA high level term *Hepatic fibrosis and cirrhosis*.

During the initial reporting period, seven serious reports containing medication errors were identified occurring with ibuprofen use. Five reports were medically confirmed. Four of the reports describe medication errors occurring in children: one report described a child being given two different alternating ibuprofen products every three hours, one report described a child receiving ibuprofen plus another NSAID, one report described an infant who was prescribed ibuprofen before the age of three months, and the fourth report described an adolescent who received an expired product. The safety update report added two serious reports containing

medication errors. One case was fatal and related to a multiple drug overdose; in the other the patient took expired medication and recovered.

As part of the safety update, PCH conducted a review of ibuprofen case report data from internal and external sources covering a one year time period identifying reports of acute kidney injury (formerly referred to as acute renal failure [ARF]) in pediatric patients. A search of Medline, Embase, BIOSIS, CAB abstracts, Current Content and Derwent, going back to January 2000, was conducted to identify articles pertaining to ibuprofen and renal failure in a pediatric population. A recurring observation from the case series and case reports was underlying hypovolemia in children who had renal impairment associated with NSAID therapy.

The safety database was searched using the timeframe June 1, 2005 to May 31, 2010 to identify all cases associated with ibuprofen that contained preferred terms within the acute renal failure SMQ (Standardized MedDRA Query, Narrow and Broad terms, MedDRA version 13.0). A total of 199 cases were identified using the specified search criteria. Of the 199 reports, 67 were identified as involving pediatric patients under the age of 18 years. All 67 pediatric reports were considered serious. One report had a fatal outcome. This report from the literature described a 17-year-old female who ingested a massive ibuprofen overdose. Sixty-six of the 67 pediatric reports were medically confirmed. In general, the pediatric cases of potential ARF included concomitant medications or concurrent conditions that predisposed patients to renal insufficiency. While many children had conditions such as fever and dehydration that may have predisposed them to renal impairment, the use of ibuprofen likely provided additional cause.

Overall, the information provided for the reporting periods supports the known safety profile of ibuprofen. While no new major findings impacting the safety profile of ibuprofen were identified, there were two actions mentioned by the sponsor as part of the postmarketing data review:

- Based on the review of the literature and case reports from the safety surveillance database, the reference safety information (RSI) is being updated to advise consultation with a physician before ibuprofen use if the child may be in a hypovolemic state.
- Based on the review, a drug-drug interaction between ibuprofen and lithium salts will be added to the ibuprofen core data sheet (CDS).

The sponsor's overall conclusion states "No new major findings impacting the safety profile of ibuprofen were identified, and no additional action is warranted at this time." FDA requested additional information regarding this apparent discrepancy and PCH clarified that acute renal failure associated with ibuprofen and the interaction of ibuprofen and lithium have been identified and addressed with appropriate warnings on the product labeling. The labeling for products indicated for adults and children age 12 years and older states:

Ask a doctor before use if

(b) (4)

PCH does not plan to seek a pediatric indication for IBU Na; it is indicated for adults and children 12 years and older. The labeling as outlined above provides warning about the potential for renal problems and also advises patients to seek advice before using ibuprofen while taking other medications.

Reviewer Comment: After review of the Wyeth database safety information, the safety update, and the additional information provided by PCH, the current labeling is felt to provide adequate warnings regarding use of ibuprofen by patients at risk for acute renal failure or who may be taking other medications.

8.2 World Health Organization (WHO) and FDA Adverse Event Reporting System (AERS) Databases

PCH provided an analysis of ibuprofen adverse event data from these two databases as part of the NDA for ibuprofen sodium. The WHO data are from the WHO's Programme for International Drug Monitoring. There are currently 97 official member countries. Each participating country's governing body has designated a National Center for Pharmacovigilance, which is responsible for the collection of individual case reports of adverse events (AEs). All of the reports for the AERS data come from the MedWatch System, which is the FDA's Safety Information and Adverse Event Reporting Program. Consumers and healthcare professionals can voluntarily report AEs using the MedWatch System, while manufacturers are required by FDA regulations to report AEs that are reported to them.

The initial reporting period covered for the WHO data was October 1, 2008 through September 30, 2009 and for the AERS data was July 1, 2008 through June 30, 2009. The safety update covered January 1, 2010 through April 23, 2010 for the WHO data and July 1, 2009 through December 31, 2009 for the AERS data. Causality was not assessed. In all cases ibuprofen was identified as the suspected or interacting medication (WHO dataset) or the primary or secondary suspected medication (AERS dataset). A summary of the reports is shown in Table 10. Several limitations in the data should be noted:

- Events may be reported to more than one database; the degree of overlap is unknown.

- An episode may be reported to the same database more than once by different sources; no effort was made to identify duplicate reports.
- Adverse event data depends on spontaneous reports. They are generally under-reported but over-reporting may occur due to stimuli such as media attention.
- A causal relationship to any medication is not usually possible
- Cases involving pregnancy were not identified in the database and may be under-reported.

Table 10: Summary of Case Reports to WHO and AERS databases

	WHO 10/1/08 – 9/30/09	**WHO 1/1/10 – 4/23/10**	**AERS 7/1/08 – 6/30/09**	**AERS 7/1/09 – 12/31/09**
# Cases mentioning ibuprofen	1351	294	1397	648
# Serious cases	919	233	1344	633
# Countries reporting	40	18	40	31
#(%) Serious cases				
from United States	492 (53.5)	77 (33.1)	704 (52.4)	234 (37)
from Germany	145 (15.8)	71 (30.5)	115 (8.6)	70 (11.1)
from France			138 (10.3)	79 (12.5)
from United Kingdom	105 (11.4)		135 (10)	107 (16.9)
from Canada		38 (16.3)		

Source: NDA 201,803, Module 5.3.6.2 and 5.3.6.6

There were three AERS cases in the initial report and one in the update reported as 'congenital abnormality.' These were:

1. Case 5807559: A male age unreported with bipolar disorder, nervous system disorder, pancreatic cyst, pancreatitis, peroneal muscular atrophy, schizophrenia, spina bifida, and type 1 diabetes mellitus who reported use of ibuprofen only.
2. Case 5807560: A female age unreported with congenital oesophageal anomaly, pain, pneumonia, and premature baby who reported use of ibuprofen, opium, and Medication Unspecified.
3. Case 6042253: Both gender and age unknown with acute myocardial infarction, arthritis bacterial, deafness, peripheral ischaemia, and pneumonia who reported use of placebo-verbatim, celecoxib, gabapentin, insulin, hydromorphone, ibuprofen, naproxen, esomeprazole, insulin human, prednisone, and lisinopril.
   Reviewer Comment: These diagnoses seem unlikely for a congenital abnormality.
4. Case 6439910: A male, age unreported, with arrhythmia, drug exposure via breast milk, and heart disease congenital who was using ibuprofen only (dose unknown).

There was no additional information available to clarify these cases.

In the initial WHO report, there were 390 serious AE (SAE) reports in which the only medication listed was ibuprofen. Of these, there were 22 deaths, 35 life-threatening events, and three cases associated with pregnancy. The most frequently reported preferred term (PT) for death was overdose (n=6). The safety update included 104 serious cases with ibuprofen as the only listed medication. These 104 case reports included 28 hospitalization events (nine were life-threatening) and six deaths.

There were 372 ibuprofen-only SAEs in the initial AERS data. Of these, there were 17 deaths, 26 life-threatening events, and two cases associated with pregnancy. The AERS safety update report included 158 ibuprofen-only cases; 74 were hospitalization events, 18 life-threatening, and five deaths.

Both the WHO and AERS databases were examined for potential differences in the safety profiles for ibuprofen sodium versus all other formulations of ibuprofen. There were only a few cases of the use of ibuprofen sodium in either data set. The WHO data had 40 cases that included ibuprofen sodium; 19 were considered serious, two were non-serious, and 19 had no rating. One serious case (11073828) included death where the only medications were Nurofen® and paracetamol (acetaminophen). Death was due to hepatic failure and attributed to accidental overdose. The WHO update had nine cases that included ibuprofen sodium; six were considered serious and there were no deaths.

The initial AERS data had eight cases that included ibuprofen sodium, all of which were considered serious. One serious case (5834878) included death where the only medications were Nurofen® and ibuprofen. Death was due to hepatic failure and attributed to accidental overdose. The AERS update included seven cases with ibuprofen sodium, all considered serious. There were two deaths and both involved other medications in addition to ibuprofen (acetaminophen, atorvastatin, diclofenac, and leflunomide). One patient died of large intestinal hemorrhage and the other of toxic shock syndrome.

The adverse events were coded by MedDRA system organ class (SOC) and PT. The AEs that occurred in >2% of the serious cases reported in the initial WHO and AERS data are shown in Tables 11 and 13. The WHO and AERS updates showed a similar pattern of common adverse events. These are shown in Tables 12 and 14.

Table 11: Adverse Events in >2% of Serious Cases (n=919): WHO database initial report

SOC	Preferred Term	Number of cases	% of AEs reported[5]	% of cases
Inj&P	Drug toxicity	56	1.9	6.1
Psych	Completed suicide	56	1.9	6.1
Inj&P	Overdose	53	1.8	5.8
Psych	Suicide attempt	50	1.7	5.4
Renal	Renal failure acute	39	1.3	4.2
Resp	Dyspnoea	38	1.3	4.1
Inj&P	Intentional overdose	37	1.3	4.0
Gastr	Vomiting	33	1.1	3.6
Psych	Drug abuse	33	1.1	3.6
Immun	Hypersensitivity	32	1.1	3.5
Skin	Urticaria	29	1.0	3.2
Gastr	Nausea	28	1.0	3.0
Nerv	Dizziness	24	0.8	2.6
Gastr	Haematemesis	21	0.7	2.3
Nerv	Coma	20	0.7	2.2
Skin	Toxic epidermal necrolysis	20	0.7	2.2
Card	Cardiac arrest	19	0.7	2.1
Gastr	Abdominal pain	19	0.7	2.1
Genrl	Condition aggravated	19	0.7	2.1
Inv	Blood creatinine increased	19	0.7	2.1
Nerv	Somnolence	19	0.7	2.1
Skin	Pruritus	19	0.7	2.1

Note: More than one AE coded by MedDRA PTs may have been mentioned in each case.
Source: NDA 201-803; Module 5.3.6.2, Table 4-3, Page 23.

Table 12: Adverse Events in >2% of Serious Cases (n=233): WHO database update report

SOC[a]	Preferred Term	Number of cases	% of AEs reported[b]	% of cases
Psych	Suicide attempt	28	3.9	12.0
Inj&P	Overdose	20	2.8	8.6
Psych	Drug abuse	18	2.5	7.7
Inj&P	Intentional overdose	16	2.2	6.9
Gastr	Nausea	14	1.9	6.0
Psych	Completed suicide	14	1.9	6.0
Gastr	Vomiting	12	1.7	5.2
Inj&P	Accidental overdose	10	1.4	4.3
Renal	Renal failure acute	10	1.4	4.3
Skin	Rash	9	1.3	3.9
Resp	Dyspnoea	9	1.3	3.9
Inj&P	Accidental drug intake by child	8	1.1	3.4
Genrl	Fatigue	8	1.1	3.4
Nerv	Somnolence	8	1.1	3.4
Gastr	Haematemesis	7	1.0	3.0
Inj&P	Post procedural haemorrhage	7	1.0	3.0
Nerv	Dizziness	7	1.0	3.0
Gastr	Abdominal pain	6	0.8	2.6
Inv	Haemoglobin decreased	6	0.8	2.6
Genrl	Death	6	0.8	2.6
Genrl	Malaise	6	0.8	2.6
Skin	Toxic epidermal necrolysis	6	0.8	2.6
Card	Tricuspid valve incompetence	6	0.8	2.6
Immun	Hypersensitivity	6	0.8	2.6
Psych	Drug dependence	5	0.7	2.1
Psych	Intentional drug misuse	5	0.7	2.1
Inj&P	Drug exposure during pregnancy	5	0.7	2.1
Card	Cardiac hypertrophy	5	0.7	2.1
Card	Cardiomegaly	5	0.7	2.1
Card	Pulmonary valve incompetence	5	0.7	2.1
Card	Tachycardia	5	0.7	2.1

Note: More than one AE coded by MedDRA PTs may have been mentioned in each case
Source: NDA 201803, Module 5.3.6.6, Table 4-3, Page 19-20

Table 13: Adverse Events in >2% of Serious Cases (n=1,344): AERS database initial report

SOC	Preferred Term	Number of cases	% of AEs reported[6]	% of cases
Renal	Renal failure acute	77	1.6	5.7
Genrl	Condition aggravated	54	1.1	4.0
Gastr	Vomiting	51	1.0	3.8
Psych	Completed suicide	49	1.0	3.6
Inj&P	Overdose	48	1.0	3.6
Genrl	Drug interaction	43	0.9	3.2
Immun	Hypersensitivity	43	0.9	3.2
Inj&P	Intentional overdose	40	0.8	3.0
Resp	Dyspnoea	40	0.8	3.0
Inj&P	Drug toxicity	39	0.8	2.9
Gastr	Nausea	36	0.7	2.7
Gastr	Gastrointestinal haemorrhage	35	0.7	2.6
Psych	Suicide attempt	35	0.7	2.6
Skin	Rash	33	0.7	2.5
Genrl	Death	32	0.7	2.4
Genrl	Drug ineffective	32	0.7	2.4
Metab	Dehydration	32	0.7	2.4
Skin	Toxic epidermal necrolysis	32	0.7	2.4
Genrl	Pyrexia	31	0.6	2.3
Inv	Haemoglobin decreased	31	0.6	2.3
Gastr	Diarrhoea	30	0.6	2.2
Nerv	Dizziness	30	0.6	2.2
Gastr	Abdominal pain	29	0.6	2.2
Skin	Urticaria	28	0.6	2.1

Note: More than one AE coded by MedDRA PTs may have been mentioned in each case.

Source: Source: NDA 201-803; Module 5.3.6.2, Table 4-4, Page 24.

Table 14: Adverse Events in >2% of Serious Cases (n=633): AERS database update report

SOC[a]	Preferred Term	Number of cases	% of AEs reported[b]	% of cases
Renal	Renal failure acute	40	1.7	6.3
Inj&P	Intentional overdose	38	1.6	6.0
Psych	Suicide attempt	37	1.6	5.8
Gastr	Vomiting	31	1.3	4.9
Genrl	Condition aggravated	30	1.3	4.7
Gastr	Nausea	23	1.0	3.6
Psych	Completed suicide	23	1.0	3.6
Resp	Dyspnoea	23	1.0	3.6
Genrl	Drug ineffective	21	0.9	3.3
Gastr	Abdominal pain	20	0.9	3.2
Inj&P	Overdose	20	0.9	3.2
Inj&P	Multiple drug overdose intentional	19	0.8	3.0
Renal	Renal failure	19	0.8	3.0
Genrl	Drug interaction	18	0.8	2.8
Genrl	Pyrexia	18	0.8	2.8
Nerv	Dizziness	17	0.7	2.7
Genrl	Asthenia	16	0.7	2.5
Inj&P	Accidental overdose	16	0.7	2.5
Skin	Rash	14	0.6	2.2
Musc	Osteonecrosis	14	0.6	2.2
Inv	Haemoglobin decreased	13	0.6	2.1
Renal	Renal impairment	13	0.6	2.1

Note: More than one AE coded by MedDRA PTs may have been mentioned in each case
Source: NDA 201803, Module 5.3.6.6, Table 4-4, Page 21

During the initial reporting periods, 166 of the 919 serious cases had fatal outcomes in the WHO data and 195 of the 1,344 cases had fatal outcomes in the AERS data. In the WHO data, death cases ranged in age from 3 years to 91 years; the majority were between the ages of 18 and 64 years (n=115; 69.2%); 14 (8.4%) cases were less than age 18, and 17 (10.2%) cases were age 65 years or older. The most frequently reported PT for death was completed suicide (n=56). In the AERS data, death cases ranged in age from <1 year to 94 years; the majority were between the ages of 18 and 64 years (n=123; 63.0%); 11 (5.6%) cases were less than age 18, and 29 (14.9%) cases were age 65 years or older. The most frequently reported PT for death was completed suicide (n=49; 25.1%). The update report included 36 fatal outcomes in the WHO data and 68 in the AERS data. The most frequently reported PT was completed suicide (n=14 for WHO and n=23 for AERS).

During the initial reporting period, there were 68 cases in the WHO data and 97 cases in the AERS data that were life threatening. The most frequently reported PT for life threatening cases was toxic epidermal necrolysis (WHO: n=10; 14.7% and AERS: n=13; 13.4%). There were 35 ibuprofen-only life threatening cases in the WHO data and 26 ibuprofen-only life threatening

cases in the AERS data. For both databases, the most frequently reported PT in the ibuprofen-only cases was dyspnoea (n=5 for each database).

The report updates included 18 cases in the WHO data and 60 cases in the AERS data that were life-threatening. Among the WHO cases, the most frequently reported PT was toxic epidermal necrolysis (n=3, 16.7%). There were nine ibuprofen-only life-threatening cases in the WHO data with dyspnoea as the most frequently reported PT. Among the AERS cases, the most frequently reported PTs for cases with life-threatening events were haemoglobin decreased and renal failure acute (both n=5; 8.3%). There were 18 ibuprofen-only cases in the AERS data; the most frequently reported PTs were hypothermia and Steven-Johnson syndrome (both n= 3; 16.7%).

During the initial reporting periods, there were 296 cases in the WHO data and 643 cases in the AERS data that met the definition of serious because the event caused or prolonged hospitalization. For the WHO cases, the most frequently reported PTs associated with prolonged hospitalization were renal failure acute (n=31; 10.5%), intentional overdose (n=19; 6.4%), and suicide attempt (n=17; 5.7%). There were 133 ibuprofen-only events that caused or prolonged hospitalization in the initial WHO data. The most common AEs were renal failure acute (n=15, 11.3%) along with angioedema and dyspnoea (n=9 for each). The age ranges for the ibuprofen-only events were: 59 (44.4%) between ages 18 and 64 years, 21 (15.8%) less than 18 years, 17 (12.8%) age greater than 65 years, and 36 (27.1%) with no age reported.

For the AERS cases, the most frequently reported PTs associated with prolonged hospitalization were renal failure acute (n=60; 9.3%) and vomiting (n=33; 5.1%). There were 140 ibuprofen-only events that caused or prolonged hospitalization in the AERS data. Of these, the most frequently reported PTs were renal failure acute (n=14; 10.0%) and dyspnoea (10). Forty-three (30.7%) patients were between the ages of 18 and 64 years, 39 (27.9%) were less than 18 years of age, and 17 (12.1%) were age 65 years or older. Age was missing for 41 (29.3%) cases.

The safety update included 64 cases in the WHO data and 355 cases in the AERS data of hospitalization events (the event caused or prolonged hospitalization). For the WHO data, the most frequently reported PTs were intentional overdose and suicide attempt (both n=7; 10.9%). In the AERS cases, the most frequently reported PT was acute renal failure (n=31; 8.7%).

There were three cases in the initial WHO data and 35 cases in the initial AERS data in which the event was disabling or incapacitating. The most frequently reported PT for these cases was Stevens-Johnson syndrome (n=5). In the update reports, there were no additional cases in the WHO data and 23 cases in the AERS data. The most frequently reported PT in the AERS cases was osteonecrosis (n=14).

Reviewer Comment: An AERS search was conducted for reports of ibuprofen use associated with osteonecrosis during the time period of Jan 1, 2009 through Dec 31, 2010. A total of 17 cases were listed. Three of these were recognized by the reporters as duplicate cases. The case reports were reviewed and I believe these are all the same case. In each case, a 42 year old female patient from the United Kingdom, weighing 65 kg, and taking sertraline and ibuprofen,

developed spontaneous bilateral osteonecrosis of the knees. The condition resolved spontaneously in six months. After review of the reports, this seems to be a single case and the relationship of the condition to ibuprofen is not clear. This does not appear to be a new safety signal.

The WHO and AERS data have insufficient details to thoroughly examine drug-drug interactions. Although there are some start and stop dates for ibuprofen and other medications, the data is very incomplete. In the initial reports, lithium was listed as a concomitant medication in one WHO case and in five AERS cases. The safety update included one WHO case and three AERS cases. Although all cases were considered serious, none resulted in death. Warfarin was listed as a concomitant medication in nine WHO cases and 13 AERS cases in the initial report and one WHO case and eight AERS cases in the update. Five of the nine initial WHO cases were considered serious and included two deaths. The one other WHO case also resulted in death though no details were provided. There were two deaths reported in the AERS data; one was a completed suicide and the other report provided no details. In all of the serious reports involving concomitant use of warfarin and ibuprofen, the patients were taking multiple other medications.

There were no cases of renal insufficiency, renal failure, renal failure acute, or renal impairment coincident with a case of cirrhosis in either the WHO or the AERS data.

In the initial WHO data, there were 204 cases of drug overdose that were coincident with the use of ibuprofen. Of these, 183 were considered serious. The majority of the cases were from the United States (89 of 183) and Germany (57 of 183). The update included 70 drug overdose events with most from Germany (28) and the United States (27). In the initial AERS data, there were 183 cases of drug overdose that were coincident with the use of ibuprofen. Of these, 181 were considered serious. The majority of the cases (100 of 181) were from the United States. The update included 121 drug overdose events; 56 from the United States and 19 each from Germany and the United Kingdom.

There were four cases in the initial data and five cases in the updated WHO database involving ibuprofen exposure during pregnancy. The relationship of ibuprofen to the effects noted is not clear. These cases are summarized in Table 15.

Table 15: Ibuprofen Exposures in Pregnancy: WHO database (initial and update)

Ibuprofen Exposure History	Concomitant Medications	Outcome/Preferred Terms
Exposure during pregnancy Ibuprofen 200 mg	None listed	Premature labour
Exposure during pregnancy Ibuprofen 600 mg 1/day	Norflaxacin, Metopimazine	Intentional overdose
Exposure during pregnancy	None listed	Ductus arteriosus stenosis foetal, Premature labour
Exposure during pregnancy Ibuprofen 8 gm total	None listed	Coagulation time prolonged, Oligohydramnios, Overdose, Platelet aggregation decreased, Platelet function test abnormal
Exposure during pregnancy	None listed	Premature Labour
Exposure during pregnancy	Candesartan, Hydrochlorothiazide	Abortion spontaneous
Exposure during pregnancy Ibuprofen 400 mg	Cefuroxime, Ephedrine, Lidocaine, Propofol, Rocuronium, Sevoflurane, Sufentanil, Tramadol	None listed except exposure
Exposure during pregnancy Ibuprofen 800 mg	Diclofenac, Tramadol, Tizanidine	None listed except exposure
Exposure during pregnancy	Budesonide, Formoterol, Fumarate, Escitalopram, Fenoterol, Folic Acid, Levothyroxine, Potassium Iodide, Methyldopa, Montelukast, Topiramate	Apraxia

Source: NDA 201803, Module 5.3.6.2, Table 4-32, Page 61-61 and Module 5.3.6.6, Table 4-37, Page 51-52

There were eight cases in the initial report and six cases in the updated AERS database involving ibuprofen exposure during pregnancy. The relationship of ibuprofen to the effects noted is not clear though ductus arteriosus complications are described on the ibuprofen labeling. These cases are summarized in Table 16.

Table 16: Ibuprofen Exposures in Pregnancy: AERS database (initial and update)

Ibuprofen Exposure History	Concomitant Medications	Outcome/Preferred Terms
Exposure during pregnancy	None listed	Ductus arteriosus stenosis foetal, Premature labour
Exposure during pregnancy	Ethinylestradiol, Levonorgestrel	Drug ineffective, Unintended pregnancy
Exposure during pregnancy	Dexketoprofen, Metamizole, Levofloxacin	Aplastic anaemia, Pancytopenia
Exposure during pregnancy	Metopimazine, Norfloxacin	Intentional overdose
#Exposure during pregnancy	Clotrimazole, Doxycycline, Itraconazole	Arthralgia, Candidiasis, Pelvic pain, Plantar fasciitis
#Exposure during pregnancy Ibuprofen topical	Clotrimazole, Doxycycline, Itraconazole	Arthralgia, Caesarean section, Pelvic pain, Plantar fasciitis, Vulvovaginal candidiasis
#Exposure during pregnancy Ibuprofen topical daily	Clotrimazole, Doxycycline, Itraconazole	Arthralgia, Caesarean section, Pelvic pain, Plantar fasciitis, Vulvovaginal candidiasis, Pubic pain, Condition aggravated
Exposure during pregnancy Ibuprofen 2 tabs/ 3-4 X week	None listed	Foetal disorder, Heart rate irregular, Maternal drugs affecting foetus, Weight increased
Exposure during pregnancy	Candesartan, Hydrochlorothiazide	Abortion spontaneous
Exposure during pregnancy	Ethinylestradiol, Norgestimate, Folic Acid, Hydroxychloroquine, Leflunomide	None listed except exposure
Exposure during pregnancy Ibuprofen on 4 occasions	Methotrexate	Abdominal pain, Abortion spontaneous, Nausea
Exposure during pregnancy Ibuprofen 400 mg, 2-3 times	Acetaminophen, Vitamin	Retained placenta or membranes, Uterine atony
*Exposure during pregnancy	Ciprofloxacin, Citalopram, Hyoscine, Omeprazole, Pregabalin, Tolperisone	Abortion induced
*Exposure during pregnancy	Ciprofloxacin, Citalopram, Hyoscine, Omeprazole, Pregabalin, Tolperisone	Abortion induced

and *: These reports are probably duplicates
Source: NDA 201803, Module 5.3.6.2, Table 4-33, Page 63-64 and Module 5.3.6.6, Table 4-38, Page 52-53

During the initial reporting period, there were 120 serious AE cases in the WHO data and 246 serious AE cases in the AERS data of ibuprofen administration in children less than 18 years of age. For the WHO data, the most common AEs coded by MedDRA PT for serious cases in pediatrics included: renal failure acute (14), vomiting (10), overdose (9), hypersensitivity (8), hypothermia (8), convulsion (7), accidental overdose (7), accidental drug intake by child (6), toxic epidermal necrolysis (5), somnolence (5), and Stevens-Johnson syndrome (5). For the AERS data, the most common AEs were: renal failure acute (30), condition aggravated (28), vomiting (15), accidental overdose (15), hypersensitivity (14), dehydration (13), toxic epidermal necrolysis (12), diarrhoea (11), accidental drug intake by child (11), and infection (10).

In the updated safety report, there were 41 serious cases in the WHO data and 141 serious cases

in the AERS data of ibuprofen administration in children less than 18 years of age. The WHO data included one death and no details were provided. The most common AEs coded by MedDRA PT were: accidental drug intake by child (7), accidental overdose (6), post procedural haemorrhage (5), renal failure acute (5), blood creatinine increased (3), overdose (3), toxic epidermal necrolysis (3), and vomiting (3). The AERS data included seven reports of death. The most common AEs coded by MedDRA PT were: condition aggravated (18), accidental overdose (14), renal failure acute (13), vomiting (10), abdominal pain (9), accidental drug intake by child (9), and Stevens-Johnson syndrome (9).

During the initial reporting period, there were 133 serious cases in the WHO data and 223 serious cases in the AERS data of ibuprofen administration in the elderly (age 65 or older). For the WHO data, the most common AEs coded by MedDRA PT included: gastric haemorrhage (10), anaemia (9), condition aggravated (8), completed suicide (7), gastrointestinal haemorrhage (7), renal failure acute (7), dizziness (6), drug ineffective (6), haemoglobin decreased (6), and melaena (6). For the AERS data, the most common AEs coded by MedDRA PT were: gastrointestinal haemorrhage (14), anaemia (12), haematoma (11), drug interaction (10), gastric ulcer (9), haemoglobin decreased (9), osteoarthritis (9), nausea (8), diarrhoea (7), gastric haemorrhage (7), urinary tract infection (7), and vomiting (7).

The safety update included 19 serious cases in the WHO data and 114 serious cases in the AERS data of ibuprofen administration in the elderly (age 65 or older). For the WHO data, the most common AEs coded by MedDRA PT were: anaemia (3) and duodenal ulcer, fatigue, malaise, and nausea (each with 2 cases reported). There were 10 fatalities reported in the AERS update. Most of these patients were on several concomitant medications. The most common AEs coded by MedDRA PT in the AERS update report were: renal failure acute (13), drug interaction (8), renal failure (7), anaemia (6), and back pain (6).

In the initial report 175 cases reporting medication errors were identified coincident to ibuprofen use in the WHO data and 176 cases in the AERS data. In both databases, the most common error was overdose (53 in WHO and 48 in AERS). Intentional overdose was also common (37 in WHO, 40 in AERS). There were 11 cases of accidental drug intake by a child reported. The safety update included 57 serious cases in the WHO data and 113 serious cases in the AERS data of prescription/ medication error events. The WHO data included 20 overdose reports, 16 intentional overdose, and eight reports of accidental drug intake by child. The AERS data included 20 cases coded as overdose, 38 cases of intentional overdose, and nine cases of accidental drug intake by child.

PCH concludes the data limitations make further comments on causality difficult. The sponsor also notes that though the numbers of adverse event cases including ibuprofen sodium were small, there were no apparent differences in the safety profile of this salt compared to other ibuprofen formulations. It is also noted that five cases of death (one in the WHO data and four of the AERS data) had exactly the same list of concomitant medications (i.e., carisoprodol, diphenhydramine, hydrocodone, ibuprofen, oxycodone, pregabalin, and warfarin). In the update report there also appeared to be at least one duplicate death report (two cases of a 42 year old

female taking Alprazolam, Aripiprazole, ibuprofen, lidocaine, and Topiramate). These are likely due to duplication of cases in the databases, although it cannot be confirmed.

PCH believes the information available from the WHO and AERS databases for the reporting periods support the known safety profile of ibuprofen. There is no need to take specific action, nor a need to make changes to the Reference Safety Information (RSI) at this time.

Reviewer Comment: The WHO and AERS data show a similar pattern. The most common events are those related to medication overdose, frequently associated with a suicide attempt. Cases of renal failure are noted but the frequency is not greater than expected for this drug class. There does not appear to be a new, significant safety signal that requires additional OTC labeling.

8.3 American Association of Poison Control Centers Database

An analysis of the American Association of Poison Control Centers (AAPCC) data was performed in support of the new formulation of ibuprofen (ibuprofen sodium). The AAPCC data come from the National Poison Data System (NPDS), a comprehensive uniform data set of cases recorded by 60 poison control centers (PCCs) throughout the United States and in Puerto Rico. The initial reporting period covered February 1, 2008, through January 31, 2009 and the update covered February 2, 2010 through June 30, 2010. There are limitations in the data:

- A case may be reported by different source and appear more than once. It is not possible to identify duplicate cases.
- The AAPCC data does not identify medications by trade name of the full generic name, so there was no way to differentiate ibuprofen sodium from other ibuprofen formulations.

The AAPCC data contained 88,315 cases of ibuprofen exposure in children and adults during the initial reporting period. Of these cases, 9,272 were determined to be serious adverse events (SAEs), including 8,866 hospitalizations, 379 major effects, and 27 deaths. Of all the SAEs, there were 2,869 hospitalizations, 49 major effects and one death where the only medication listed was ibuprofen. There were 162 cases associated with pregnancy, but none included deaths or major effects.

Ibuprofen was ranked as the primary drug exposure that led to the contact with the PCC in 4,465 (48.2%) of the serious cases. The dose of ibuprofen was missing, incomplete, or unusable (e.g., “one bite”) 38.7% of the time and the duration of exposure for all SAEs was generally left blank (n=8,205; 88.5%). Because the route of administration was not attributed to individual medications, reviewing the routes of administration was not informative except when only one medication was mentioned. In the case of ibuprofen, it was assumed that all ibuprofen exposures were via oral ingestion, as there are no other marketed forms of ibuprofen in the United States. Among patients with SAEs, exposures to all drugs taken were most often recorded as Intentional – Suspected suicide (n=8,166; 88.1%), and most of the exposures took place in the patient’s own residence (n=8,761; 94.5%).

The AAPCC data update contained 34,464 cases of ibuprofen exposure in children and adults. Of these cases, 4,039 were determined to be serious, including 3,854 hospitalizations, 173 major effects, and 12 deaths (nine of which were Intentional - Suspected suicides). There were 61 cases associated with pregnancy, 28 of which were considered serious cases because they included hospitalizations. Among the serious cases, exposures (to all drugs taken) were most often recorded as to Intentional – Suspected suicide (n=3,562; 88.2%). No cases that were associated with pregnancy included deaths or major effects. Of the 4.039 serious cases, there were 1,301 hospitalizations that did not overlap with deaths or major effects, 17 major effects, and no deaths where the only medication listed was ibuprofen. The 17 ibuprofen-only cases with major effects ranged in age from 1 year to 58 years. No pregnancies were reported and most of these cases were Intentional – Suspected suicide (n=13, 76.5%).

Each AAPCC case is coded for Clinical Effect (CE) frequency. There are up to 131 different CEs which are signs, symptoms, or laboratory abnormalities that can be coded for each case. CEs are not recorded using MedDRA terms. During the initial reporting period, there were a total of 30,331 CEs in the 88,315 cases of exposures in the AAPCC data, of which 15,799 were associated with the 9,272 serious cases (i.e., deaths, major effects, and/or hospitalizations). The safety update included a total of 13,589 CEs in the 34,464 cases with ibuprofen exposures of which 7,342 CEs were associated with the 4,039 serious cases. If a CE was reported as “related” that meant that the CE was deemed related to some or all of the drugs taken by the individual; it is not possible to determine which single drug or combination of drugs may have been responsible for the CE when more than one drug was mentioned. CEs that occurred in >2% of all serious cases are presented in Tables 17 and 18.

Table 17: Clinical Effects in >2% of SAEs (n=9,272): AAPCC initial report

Clinical effects	n	%	Not Related	Related[a]	Unknown
Drowsiness/lethargy	2,506	27.0	1.6%	94.3%	4.1%
Tachycardia	1,790	19.3	3.9%	87.2%	8.9%
Vomiting	1,745	18.8	3.4%	91.9%	4.7%
Nausea	1,201	13.0	1.4%	94.8%	3.8%
Abdominal Pain	857	9.2	2.3%	89.8%	7.8%
Agitated/irritable	589	6.4	10.0%	73.2%	16.8%
Hypertension	529	5.7	20.4%	55.8%	23.8%
Other	468	5.0	15.8%	66.9%	17.3%
Hypotension	425	4.6	5.4%	81.4%	13.2%
Confusion	395	4.3	3.0%	90.4%	6.6%
Electrolyte abnormality	384	4.1	6.5%	73.2%	20.3%
Acidosis	311	3.4	1.9%	89.4%	8.7%
Slurred speech	276	3.0	0.4%	97.1%	2.5%
Coma	256	2.8	1.2%	93.4%	5.5%
Conduction disturbance	217	2.3	11.1%	65.4%	23.5%
Dizziness/vertigo	208	2.2	3.8%	83.2%	13.0%
Creatinine increased	197	2.1	6.6%	71.6%	21.8%

Source: NDA 201803, Module 5.3.6.3, Table 4-2, Page 12-13

Table 18: Clinical Effects in >2% of SAEs (n=4,039): AAPCC update report

Clinical effects	Number of cases	% of cases	"Not Related"	"Related"[a]	Unknown
Drowsiness/lethargy	1,148	28.4	1.7%	94.7%	3.7%
Tachycardia	854	21.1	5.6%	85.2%	9.1%
Vomiting	777	19.2	2.8%	92.3%	4.9%
Nausea	540	13.4	1.7%	93.7%	4.6%
Abdominal Pain	365	9.0	1.4%	90.1%	8.5%
Agitated/irritable	292	7.2	10.3%	76.7%	13.0%
Hypertension	292	7.2	24.3%	58.6%	17.1%
Other	236	5.8	13.6%	74.6%	11.9%
Hypotension	186	4.6	2.2%	83.9%	14.0%
Confusion	179	4.4	0.0%	91.1%	8.9%
Electrolyte abnormality	166	4.1	5.4%	69.9%	24.7%
Slurred speech	146	3.6	2.1%	95.2%	2.7%
Acidosis	145	3.6	0.7%	89.7%	9.7%
Coma	122	3.0	1.6%	91.0%	7.4%
Dizziness/vertigo	102	2.5	1.0%	91.2%	7.8%
Bradycardia	94	2.3	28.7%	51.1%	20.2%
Conduction disturbance	92	2.3	6.5%	71.7%	21.7%
AST, ALT>100<=1,000	85	2.1	7.1%	75.3%	17.6%
Creatinine increased	83	2.1	6.0%	67.5%	26.5%

Source: NDA 201803, Module 5.3.6.7 Table 4-2, Page 13-14

Patients involved in the initial report ibuprofen-only SAE cases ranged in age from 7 days to 91 years; the majority were between the ages of 18 and 64 years (n=1,709; 58.5%), with 1,156 (39.6%) patients less than 18 years of age, and 23 (0.8%) patients in age 65 years or older. In the 2,919 ibuprofen-only initial report cases, the reason for exposure was most often Intentional - Suspected suicide (n=2,506; 85.9%). The most common CEs associated with SAEs in the initial ibuprofen-only cases were: vomiting (n=463), nausea (n=366), abdominal pain (n=350), drowsiness/lethargy (n=333), and tachycardia (n=267).

In the update report, there were 1,318 ibuprofen-only serious cases. Ibuprofen-only serious cases ranged in age from 9 months to 94 years; the majority were between the ages of 18 and 64 years (n=827; 62.8%), with 467 (35.4%) cases less than 18 years of age, and 12 (0.9%) cases age 65 years or older. The reason for exposure was most often Intentional - Suspected suicide (n=1,143; 86.7%). The most common CEs associated with serious ibuprofen-only cases in the safety update were: vomiting (n=211), drowsiness/lethargy (n=191), nausea (n=174), tachycardia (n=156). and abdominal pain (n=148).

In the initial report, ibuprofen was ranked as the primary drug exposure that led to the contact with the PCC in three deaths, secondary drug exposure in seven deaths, and tertiary exposure or lower in 17 deaths. Of the 27 deaths, the dose of ibuprofen was reported in only four and ranged

from 10 grams to 250 tabs/pills/capsules (amount of active ingredient not reported). Information on the duration of exposure was available for only one case. There were no cases of death for individuals 18 years of age or younger. Cases ranged in age from 21 years to 90 years; the majority were between the ages of 18 and 64 years (n=22), and four cases in age 65 years or older. There was only one death in ibuprofen-only cases. This was a 90 year old male admitted to the coronary care unit for unknown reasons, who had consumed 200 tabs/pills/capsules (dose unknown) and experienced the following CEs: drowsiness/lethargy, fever/hyperthermia, pulmonary edema, respiratory depression, and tachycardia.

The update report listed ibuprofen as the primary drug exposure that led to the contact with the PCC in one death, secondary drug exposure in six deaths, and tertiary exposure or lower in five deaths. Of the 12 cases with reported death, the dose of ibuprofen was reported in only four and ranged from 1 tabs/pills/capsules to 500 tabs/pills/capsules (amount of the active ingredient not reported). Information on the duration of exposure was available for only one case. Cases ranged in age from 19 years to 57 years. There were no ibuprofen-only cases with reported death.

During the initial reporting period, there were 379 events related to ibuprofen data that met the definition of serious because they were major effects (all of which were considered life threatening events). The update included 173 cases with events “related” to ibuprofen that were considered serious. The initial report included 49 life threatening events for ibuprofen-only cases, including nine in ages 18 or less, 39 in age 18 to 64, and one in age 65 or older. Most were Intentional-Suspected suicides (n=37; 75, 5%). The update listed 17 ibuprofen-only cases with major effects. Most were Intentional - Suspected suicides (n=13; 76.5%).

The AAPCC data set has insufficient details to examine drug-drug interactions, such as the patients' clinical course, dose and frequency of medications, and medical history. The initial report included one case where both lithium and warfarin were listed as medications that were coincident with the use of ibuprofen; it was neither a death nor a major effect, but did result in hospitalization. This was a 75 year old male who was admitted due to Intentional - Misuse, and experienced the following CEs: bradycardia, conduction disturbance, confusion, drowsiness/lethargy, hyperventilation/tachypnea, and hypotension. His concomitant medications included: calcium antagonists, aspirin, angiotensin receptor blockers, antihyperlipidemics, laxatives, furosemide, glucosamine, selective serotonin reuptake inhibitors, proton pump inhibitors, warfarin, long-acting nitrates, potassium, lithium, ibuprofen, alpha blockers, atypical antipsychotics, benzodiazepines, and naproxen. There were 15 cases in the initial AAPCC data where warfarin, but no lithium, was listed as a medication that was coincident with the use of ibuprofen. Of these, there were no deaths and no major effects. All cases were of Intentional - Suspected suicide. In addition, there were 75 cases in the initial report where lithium, but no warfarin, was listed as a medication that was coincident with the use of ibuprofen. Of these, 49 were considered serious - one death and four major effects. The reason for exposure was most often Intentional - Suspected suicide (n=41; 83.7%).

The update report listed no cases where both lithium and warfarin were listed as medications coincident with ibuprofen. There were 10 cases in the AAPCC data where warfarin, but not

lithium, was listed. All cases were of Intentional - Suspected suicide. There were no deaths. In addition, there were 33 cases where lithium, but not warfarin, was listed as a medication. The majority of the serious cases with lithium were age 18-64 (n=20; 80.0%); and five (20.0%) were less than age 18. There were no deaths. The reason for exposure was most often Intentional - Suspected suicide (n=23; 92.0%).

During the initial and update reporting periods, information on cirrhosis was not provided, so cases of renal insufficiency, renal failure, renal failure acute, or renal impairment coincident with a case of cirrhosis could not be evaluated.

During the initial reporting period, there were 162 pregnant women, including 94 ibuprofen-only cases. Ibuprofen was ranked as the primary drug exposure that led to the contact with the PCC in 117 (72.2%) of the cases in pregnant women. Of the patients who were pregnant, their exposures were most often related to Intentional - Suspected suicide (n=114; 70.4%). The 28 ibuprofen-only hospitalizations of pregnant women ranged in age from 17 years to 40 years and all but one were Intentional - Suspected suicides.

In the update report, there were 61 cases with pregnancy, including 38 (62.3%) ibuprofen-only cases. Ibuprofen was ranked as the primary drug exposure that led to the contact with the PCC in 40 (65.6%) cases with pregnancy. Of the cases with pregnancy, exposure was most often related to Intentional - Suspected suicide (n=43; 70.5%). There were 11 ibuprofen-only serious cases with pregnancy and all were Intentional - Suspected suicides.

There were five cases in the initial report that were attributed to exposure from lactation, one of which was an SAE. The SAE was a 7 day only male admitted with an adverse drug reaction recorded as “bleeding (other)” where ibuprofen (dose unknown) was the only medication and therefore the primary drug. The medical outcome was reported as “exposure probably not responsible for the effect(s).” The updated report had no cases related to exposure from lactation.

During the initial reporting period, there were 67,297 (of the 88,315) cases in the AAPCC data of ibuprofen exposures regarding children less than 18 years of age; of these 2,886 (4.3%) were serious (2,835 hospitalizations, 51 major effects, and no deaths). The pediatric serious cases constituted 31.1% of all of the serious cases. Of all pediatric SAEs, 1,156 were ibuprofen-only cases; all but two included hospitalizations and nine also included major effects. For the ibuprofen-only SAE cases in children, the majority were females (n=883; 76.4%), two of whom were pregnant. Most were Intentional - Suspected suicides (n=964; 83.4%).

During the update period, there were 25,687 (of the 34,464) cases in the AAPCC data of ibuprofen exposures regarding children less than 18 years of age; of these 1,190 (4.6%) were serious (1,161 hospitalizations and 29 major effects). The serious pediatric cases constituted 29.5% of all of the serious cases. The majority were 10-18 years old (n=1,117; 93.9%) and 73 (6.1%) were 0 to 9 years old. Of all serious pediatric cases, 467 were ibuprofen-only cases; all included hospitalizations and three also included major effects. Most were Intentional – Suspected suicides (n=388; 83.1%).

During the initial reporting period, there were 606 cases in the AAPCC data of ibuprofen exposure regarding the elderly (age 65 or older); of these 77 (12.7%) were serious (65 hospitalizations, 8 major effects, and 4 deaths). They constituted 0.8% of all of the serious events. Of these, SAEs 23 were ibuprofen-only cases. The most common CEs for these cases were: drowsiness/lethargy (n=23), hypotension (n=12), confusion (n=10), creatinine increased (n=10), and electrolyte abnormality (n=10). The 23 ibuprofen-only cases where ibuprofen was the only drug exposure in the case ranged in age from 65 years to 91 years. Most were Intentional - Suspected suicides (n=16; 69.6%).

During the update period, there were 278 cases in the AAPCC data of ibuprofen exposure regarding the elderly (age 65 or older); of these 43 (15.5%) were serious (38 hospitalizations, five major effects, and no deaths). Of the serious elderly cases, 12 were ibuprofen-only cases. The majority were Intentional - Suspected suicides (n=7; 58.3%).

There were 16,165 cases reporting medication errors in the initial reporting period identified coincident to ibuprofen use. Of these, 49 were considered serious; and 16,116 were considered non-serious. There was one death. The most common CEs associated with serious cases and medication errors were: drowsiness/lethargy (n=10), other (n=9), vomiting (n=8), creatinine increased (n=6), confusion (n=5) and nausea (n=5). The medication errors coded by the AAPCC are shown in Table 19.

Table 19: Serious Medication Errors (n=49): AAPCC database initial report

Scenario	n	% of Cases
Medication doses given/taken too close together	14	28.6
Other incorrect dose	10	20.4
Other/unknown therapeutic error	7	14.3
Health professional/iatrogenic error (pharmacist/nurse)	5	10.2
Inadvertently took/given medication twice	5	10.2
More than one product containing same ingredient	4	8.2
Incorrect formulation or concentration given	3	6.1
Inadvertently took/given someone else's medication	2	4.1
Wrong medication taken/given	2	4.1
10-fold dosing error	1	2.0
Confused units of measure	1	2.0
Incorrect formulation or concentration dispensed	1	2.0

Source: NDA 201803, Module 5.3.6.3, Table 4-13, Page 39

There were 6,426 cases with medication errors were identified coincident to ibuprofen use in the update data; of these 24 were considered serious, and 6,402 were considered non-serious. There were no deaths. The medication errors coded by the AAPCC are shown in Table 20.

Table 20: Serious Medication Errors (n=24): AAPCC database update report

Scenario	Number of cases	% of cases
Other incorrect dose	7	29.2
10-fold dosing error	3	12.5
Incorrect formulation or concentration given	3	12.5
Medication doses given/taken too close together	3	12.5
Other/unknown therapeutic error	3	12.5
Health professional/iatrogenic error (pharmacist/nurse)	2	8.3
Inadvertently took/given medication twice	2	8.3
Wrong medication taken/given	2	8.3
Inadvertently took/given someone else's medication	1	4.2
More than 1 product containing same ingredient	1	4.2

Source: NDA 201803, Module 5.3.6.7, Table 4-28, Page 39-40

Based on the AAPCC data, PCH concludes that limitations of the data make interpretation of causality difficult. It is not possible to distinguish ibuprofen sodium from other ibuprofen formulations. In addition, when a CE was reported as "related" that meant that the CE was deemed related to some or all of the drugs taken by the individual. The CEs were not recorded as MedDRA terms, so comparison with other databases is not possible. When multiple drugs were involved in a single case, it is not possible to determine which single drug or combination of drugs may have been responsible for the CE. There are insufficient details to examine drug-drug interactions, such as the patients' clinical course, dose and frequency of medications, and medical history. It is not possible to determine whether there was a drug interaction contributing to the CEs. Data is often incomplete. For example, in the initial report, almost 75% of cases did not have hospitalization information; the dose of ibuprofen was missing or incomplete or unusable for 38.7% of ibuprofen mentions; and the duration of exposure for all SAEs was generally left blank (88.5%). The update report also had significant missing data; 71% had no hospitalization information, 38.1% had incomplete or missing dosing information, and 88.5% of the time the duration of exposure for the serious cases was blank.

In spite of these limitations, however, PCH believes the information available for the reporting period is consistent with the known safety profile of ibuprofen. No new safety risks were identified and there is no need to take a specific action or make changes to the Reference Safety Information (RSI) at this time.

Reviewer Comment: The AAPCC data follows a pattern similar to the WHO and AERS data. Intentional overdose/suicide attempt cases are the most common reason for clinical events. There is no significant safety signal identified that would require a change in OTC labeling.

9 Appendices

9.2 Labeling Recommendations

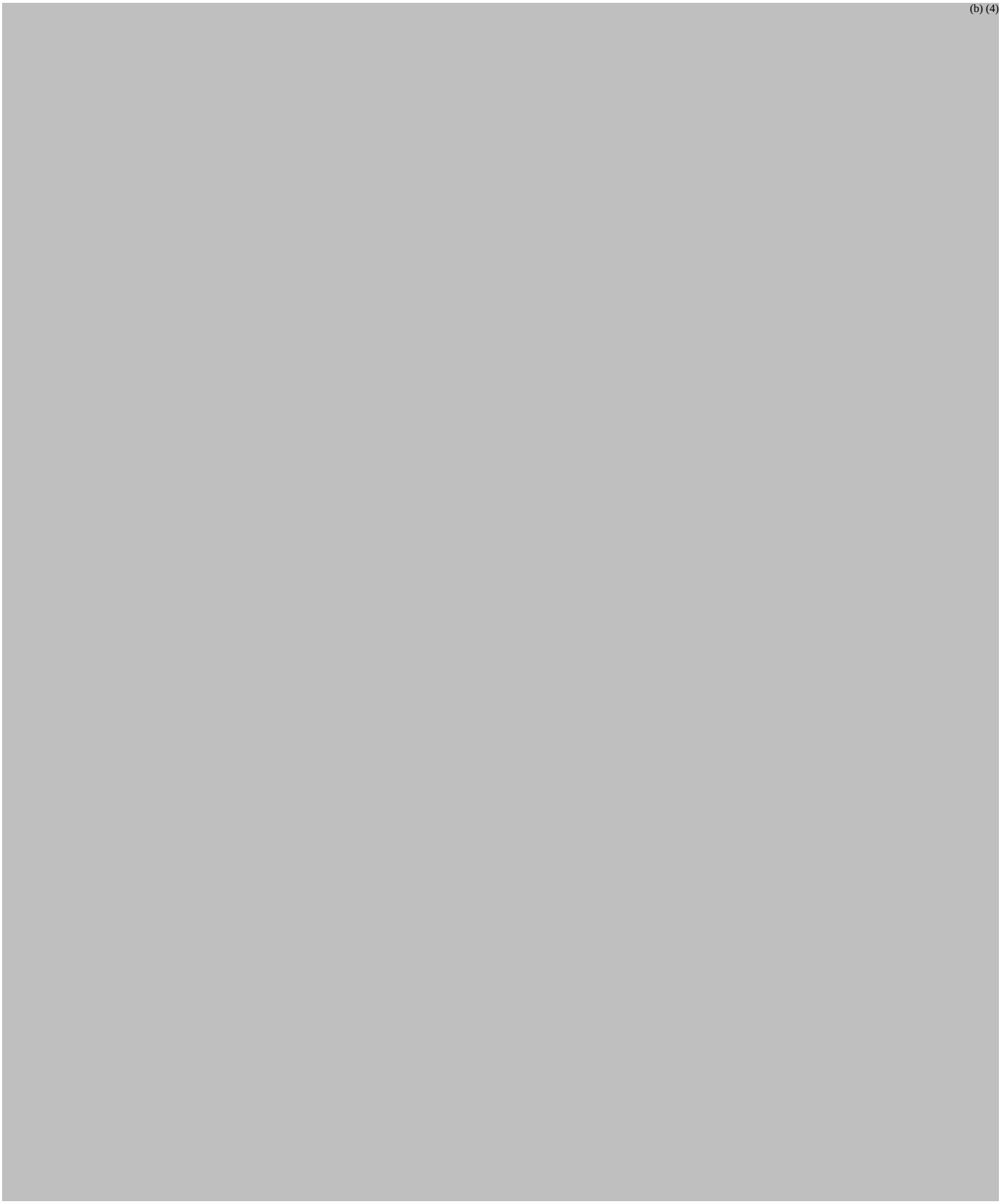
Proposed drug facts/outer container labeling as provided by the sponsor is shown below. The labeling is based on approved class labeling for pain relievers/fever reducers, specifically that for Advil tablets (NDA 18-989) and Advil Liqui-gel (NDA 20-402).

Reviewer Comment: The class labeling is acceptable based on the clinical review of this application. The active ingredient naming is still under discussion with the chemists, but will likely be changed to: Ibuprofen 200 mg (provided as 256 mg ibuprofen sodium). This is a more accurate nomenclature for the active ingredient as the sodium is not 'active' and it is believed this will be less confusing for consumers.

Proposed Drug Facts Labeling

(b) (4)

(b) (4)



The proposed labeling is also being reviewed by the Interdisciplinary Science (IDS) reviewer. Please refer to the IDS review for additional information.

PCH was notified October 8, 2010 that the Division of Medication Error Prevention and Analysis found the sponsor's initial proposed proprietary name, Advil (b) (4), to be unacceptable. The proposed name implied superiority over similar products and misleadingly implied the drug offers a clinical improvement over existing therapies by (b) (4) the efficacy of similar products.

PCH has submitted a request for the proprietary name "Advil (b) (4)" with a proposed alternate name "Advil (b) (4)." Review of the proposed name is in process.

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/s/

PRISCILLA R CALLAHAN-LYON
02/25/2011

LESLEYANNE A FURLONG
02/25/2011